INTEGRATING TREATMENT OF TOBACCO USE AND DEPENDENCE IN A COMPREHENSIVE STRATEGY TO APPROACH RESPIRATORY HEALTH

- HABILITATION THESIS -

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ABSTRACT

The Habilitation Thesis reflects my professional and scientific activity developed after the graduation of the Ph.D. (1997-presently), in the speciality of pulmonology.

The Thesis is describing activities of development of a strategy to approach respiratory health from the perspective of tobacco use prevention and treatment, as tobacco has been a recognized risk factor in the major chronic respiratory disorders encountered in the current practice of the pulmonologists.

This topic has represented a constant preoccupation of mine, since my scientific activity within Ph.D. and has continued in the immediate stage afterwards. By studying lung development for my Ph.D, as well as by acquiring expertise inside bronchological investigations department of the Clinic of Pulmonary Diseases Iasi where I worked as junior pulmonologist, premises of research in the field of impact of tobacco exposure at respiratory system level have risen. As well, by integrating my professional activity in the pulmonary diseases specialty with a teaching and academic component for undergraduates and postgraduates, in time, I had the opportunity to add a research component to my work, at first by clinical multicentric studies – as principal investigator and secondly within research and educational projects aiming to treat smoking patients – as director, responsible or member of grants awarded by international and national competitions.

This work illustrates my continuous interest for developing actual stage of knowledge in research areas characteristic for the pulmonology domain, having in view in the same time an academic evolution according to the curricula and standards of university studies at European Union level. In the last decades, World Health Organization has demonstrated a growth of the respiratory disease burden, globally, based on increasing infectious agents diversity and aggresivity, on indoor and outdoor pollution, specifically refering to tobacco and other respiratory toxicants exposures. Among these, mostly chronic obstructive pulmonary disease (COPD) and lung cancer, both tobacco induced diseases, register an alarming increase, overlapling the ascendent trend of tobacco consumption.

The habilitation thesis is structured in three main sections, in respect to the CNATDCU recommended and approved criteria.

SECTION I, entitled Scientific, professional and academic achievements – overview, essentially contains in chapter Scientific activity, a synthesis of research areas developed after the graduation of the Ph.D., structured in two big chapters, dedicated each to a prioritary research direction, in my professional portfolio. Professional achievements are presented systematically, by research directions and documented with examples of the most relevant personal contributions in the field, preceded by state of art short review of data from literature or by a background to justify my interest in the respective area.

Chapter 1, Research contributions in the field of tobacco use impact on the respiratory system, opens by description of the premises that paved my way in developing the concept of approaching a „smoke-free” respiratory health, starting from expertise I have acquired during my Ph.D. scientific activity and immediately after that. Further, are presented some aspects about the need to raise awareness for the respiratory disaese burden, in the actual global risk context and possible research directions for improving and maximizing respiratory health in tobacco using patients. The next independent subchapter highlights the
role of assistance in maintaining health of the respiratory system through improved air quality in daily life. In succession of this chapter, it is approached the „quality of life” concept, in particular for COPD and pulmonary tuberculosis patients, by introducing specific evaluation tools, with justifications from available literature. This aspect is exemplified in the thesis by a relevant personal contribution due to an article published in April 2017, in a journal indexed in ISI Web of Science, referring to correlations between tobacco use, disease severity and quality of life in COPD patients with depression, anxiety and panic disorders. The chapter continues with a sub-section dedicated to dissemination of skills for reducing the risk for tobacco induced diseases among health professionals, followed by the most consistent part of the chapter describing on one side biomarkers of tobacco exposure –for both clinical use and scientific research validation use – and on the other side presents active and passive smoking pathological findings at respiratory level. This chapter ends with the basis of scientific criteria definition for tobacco use and dependence, defined as a chronic relapsing disease, demanding for the same approach as any other chronic condition (e.g.: hypertension, hypercholesterolemia, etc.), according to current guidelines in use.

Chapter 2. Research contributions to developing treatment and prevention health strategies for tobacco use and dependence brings to the fore my personal contributions to developing personalized smoking cessation treatment programs for high risk smokers, at both national and European level. This chapter is built from six sub-chapters. The first four of them refer to: experience with pilot programs for prevention and treatment of tobacco use and dependence, design and implementation of health smoking cessation programs based on pilots’ expertise, to developing smoking cessation guidelines, and to developing resources in this field. The last two sub-chapters reveal personal contributions at European level in developing personalized tobacco treatment programs for high risk smokers (smokers with diabetes, cardio-vascular, COPD, pregnant women, adolescents) and respectively in developing specific tools for evaluation of the impact of tobacco consumption at populational level, based on 6 European countries surveys. Both these two last sub-chapters present relevant personal results obtained within an European grant (TOB G project for developing smoking cessation guidelines for high risk smokers-call 3-rd EU Health Programme of H2020 program) and respectively within EUREST PLUS – European research grant within H2020 program – dedicated to developing European Regulatory Science on Tobacco Policy Implementation to Reduce Lung Disease – based on Tobacco Products Directive framework in EU.

SECTION II, entitled Career perspectives, presents plans for future developments of my professional and scientific activity, centered on the following research directions: design of new smoking cessation programs for adults from high risk groups - in particular for respiratory disease smokers and adolescents, a more in depth investigation of biomarkers of tobacco exposure, exploring particular patterns of tobacco use and dependence among smokers with respiratory diseases, build up and evaluation of monitoring tools for tobacco control measures in Romania by targeting optimization of existing respiratory health strategies.

Future plans for the academic activity progress include elaboration of manuals for students, involving students and Ph.D. students in research and respiratory health promotion activities, providing post-graduate courses for doctors willing to train in the field of tobacco
use and dependence therapy, as well as national and international collaboration activities with involving young doctors and Ph.D. students.

SECTION III, entitled References is including bibliography to sustain information presented in the habilitation thesis.

REZUMAT

Teza de abilitare reflectă activitatea mea profesional - științifică desfășurată în perioada ulterioră tezei de doctorat (1997-prezent), în domeniul pneumologiei.

Teza descrie activiții de dezvoltare a unei strategii pentru abordarea sănății respiratorii din perspectiva prevenirii și tratamentului consumului de tutun, dovedit ca factor de risc major al principalelor afecțiuni respiratorii cronice întâlnite în practica pneumologică.

Această temă a reprezentat o componentă constantă a preocupărilor mele, încă din perioada de activitate științifică din cadrul doctoratului, continuându-se și după susținerea tezei de doctorat. Prin studiul dezvoltării pulmonare prilejuit de lucrarea de doctorat, dar și ca urmare a expertizei acumulate în departamentul de investigații bronhologice al Clinicii Pneumologice Iași, unde am lucrat inițial ca medic specialist pneumolog, s-au creat premizele de a studia impactul expunerii îndelungate la tutun la nivelul aparatului respirator. Totodată, activitatea profesională medicală în specialitatea pneumologie, cu integrarea componente de învățământ universitar și postuniversitar, a adăugat în timp și o componentă de cercetare, inițial sub forma studiilor clinice multicentrice – ca investigator principal, iar mai apoi în cadrul unor proiecte de cercetare și educaționale de prevenire și tratare a pacienților fumători - ca director, responsabil și membru în echipe de granturi câștigate prin competiții internaționale și naționale.

Lucrarea ilustrează interesul continuu pentru dezvoltarea stadiului actual al cunoașterii în domeniul pneumologiei, avându-se în vedere totodată evoluția academică în acord cu cerințele curriculare și cu standardele învățământului superior medical, la nivelul Uniunii Europene. In ultimele decenii, Organizația Mondială a Sănătății a demonstrat creșterea ponderii și gravității maladii respiratorii la nivel global, pe fondul creșterii numărului și agresivității agenților infecțiosi specifici, al poluării și al expunerii la tutun și la alte substanțe toxice la nivel respirator. Între acestea, cu precădere bronhopneumopatia obstructivă cronică (BPOC) și cancerul bronho-pulmonar, ambele cauze de fumat, înregistrează o creștere alarmantă, care se aliază trendului ascendent de consum al produselor din tutun.

Teza de abilitare este structurată în trei secții principale, respectând criteriile recomandate și aprobate de CNATDCU.

SECTIUNEA I, intitulată Contribuții științifice, profesionale și academice, conține în esență în Capitolul Activitatea științifică, o sinteză a arilor de cercetare dezvoltate după susținerea tezei de doctorat, structurată în două mari capitole, dedicate fiecare unei direcții de cercetare prioritare pentru portofoliul meu profesional. Sunt prezentate aceste realizări, sistematizat, pe direcții tematice și documentate prin exemplificări și trimiteri la cele mai relevante contribuții personale în domeniul, precedent de o scurtă trecere în revistă a datelor

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cunoscute din literatură sau de o justificare a interesului meu pentru respectiva direcție de studiu.

**Capitolul 1. Contribuții la cercetarea în domeniul impactului consumului de tutun la nivelul aparatului respirator** abordează în deschidere premizele dezvoltării conceptelor de abordare a unei sănătăți respiratorii fără consum de tutun, pornind de la expertiza acumulată în domeniul de doctorat și în perioada imediat următoare. În continuare sunt evidențiate aspecte referitoare la necesitatea mențiunii în atenție a riscului de boli respiratorii în contextul de risc global actual, și direcții de cercetare pentru a îmbunătăți și maximiza starea de sănătate respiratorie la pacienții consumatori de tutun. Următorul subcapitol independent subliniază rolul integrării asistenței medicale respiratorii în strategii comunitare de menținere a calității aerului în viața de zi cu zi. Calitatea vieții pacienților cu boli respiratorii cronice, îndeosebi cei cu BPOC și cu tuberculoză pulmonară este abordată în succesiunea acestui capitol prin introducerea instrumentelor de lucru specifice și justificarea oferită de literatura disponibilă, exemplificând prin contribuția personală relevată de un articol publicat în aprilie 2017 într-o revistă indexată în ISI Web of Science, articol dedicat corelațiilor între consumul de tutun, severitatea bolii și calitatea vieții la pacienții cu BPOC care prezintă depresie, anxietate și atac de panică. Capitolul se derulează în continuare cu o secțiune referitoare la modalități de diseminare a expertizei în domeniul prevenirii și tratării consumului de tutun în rândul profesionistilor din sănătate, urmată de partea cea mai consistentă a capitolului care tratează pe de o parte biomarkerii expunerii la tutun, catalogații în teste de uz clinic curent și teste de validare utilizate mai mult în cercetarea științifică, iar pe de altă parte prezintă modificările patologice descrise la nivelul aparatului respirator ca urmare a fumatului activ și pasiv. Acest capitol se începe cu bazele definiției științifice medicale, bazate pe ghiduri de specialitate, ale consumului și dependenței de tutun, ca boala cronicolă recidivantă ce necesită un algoritm de abordare diagnostică și terapeutică similar cu cel din alte condiții cronice precum hipertensiunea arterială sau hipercolesterolemia.

**Capitolul 2. Contribuții de cercetare în dezvoltarea unor strategii de sănătate pentru prevenirea și tratarea consumului și dependenței de tutun** aduce în prim plan contribuția personală la dezvoltarea de programe personalizate de tratament pentru fumători cu risc crescut, la nivel național și European. Capitolul este construit dintr-o succesiune de șase subcapitole. Dintre acestea, primele patru se referă la: experiența demonstrată de programele pilot de renunțare la fumat, designul și implementarea de programe de sănătate de renunțare la fumat având la bază expertiza acumulată în programele pilot, dezvoltarea de ghiduri pentru renunțare la fumat și respectiv de resurse de specialitate în domeniul renunțării la fumat. Ultimele două capitole sunt dedicate contribuției personale la nivel European în dezvoltarea unor programe personalizate de tratament pentru fumătorii cu risc crescut (fumătorii cu diabet, boli cardio-vasculare, BPOC, gravidie, adolescenții) și respectiv în dezvoltarea unor mijloace specifice de evaluare a impactului consumului de tutun la nivel populațional, bazat pe chestionare și anchete epidemiologice în mai multe țări europene. Ambele aceste ultime două subcapitole prezintă rezultate personale relevante obținute în cadrul unui grant European de tip Programul de Sănătate 3 EU al apelului H2020 (Proiect TOB G: dezvoltarea de ghiduri de renunțare la fumat pentru pacienți fumători cu risc) și respectiv în grantul European EUREST PLUS- un grant de cercetare în cadrul programului H2020 dedicat dezvoltării
cercetării științifice pentru implementarea directivei Europene pentru produse din tutun în Europa).

SECTIUNEA II, intitulată *Perspective de dezvoltare a carierei*, prezintă planul de dezvoltare al viitoarei mele activități științifice și profesionale, centrat pe următoarele direcții de studiu: dezvoltarea de noi programe de renunțare la fumat pentru grupuri specifice de risc, cu precădere adolescenții și fumători cu afecțiuni respiratorii cronice, studiul aprofundat al biomarkerilor expunerii la tutun, explorarea particularităților dependenței de tutun la pacientul respirator cronic, studiul instrumentelor de evaluare a măsurilor de control al tutunului în societate în scopul optimizării strategiilor existente de abordare a sănătății respiratorii.

Planurile de dezvoltare academică includ elaborarea unor materiale didactice pentru studenți, implicarea studenților și doctoranzilor în activități de cercetare și promovare a sănătății respiratorii, realizarea de cursuri post-universitare pentru medici care doresc sa se specializeze în terapia consumului de tutun, precum și de activități de cooperare națională și internațională cu implicarea tinerilor medici și doctoranzi.

SECTIUNEA III, intitulată *Referințe Bibliografice*, include bibliografia care susține datele prezentate în Teza de abilitare.
SECTION I - SCIENTIFIC, PROFESSIONAL AND ACADEMIC ACHIEVEMENTS

Professional activity

A. Education, degrees and diplomas

I graduated in 1986 “Gr. T.Popă” University of Medicine and Pharmacy Iasi, Romania, Faculty of General Medicine and the title of my Graduation Dissertation was: “Pseudotumoral stroke”, representing my first contact with the research in the tobacco induced cardiovascular disease area.

After completion of the mandatory postgraduation three years probation period (“C.I.Parhon” Hospital, Iasi - 1986-1989) and a one year mandatory General Practitioner stage in the rural general practice Mircesti-Iasi (1990), following admission to the national foundation programme (oct. 1990) in the specialty of „pulmonology”, I started my formation as junior pulmonologist in the Clinic of Pulmonary Diseases of the “Gr. T. Popă” University of Medicine and Pharmacy Iasi, on January 1991. Thus, I had a great opportunity to be accepted in the teamwork of Dr. Pavel Cucu, in the bronchoscopy investigational department of the Clinic of Pulmonary Diseases Iasi, where my research education began, by preparing my Ph.D. with the thesis „Pulmonary Hypoplasia” in parallel with acquiring skills to investigate tracheo-bronchial morphology and pathology. For about the next six years, my activity focused on detection of various anatomic anomalies and abnormalities of the tracheo-bronchial tree and their relationship with known risk factors for the lung development and respiratory health.

In May - June 1994, I was recipient of the private grant „In memory of dr. Valeriu Stinghe”, offered annually under the patronage of the Romanian Society of Pulmonologists to a junior pulmonologist, for a six weeks training in advances in pulmonology, in the Respiratory Diseases department of the „Centre Hospitalier Universitaire de Geneve”, Switzerland – under supervision of Prof. Dr. Thierry Rochat - Head. (Certificat 30.05 - 01.07.1994 - Dr. Thierry Rochat – division de Pneumologie, Hopital Cantonal de Geneve). In the same period, I attended a training in Thoracic Computed Tomography at Clinique de la Colline – Institut de Radiologie” from Geneve, with Dr. Dan Mirescu – Head (Certificat 01.07.1994, dr. D. Mirescu). As such, I had the chance to attend several research teams meetings, as young trainee and to study imagistics and biological samples of airways secretions delivered from patients with mucoviscidosis, secondary bronchiectasies, primary and secondary lung cancer, orphan lung diseases and pulmonary fibrosis, in the Geneve pulmonology department run by Prof. Dr. Thierry Rochat and in the private unit” Clinique de la Colline” from Geneve, with Dr. Dan Mirescu.

I obtained my Ph.D title in 1997 at the “Gr. T. Popa” University of Medicine and Pharmacy Iasi, Romania, the title of dissertation being “Pulmonary Hypoplasia” (coordinator Prof. Dr. Victor Tacu – Internal Medicine Department) as my first coordinator, Professor Dr. C. Ionescu has passed away in 1996.
To further sustain my skills in the field of bronchoscopic examination techniques, I obtained the competence certificate in *Bronchology*, by national contest-examination, in 1997, at the National „Marius Nasta” Institute of Pulmonology, in Bucharest, *Competence in Bronchology techniques* (Certificate.series 000616/18.06.1997), provided by Health Ministry - Continuous Education and Training Institute for Postgraduates doctors and Pharmacists.

In 2006, I received training in the field of “Treatment of tobacco use and dependence” (Certificate series E, Nr. 07505/14.12.2004) and “Cognitive-behavioral techniques for treating tobacco use and dependence” (Certificate series E, Nr.07816/27.01.2005), provided by Health Ministry - National Center for Post-university studies training development for Health Professionals - Bucharest. These two certificates were equivalent for specialized competence in smoking cessation, at the time.

*I participated to several courses for professional improvement, such as:*

- “Central and Eastern European Tobacco Control Institute” (7-12 May 2000, Warsaw, Poland)
- “Effective Advocacy and Movement Building for Tobacco Control” (23-25 April 2003, Bucharest, Romania)
- “Framework Convention Alliance (FCA) awareness Raising and Capacity Building Workshop on Tobacco Control and the WHO Framework Convention on Tobacco Control” (20-23 May 2004, Sinaia, Romania)
- Postgraduate Course: “How to conduct a scientific survey of respiratory health” (at the 14th Congress of the European Respiratory Society, 4-8 Sept 2004, Glasgow, UK)
- Postgraduate Course: “Application of genomics and proteomics to pulmonary disease” (at the 14th Congress of the European Respiratory Society, 4-8 Sept 2004, Glasgow, UK)
- Postgraduate Course: “Writing and presenting scientific work at meetings: an interactive, hands-on course” (at the 17th Congress of the European Respiratory Society, Sept 15-th 2007, Stockholm, Sweden)
- Postgraduate Course: “Lung function measurement in the community” (at the 17th Congress of the European Respiratory Society, Sept 15-2007, Stockholm, Sweden)
- EBUS (Endobronchial Ultrasound Diagnostic Procedure) Training Course, January 25-26th 2008, Copenhagen, Denmark
- “Advanced Good Clinical Practice for Clinical Research Professionals”, 03 Dec 2009, Bucharest
- “Actualities in pulmonary rehabilitation and non-invasive ventilation at home”, 20-22 May 2010, Iasi
- “Sleep Medicine” – Program for Eastern Europe”, 20-22 May 2010, Iasi
- European Respiratory Society School Course on “Smoking cessation” (10-12 Dec 2004, Bucharest, Romania)
- Spring school regarding smoking prevention among young people organized by European Network for Young People and Tobacco (14-18 March 2005, Helsinki, Finland)
B. Professional experience

Between 1991-1994, I made my internship at Clinical Hospital of Pulmonary Diseases from Iasi and I continued to work as junior, then senior pulmonologist in the Pulmonology I Dept. of this Hospital, in charge with in-patients with respiratory diseases, bronchoscopy exams and smoking cessation specialized care.

Since 1995, I work at the Discipline of Pulmonology – part of the Internal Medicine Dept. from the “Gr. T. Popa” University of Medicine and Pharmacy Iasi.

I acted as member of several professional associations, and served as member in their executive or working various committees, such as:
- 1992-2013- presently, member and collaborator of the European Respiratory Society (ERS) (www.ersnet.org), serving as:
  a) Member of the “Tobacco Control Committee” (2006-2009)
  b) Secretary of Group 06.03 for “Tobacco, Smoking Control & Health Education”, within Assembly 06 of the ERS (2009-2012)
  c) Member of the Standing Evaluation Committee for the review of fellowship and professorship applications and of the College of Experts of the European Respiratory Society (ERS), in charge with evaluation of applications for long term ERS fellowships, short term ERS fellowships and research fellowship, in the field of Chronic obstructive pulmonary disease (COPD) since 2011 – ongoing.
- 2008, Fellow of the American College of Chest Physicians
- Since 2001, I am a member of the Non Governmental Association “Aer Pur Romania”, involved in numerous projects and programs dedicated to tobacco control and health promotion.
- 2008- presently, I am an associated member of the European Network for Smoking Prevention (www.ensp.org)
- Since 1991-presently, I am a member of the Romanian Society of Pulmonology (SRP, www.srp.ro), serving as:
  a) Vice-president of the Bronchology section of the Romanian Society of Pulmonology (2005-2009)
  b) President of the Tobaccology Section of the Romanian Society of Pulmonology (2007-2011)
  c) Member in the Steering Committee of the Romanian Society of Pulmonology (2010-2014)
  d) Member in the Steering Committee of the of the Tobaccology Section of the Romanian Society of Pulmonology (2011-ongoing)

Besides my current medical activity in the Clinic of Pulmonary Diseases Iasi, my professional activity included development, implementation and evaluation of educational activities and treatment programs for a healthy lifestyle promotion, specifically addressing tobacco use and dependence, such as the following:
Involvement in the development and implementation of several projects of smoking prevention among adolescents, including the implementation in 2005 of the first peer led smoking cessation program for adolescents from Romania. Based on the results, the Romanian Ministry of Health decided to fund the dissemination of the program at national level in 2007/2009.

- In 2005 I was the Romanian coordinator of a smoking cessation program for teenagers called Adolescents Smoking Cessation funded by the European Commission through its program’s Public Health. This program was implemented in 15 European countries, firstly coordinated by the welsh Government in 2004.

- I developed and coordinated ever since 2000 the smoking cessation center in the Clinic of Pulmonary Diseases Iasi, acting as local responsible in the national “Stop Smoking” Health Ministry smoking cessation program from 2006-2010.


My professional horizon has extended with clinical research activities since 2000. I acted as Principal Investigator in 30 international, multicentre, pharmaceutical industry phase II and phase III clinical trials for patients with asthma, COPD and for healthy smokers. In this respect, I have established a private clinical research small microenterprise, S.C. ANLET MED S.R.L. (J 22-2328-2007), running clinical research activities, medical and research consultancy, and managing educational and research international projects.

Thus, over the last decade, I developed my experience in conducting clinical and scientific research activities, including as project manager of an international grant “Tobacco Cessation Guidelines for High Risk Groups - TOB G”, awarded by the European Commission in 2015.

Academic activity

My teaching career has started in 1995, as Junior Teaching Assistant, position held by competitive examination, at ”Gr. T. Popa” University of Medicine and Pharmacy, Iași, Faculty of Medicine, Pulmonology/Internal Medicine Department, and gradually advanced to the Lecturer position (1999) and than to the Associated Professor position, that I hold since 2002.

My academic activity includes:

1. Tutorials, courses, seminars, clinical demonstrations and practical lessons of Pulmonology for the II\textsuperscript{nd} year students of the Faculty of Dental Medicine (in Romanian, English and French sections), for the V-th year students of the Faculty of General Medicine (between 1995-2002 and occasionally thereafter) and for the Nursing College School ( based in Botosani - under the umbrella of the ”Gr. T. Popa” University of Medicine and Pharmacy Iasi, between 1999-2003). Along with a personalized syllabus of the pulmonology course (adapted since 2001) and of practical workshops, aimed at specific needs of the students in Dental Medicine Faculty, I also developed two optional courses targeting the same audience, in 2007-
2. **Improving foreign languages skills** for teaching at the English and French students series – by graduation of the TOEFL exam (Bucharest, March 1992) and Certificates of Attainment for English language-level B2 (no.310/05.06.2013, ˝Al. I. Cuza˝ University of Iasi) and for French language, level C1 (no 298/05.06.2013, ˝Al. I. Cuza˝ University of Iasi).

3. **Coordination of graduation thesis for students**

I have coordinated 8 research activities for graduation theses of students from the “Gr. T. Popa” University of Medicine and Pharmacy Iasi, Romania, some examples being pulmonary hypoplasia, tobacco induced pulmonary diseases, tuberculosis relapse risk factors, pulmonary hil lymph nodes enlargements, evaluation of tobacco exposure risk for periodontal disease and benefits of smoking cessation counseling in patients with oral cancer.

4. **Post-graduate courses for physicians**

The regular teaching activity for undergraduates has been completed, starting with 2002, as Associated Professor by lectures and courses with residents in the Pneumology specialty mainly, but also with residents in other specialties that are attending Pneumology modules during their specialist trainings (internal medicine, pediatry, geriarty, alergology, work medicine, etc.).

In the same time, since 2000, I developed new teaching domains in my activity, such as the postgraduate “Smoking Cessation” course in the “Gr. T. Popa” University of Medicine and Pharmacy Iasi, addressed to medical school postgraduates involved in assisting smokers patients. Also, I have implemented new teaching modules for specific smoking cessation activities in the „Stop Smoking” Health Ministry centers, newly acquired in Iasi, Romania, to address doctors, nurses and other health professionals who assist smoking patients; these training courses, workshops and lectures were provided in various types of CME activities, under the umbrella of governmental bodies and national health professional societies, at both national and international level.

Within this new field, lectures were focused on providing clear and accurate information about tobacco use and dependence, defined as a chronic relapsing disease, on clinical and biological assessment of active and passive exposure to tobacco, on highlighting noxious consequences of tobacco consumption for human health, in particular for respiratory health, and on identifying best practices for quitting smoking. Workshops provided skills to offer an individualized treatment plan, using evidence-based treatment strategies, for all categories of smoking patients. The main purpose of acquiring theoretical and practical knowledge in this new area is to substantiate the concepts related to chronic and avoidable disease risk of chemical compounds in all tobacco products and to reveal the chronic relapsing nature of the tobacco dependence disease, on a strong evidence based background. Thus, by optimal demonstration of the relationship between chemical composition and exposure characteristics on one side and biological impact of the tobacco smoke, on the other side, a better and more clear view upon the applicability of the clinco-biological knowledge
within the management of the systemic and oral health status is enabled for individuals who are tobacco consumers.

5. Training and capacity building for students and health professionals


b. Invited speaker for the Workshop Cessation/Reimbursement (worksite) organized during the Conference Tobacco or Health (Mumbai, India, 08-12 March 2009); title of presentation: “Benefits and concerns of national smoking cessation programs – does reimbursement increase smoking cessation rates?” http://www.indianjcancer.com/article.asp?issn=0019-509X;year=2010;volume=47;issue=5;spage=109;epage=210;aulast

c. Invited speaker for European Commission TAIEX conference: “Fighting against Tobacco in Western Balkans and Turkey”, 29 Nov-01 Dec 2010, Bruxelles, Belgium, with the lecture:” Development at national level of smoking cessation and treatment strategies”, http://ec.europa.eu/enlargement/taix

d. Invited speaker for European Network for Smoking Prevention (ENSP)’s event at the European Parliament: “Working together to put an end to the tobacco epidemic”-Launching the European Smoking Cessation Guidelines, 03 Oct 2012, Bruxelles, Belgium, with the presentation:”European Smoking Cessation Guidelines – Short overview of Part II Treatment of Tobacco Dependence”, www.ensp.org

e. Invited speaker for the Scientific Meeting of European Network for Smoking and Tobacco Prevention (Bucharest, 21-23 May, 2014); title of presentation: “Smoking Cessation in Romania”, www.ensp.org

6. Books and books chapters

A consistent concern is represented by the continuous preoccupation for improving the curriculum content and teaching materials. During all these years, I have worked in editing 26 books and chapters (three of them as invited author for internationally printed publications). Some of these works are summarizing the results of the research activity, useful for dental and general medicine practitioners’ work and education, while others are useful for license exam and examinations for the title of specialist doctor in the field of pulmonology and tobaccology, or for specialists in the treatment of tobacco dependence. I am the single author of two books (a monograph and a course), co-author of 6 books (4-national, 2-international), author of 8 book chapters, co-author of 3 book chapters, and coordinator of 3 updated editions of the Romanian smoking cessation guideline.
7. Editorial board and peer-review activities for scientific journals:
- Editor for Tabaccologia, www.tabaccologia.it

Scientific activity - Introductive remarks

This chapter is introduced by some remarks about premises that have paved the way of my scientific career and by a short presentation of its content’s structure with overview of the most relevant research development and scientific results.

Premises of my scientific activity

After obtaining my Ph.D., in December 1997, in the coming three years, I have consolidated my research in the field of pulmonary abnormalities by a more in depth research materialized in few studies published in local, national and international journals (approaching bronchological investigation of pulmonary hypoplasia-1998, prevalence and clinical picture of lobar pulmonary hypoplasia (2000), ethiopathogenic aspects of pulmonary hypoplasia and difficulties in diagnosis of partial pulmonary hypoplasia - 2001). These thorough preoccupations were brought together in the monograph „Pulmonary Hypoplasia”, published in 2000, dedicated exclusively to the subject and gathering all my clinical experience about this condition during doctoral and postdoctoral research and a literature review up to date.

Meanwhile, and moreover in connection with my academic career began in 1995, as junior assistant, my research trajectory was restarted, under the supervision of Prof. Dr. Tr. Mihaescu, Head of the Pulmonary Diseases Clinic, and of Dr. Pavel Cucu, a well recognized expert in the field of broncho-pulmonary development and endoscopic laboratory investigations. My teaching activity based initially mostly on seminars, workshops and lectures at the Faculty of General Medicine, began to diversify, by my promotion at the position of lecturer, in 1999, at the Faculty of Dental Medicine, in the same University of Medicine and Pharmacy „Gr. T. Popa” Iasi. This step constituted a new and exciting challenge for choosing some new directions and for further developing unexplored subdomains of work, considering the specific needs of the students in Dentistry, the interrelation between oral and respiratory health and my newly arisen interest for the impact of tobacco smoking on respiratory health.

In 1999, I was recipient of a multicentric clinical research grant, provided by the Romanian Society of Pulmonologists in partnership with the pharmaceutical company Glaxo Smith Kline, to study efficacy and safety of bupropion hydrochloride, as a smoking cessation medication administered to healthy volunteers recruited among doctors and nurses in the
Clinic of Pulmonary Diseases Iasi. By this occasion, I was invested to implement and coordinate at regional level, a center for smokers willing to stop using tobacco. This action was part of a national plan, to set at the beginning 8 such centers in Romania (in Bucharest, Cluj, Tg. Mures, Timisoara and Iasi), as a feasibility stage towards a future plan to develop national smoking cessation services. Here, I performed clinical and scientific research activities to identify best practices to assist all categories of smokers, to clinically and biologically assess smoking abstinence, and introduced in routine daily practice the technique of determining carbon monoxide (CO) in exhaled air, as a biomarker of tobacco exposure. The main outcomes in this field, from 1999 to 2017 are summarized in my CV and publications list.

In the same time, in 2001, I became recipient of the clinical research grant, within the TORCH (Towards a Revolution in COPD Health) study, a multicentre, randomized, double-blind, parallel group, placebo-controlled clinical study, to evaluate long term (3 years) survival in patients with moderate-severe forms of COPD.

These two moments represented my basic contact with the scientific and clinical research domain and in the same time, with the new domain of approaching tobacco use and dependence as a disease and assisting smokers to quit.

Eversince, all my ongoing scientific and research activity has continued, by developing and by linking these two main driving objectives: improving management of chronic respiratory diseases and developing tools to assist smokers with respiratory diseases, with focus on prevention and treatment of tobacco exposure related respiratory diseases, thus emmerging into the concept of finding best approaches to preserve respiratory health.

**Short presentation of the structure of chapter**

This chapter presents the areas of research after the graduation of the PhD and it is structured in two parts:

- **Chapter 1** describing my early career developments on research in the field of effects of tobacco exposure at the respiratory system level

- **Chapter 2** showing my research contributions for development of treatment and prevention health strategies to adress tobacco use and dependence disease.
CHAPTER 1. RESEARCH CONTRIBUTIONS IN THE FIELD OF TOBACCO USE IMPACT ON THE RESPIRATORY SYSTEM

1.1. Lung development expertise: premises for a healthy, „smoke-free” approach

A. Background

During my Ph.D research about „Pulmonary Hypoplasia”, I have gained expertise in the field of lung development interfering factors and in particular in diagnosis and management of abnormalities of lung development, among which hypoplastic lung or lobes are the most frequent.

In the next period after obtaining my Ph.D, consistent with this achievement, I remained in the same area of study and consolidated my expertise by working in the endoscopy department of the Clinic of Pulmonary Diseases Iasi to improve my skills in bronchoscopy and bronchography, the two techniques used at the time for diagnosis of trachea-bronchi-pulmonary disorders. It was in that time when I had the opportunity to observe and to study the difference between the apparent normal aspects and the morphological modifications described in various tracheo-broncho-pulmonary disorders in smokers versus non smokers or former smokers. This gave me the idea of finding modalities to assist smokers with respiratory diseases for quitting smoking and to promote a healthy „smoke-free” life style in the respiratory disease service where I worked.

B. Personal contributions

**Scientific, professional and academic achievements in this field**

**Professional training in this field:**

- Competence in Bronchology techniques (Certificate series 000616/18.06.1997), provided by Health Ministry – Continuous Education and Training Institute for Postgraduates doctors and Pharmacists.

**Publications in this field:**

*After graduation of my PhD I continued my work in the field of bronchopulmonary abnormalities by publishing a monograph, a book chapter and three related articles.*

1. **Books and books chapters**
In relation with my continuous work in the department of tracheo-bronchial endoscopic investigations, I kept my interest for the whole spectrum of chronic broncho-pulmonary disorders that can negatively impact respiratory health, regardless of patients’ smoking behaviour, in a hollistic view about this concept and in direct connection with real life respiratory burden in my current practice.

Previous accumulations have conducted to the elaboration of two articles, one article about difficult to manage TB cases, and the other one as an evaluation article about the long term effect of inhaled gentamicin in particular forms of bronchiectasis. These 2 articles were published in journals indexed in ISI Web of Science and summary of the most important data are presented here, in the followings:

**Tuberculous constrictive pericarditis complicated with tuberculous mediastinitis – case report**

Milena Adina Man, Mimi Floarea Nitu, Lelia Strambu, Cristina Florescu, Costin Teodor Streba, Antigona-Carmen Trofor,


**Abstract**

Constrictive pericarditis is a rare and severe disease. A 37-year-old patient was admitted in the hospital for dyspnea, precordial pain, right sided cardiac failure. Chest X-ray showed cardiac enlargement and an opacity suggestive for pleural effusion. Echocardiography revealed an adhesive–effusive–constrictive pericarditis, a very thickened pericardium and bilateral pleural effusion. After a pericardectomy done to restore cardiac compensation and to identify etiological factors, a tuberculous pericarditis (TBP) was diagnosed. After surgery and starting anti-TB treatment, the patient presented altered clinical status, dyspnea, dry cough, fever and delayed callus formation at sternum level. Thoracic scan revealed mediastinal air collections, pericarditis and pleurisy. Thus, the TBP diagnosis was extended to mediastinal
TB and anti-TB therapy was continued. After four months of treatment, another thoracic scan showed disappearance of the mediastinal air-leakage bubbles, multiple new micro-nodules in both lungs and lymph nodes of up to 15 mm; also increasing pericardial and pleural effusions. This case was interpreted as a TB treatment failure situation. A retreatment regimen was started, resulting in a slow favorable outcome. Pericardial TB is a rare condition, usually with delayed diagnosis and poor treatment benefits. Whenever possible, precocious diagnostic can contribute to better management of these cases.

**Inhaled gentamicin in non-cystic fibrosis bronchiectasis: effects of long-term therapy**


Sabina A Antoniu, Antigona C. Trofor


**Expert opinion**

In bronchiectasis of various etiologies, the chronic airways colonization with various bacteria is favored by the impaired local defense mechanisms. Among the bacterial strains most commonly detected were *S. aureus*, *H. influenzae* or *P. aeruginosa*. This chronic colonization increases the risk of recurrent infections and represents a major therapeutic challenge especially in the case of *P. aeruginosa* which is among the few bacterial strains the most difficult to eradicate.

Currently available options of antibiotic therapy include systemic or inhaled compounds. The former category is still the most widely used and includes various antibiotic classes among which commonly used are the aminoglycosides due to their broader antibacterial spectrum and to its strong bactericidal effects on *P. aeruginosa*. However eradication of *P. aeruginosa* at bronchial level requires high doses and longer courses of aminoglycoside antibiotics and the beneficial effect of bacterial clearance could be associated with occurrence of side effects such as renal toxicity. Furthermore, the structural abnormalities in the bronchial wall represent a barrier against antibiotic penetrability at bronchial level and therefore lower concentrations of drug are available despite high systemic dosage.

These inconvenient can be solved with topical administration of aminoglycosides, and tobramycin for dry powder inhalation is already authorized to treat *P. aeruginosa* in patients with cystic fibrosis. The main advantage of using inhaled aminoglycosides is the high concentrations which can be achieved at bronchial level with minimal systemic exposure and with minimal risk of side effects especially if chronic administration is contemplated.

However, administration of inhaled gentamicin is sometimes associated with development of bronchospasm which might be due to the active substance or to the excipients. This can be rapidly relieved with inhaled b2 agonist bronchodilators but other preventive methods might be also required. The eradicating effect of inhaled gentamicin
against *P. aeruginosa* might be modest, but reduction of bacterial load at bronchial level might also result in the reduction of number of exacerbations. Based on increased bactericidal efficacy of the inhaled formulation of gentamicin, it can be concluded that it can be used on long-term basis to prevent exacerbations in patients with bronchiectasis and chronic bacterial colonization.

*Also, in the same research directions, I have contributed to an article about solitary pulmonary nodule – developing a malignancy probability calculation model and to another article on comparative study of the late lung cancer stages. These 2 papers were published in proceedings of international conferences indexed in ISI Web of Science and summary of their results are described below:*

<table>
<thead>
<tr>
<th>Solitary Pulmonary Nodule – Developing A Malignancy Probability Calculation Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dana Alexandescu, Milena Man, Antigona Trofor, Bogdan Ratiu Duma</strong></td>
</tr>
<tr>
<td><em>Recent Advances in Clinical Medicine – Proceedings of the International Conference on ONCOLOGY</em></td>
</tr>
<tr>
<td>(ONCOLOGY ’10) University of Cambridge UK, 23-25.02 2010, page 213-219</td>
</tr>
</tbody>
</table>

**Summary of relevant results**

*Problem formulation: The purpose* of this study is to create a calculation model of SPN malignancy probability by using some CT morphologic criteria associated to clinical or biological conditions. SPN Bucharest batch; *Available population:* patients with respiratory symptoms, but most smaller or equal to 3 cm solitary pulmonary nodules at plain chest radiography. The patients were admitted to Thoracic Surgery Ward, Marius Nasta Pneumology National Institute between January 2001 and September 2006, to establish the ethiology of the identified lesion through surgical resection.

All patients were diagnosed and the stage of the disease established through anamnisis, prior and current medical history, lifestyle, personal habits, phisycal examination, complete blood tests (CBC, ESR, CRP), spontaneously produced sputum (citopathology report), chest radiography (PA, lateral), bronchoscopy with bronchial material drawing samples (bronchial aspiration, bronchoalveolar microlavage, bronchial mucosa biopsy), CT of lungs, mediastinum, brain pan, abdomen (with contrast).

All patients’ data were colected and inserted into a table containing clinical data, smoking status, personal history of tuberculosis and neoplasia, the presence of Koch’s bacillus in sputum, histopathologic exam, and citology adding to those a few CT image description criteria of the solitary pulmonary nodule. These image descriptive criteria led to presumtuous CT diagnosis and that was compared to the histopathologic diagnosis.

*Problem solution:* SPN Bucharest batch with 87 patients was divided into two groups depending on malignancy profile: first group – 29 patients (33.33 %) as having malignant SPN and a second group – 58 patients (66.66 %), as having benign SPN. Statistic analysis used *t* test method made for observing the parameter’s average value variation which were
chosen depending on malignancy profile. There were significant statistic differences between average values of the following parameters: age and the number of year-pack of smoked cigarettes. In our study one may observe that malignant SPN has a significant statistic higher diagnosis average age and development age towards benign SPN [59.97 years towards 44.28 years, \( p= 0.000 \)]. This suggests that a 50 years aged patient SPN diagnosed has a higher probability of being malignant while a 40 years aged patient SPN diagnosed has a higher probability of being benign. Pack-year (no. of daily smoked cigarettes multiplied by no. of smoking years) parameter has a significant higher average value among malignant SPN patients than benign SPN patients (20.52 towards 6, \( p=0.001 \)). We also calculated a modified Swensen model by replacing smoking status with pack-year:

**Table 1.** Modified Swensen model and its parameters (Variable Malignancy odds ratio 95% CI) (Alexandrescu et al, 2010)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Malignancy odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.1113</td>
<td>1.0177 to 1.2136</td>
</tr>
<tr>
<td>Pack‐year</td>
<td>1.0114</td>
<td>0.9694 to 1.0551</td>
</tr>
<tr>
<td>Neoplasia history</td>
<td>5.3015</td>
<td>0.7487 to 37.5417</td>
</tr>
<tr>
<td>Nodule's size</td>
<td>1.5857</td>
<td>0.4697 to 5.3537</td>
</tr>
<tr>
<td>Spiculi presence</td>
<td>54.9376</td>
<td>8.7917 to 343.2931</td>
</tr>
<tr>
<td>Superior lobe site</td>
<td>0.6200</td>
<td>0.1248 to 3.0808</td>
</tr>
</tbody>
</table>

**Conclusions**

1. The appearance of a SPN around 50 years of age pleads for malignancy, especially to the great smokers, while a SPN diagnosis under 40 years of age pleads for a benign appearance.

2. SPN Bucharest statistical model containing the following parameters: age, smoking status, personal malignancy history, nodule's size, spiculi presence and the superior lobe site, offers a good division of the cases into benign and malign superior to Swensen model.

3. Creating and also continuous improvement of a statistical model for calculation of the benign or malign feature of a case, particularly SPN is not only important for establishing the type of its feature but also for the course of action following initial diagnosis as well as a screening procedure for the type of SPN, a non invasive screening procedure which is well tolerated by the patient in its initial approach.
Lung cancer-late stage at diagnosis in two comparative groups

Milena Adina Man, Dana Alexandrescu, Antigona Trofor, Monica Pop


Abstract

Bronchi-pulmonary cancer represents the main cause of death through neoplasia in numerous industrialized countries. We conducted a survey from January 1999 to December 2005 on 116 patients admitted in Cluj Napoca Pneumology Clinical Hospital and we compared with a second group admitted in the Baia Mare Hospital (153 cases). We introduced in the study patients diagnosed with lung cancer and analyzed age, gender, environment of provenance, smoking status, exposure to professional noxious, the average time span from the inception of the clinical symptoms until diagnosis, confirmation of the neoplasia, diagnosis of hepatitis metastases. The survival rate of lung cancer patients depends on the moment of diagnoses. Statistical data and the analysis of the two groups included in the study, reveal that most patients went to the doctor in late stages and the surgical moment was excelled and for this reason we recommend an increase in the family physicians’ attention with regard to patients who smoke and come in for consults even with minimal respiratory symptoms and to direct them as quickly as possible to a pulmonary disease department.

1.2. Raising awareness for the respiratory diseases burden

A. State of the art

For the past three decades, it has been well recognized that respiratory disease burden has increased globally, becoming a leading cause of death worldwide. All together, lung infections (in majority pneumonia and tuberculosis), lung cancer and chronic obstructive pulmonary disease (COPD) accounted for 9.5 million deaths worldwide during 2008, which represented one-sixth of the total, globally. The World Health Organization (WHO) estimates that the same four diseases accounted for one-tenth of the disability adjusted life-years (DALYs) lost worldwide in 2008 (Gibson et al, 2013).

At both individual and collective level, everyone is at some degree of risk, being exposed to either air transmitted infections or inhalation of various air pollutants. In general terms, anything that is inhaled into the lungs can put individuals at risk, whether it is an air pollutant, tobacco smoke, marijuana, solvent fumes, or other inhaled drug or substance (Canadian Lung Association, 2010).

For infectious respiratory diseases, standardized treatment and infectiousness control measures represent the only recommended approach.
For non-infectious respiratory diseases, the two most understood, preventable or modifiable risk factors are active and passive tobacco smoke and air quality (both indoor and outdoor). Tobacco use prevention and cessation treatment is the most efficient tool to avoid tobacco related diseases such as chronic obstructive pulmonary disease (COPD) and respiratory cancers. Occupational exposure represents also a major area of interest, permanently changing nowadays, due to continuous industry developments, where exposure to irritating or toxic substances may cause a number of acute or chronic respiratory injuries, here included as well COPD and various respiratory epithelium derived cancers.

Actually, concerns about respiratory health should be prioritized, by acknowledging the most recent trends in the field. In the next two decades, the proportion of deaths caused by respiratory disease in Europe is likely to remain stable, with a decrease in deaths from lung infections balanced by a rise in lung cancer and COPD mortality (Gibson et al, 2013). According to the Global Burden of Disease (GBD) Study, that recently compared the contribution of major diseases to deaths and disability worldwide for 1990 and 2010, among the leading causes of death, lower respiratory infections were ranked 3rd in 1990 and 4th in 2010, whereas COPD was ranked 4th in 1990 and 3rd in 2010 and lung cancer rose from 8th - to 5th commonest cause of death, while tuberculosis fell from 6th to 10th position in the ranking (The Global Burden of Disease Study, 2010).

Not only morbidity data, but also analysis of deaths and in particular of respiratory deaths contribution to all deaths causes may add value to raising awareness for respiratory disease toll. So, in the WHO European Region, the four most commonly fatal lung diseases mentioned above accounted for one-tenth of all deaths and 7% of the DALYs lost in 2008, with taking into account that the proportion of all deaths due to lung diseases is influenced by the age of the population, and the age-specific death rates from respiratory and non respiratory causes (Gibson et al, 2013). Tobacco smoking appears as a common landmark here, not only especially as risk factor for lung cancer and COPD, but also as frequent causing agent of pneumonia and pulmonary vascular disease, often encountered as accompanying conditions.

European experts raise a warning” the burden of lung disease in Europe remains as large today as it was at the turn of the millennium, and is likely to remain so for several decades”. Moreover, they say: “More than half of all the deaths from lung disease in Europe, and at least one-quarter of all respiratory hospital admissions, are due to diseases caused by smoking (Gibson et al, 2013). This affirmation is of great impact to all health professionals involved in respiratory care of patients that are tobacco users and must impose adequate and permanent measures to reduce deaths due to tobacco exposure.

Even if, in the first decade of this century, statistics showed a decline in mortality rates from lung disease across the EU, overlapping the declining trend of smoking rate, there is still a great number of former smokers at risk that add an important contribution to present lung disease burden, due to higher rates of smoking in the past. Thus, being well known that smoking is a “long term killer”, equal attention should be paid also to former smokers, smoking relapses and reducers that keep the same risk as current smokers, for one-two decades after quitting. Respiratory diseases are therefore likely to remain a great health problem in European countries for the next 20-30 years.
B. Personal contributions

Scientific, professional and academic achievements in this field

After the graduation of my PhD thesis I was involved in clinical research programs regarding healthy smokers and then smokers with COPD, thereafter in developing the first smoking cessation center in the Clinic of Pulmonary Diseases Iasi.

It is how I have studied the noxious role of tobacco consumption on respiratory health and on already installed tobacco induced respiratory disorders and I concretized these observations by several works presented in international congresses, mainly for the European Respiratory Society international congress, published in abstract in supplements of the ISI Web of Science indexed European Respiratory Journal (ERJ) and one abstract published in abstract in the American Journal of Respiratory and Critical Care Medicine, also indexed in ISI Web of Science. Most relevant such studies are listed here below:


Since early 90’s, European Respiratory Society (ERS) has been a recognized leader in the field of scientific research and education across Europe and worldwide, by providing best tools and resources for education and training, not only for respiratory physicians, but also for allied health care professionals. By its prestigious bodies and members, the ERS took numerous initiatives aiming to reduce respiratory disease burden, among which fighting against tobacco smoking plays a very important role.

In 2004, Romania was hosting for the first time a Smoking Cessation training course, with participation of numerous European experts within ERS School faculty, by involving also Romanian speakers. I participated with two lectures: “Health disorders related to tobacco use and passive smoking”, Antigona Trofor, p. 35-61, “Poly-addictions” -part I, pg. 115-135 and “ABC of health disorders related to tobacco use and passive smoking”, Antigona Trofor, p. 311-323 (Course Educational Material (ERS School Interactive Course on “Smoking Cessation”- Bucharest, 10-12 Dec. 2004):(www.ersnet.org/schoolcourses). This event gave me the opportunity to start a long and fruitful collaboration with the European Respiratory Society, still ongoing ever since, as member of the “Tobacco Control Committee” of ERS: 2006-2008, Secretary of Group 6.3, Tobacco, Smoking Control and Health Education of ERS (2009-2013) and than on as reviewer for Long Term/ Short Term and Research Fellowships recipients of the same society.
In the same time, my interest in the field of raising awareness for health hazards of tobacco consumption has materialized in publication of the book *Smoking- from habit to disease: 101 questions about smoking* (Antigona Trofor, Cornel Radu-Loghin, Tehnopres Publishing House Iasi) in 2004. This book was revised and updated in a second edition published in 2005 and in recognition, it was awarded for publishing the 2nd edition in 2005 with support from the National Agency for Scientific Research (ANCS).

1.3. A comprehensive approach for improving and maximizing respiratory health in tobacco exposed patients

A. State of the art

To assist respiratory ill patients as best we can is our main destined professional goal, as respiratory physicians. To achieve this goal, except our knowledge and skills, one must also address environmental hazards that may influence respiratory health and do not neglect patients’ education about how to prevent and treat respiratory disease risks (The Lung Association - National Office Anual Report, 2011-2012). However, except voluntarily assumed risk factors like tobacco use or known toxicants, in many circumstances, respiratory health depends on unchangeable factors, such as air quality, pollution or high prevalence of transmissible disease in a certain geographic area, all those being difficult to influence by customary medical assistance (Wesche et al, 2011). Moreover, even in the case of voluntary exposure to tobacco or its toxicants, the patients might not have the will or the motivation to stop exposure and doctors may face the same difficulties to treating smoking related disease, as for the case of unavoidable hazards.

A first step in approaching respiratory conditions related to environmental agents is to identify all potential dangers and their consequences on respiratory health (The Lung Association - Air Quality, 2016).

For the case of tobacco exposed patients, it is crucial to develop especially designed health programs for all categories of respiratory patients who smoke, adapted to their family, age, gender and community special needs (Coleman, 2004). It is also recommended to investigate pattern of smoking (highly addictive or moderate smoker) and other individual variables like age, gender, occupation, co-dependencies, co-morbidities, etc, that determine vulnerability towards smoking behavior. For instance, adolescent age is associated with initiation of smoking most frequently, due to peer or adult mimetizing behaviors. Overview of the literature about smoking in adolescents showed a high prevalence of smoking among young people. According to CDC data in 2005, 23% of high school students report smoking in the last month, compared to 21.3% in 2003 and 36.4% in 1997. The prevalence of any form of tobacco use among 14-18 years old students in US was 28% (Giovino, 2007). In Romania, ESPAD study in 1999 showed 21% of Romanians over 15 to be daily smokers (Trofor et al, 2009) and 34.8% of young people 15-24 years old were found current smokers.

The type of tobacco product is another factor that may determine various negative health consequences of smoking, depending on its particularities. Doctors must be aware and up to date with all these available and new products in order to react promptly for the health
benefit of their patients. Cigarettes are the most dangerous and the most addictive ones, but specific health risks are described for the case of cigar or pipe consumers (ex.: increased risk of oral and superior digestive cancers), for smokeless tobacco users as well and for the newly recognized e-cigarette product. Electronic cigarettes (e-cigarettes) are devices that deliver to the lung aerosols usually containing nicotine and other compounds (Schraufnagel et al, 2014). They are promoted as an alternative to traditional tobacco cigarette smoking, but there are several concerns regarding their use: evidence about their safety and efficacy for smoking cessation remains limited, while they may increase the risk of non-smokers developing nicotine dependence and of current smokers maintaining their dependence (Schraufnagel et al, 2014; Carr, 2014; Durmowicz, 2014; Dautzenberg et al, 2013; Lotrean, 2015). Moreover, their novel nature and flavouring combined with an unrestricted marketing and sale in several countries may appeal to youth and e-cigarette experimentation might result in use of other tobacco products (Goniewicz et al, 2012; Kinnunen et al, 2015).

The type of tobacco product used gives also an idea about the level of addiction, since nicotine dependence is more severe in cigarette consumers, compared to those who use cigars, pipes, water pipes, e-cigarettes or oral tobacco (Behrakis, 2012).

Cigarette smoking or using other than cigarette tobacco products is often associated to coffee, tea, and alcohol use, or even with some illicit drug abuse, and this is an important aspect of the smokers’ behavioral profile that needs to be understood in order to have a comprehensive approach of the phenomena of smoking. It is well recognized that an addiction, in this case, the nicotine addiction can open the gate to add other addictive behaviors, thus leading to polyaddictions like tobacco (nicotine) + alcohol/coffee/tea. Very oftenly, heavy smokers ( > 20 cigarette packs-years) are also heavy drinkers or heavy coffee consumers (more than 7 cups of coffee/day). Regular smokers drink in 1.32 times more than no-smokers, while heavy smokers have a 2.7 fold higher chances to become alcoholics compared to average smokers (Trofor et al, 2001). Coffee addiction is due to caffeine, a xantine derivate, that can be found in an amount of 0.10-0.30 grams in a normal sized cup of coffee. Tea addiction is related to theine, an isomeric structure of caffeine, found in a percentage of 2% in the black tea and 5% in the green tea. Nicotine from tobacco, all together with caffeine structures from tea, coffee or cola, are the most used licit drugs, nowadays. Their interactions and potential common harmful health effects are determined by a characteristic dual dependence.

An overview of the major social and individual factors that define different patterns of smoking should have in view also some paradoxical situations, like the case of „moderate” or „low-rate” smokers. This is a special category of smokers, more and more frequent nowadays and they need careful consideration as their moderate smoking it is not mandatory reflecting their tobacco dependence or ease to quit. It seems some smokers still believe they are protected from harm if they smoke "just a few" cigarettes each day. But smoking less does not diminish tobacco induced health hazards! Moderate smokers are defined as those individuals smoking less than 10 cigarettes daily/10 packs-years (PY) and sometimes also having low-moderate nicotine dependence (Trofor et al, 2009; Schane et al, 2010). The U.S. Surgeon General has stated that there is no safe level of tobacco smoke or nicotine for the body, so, despite lower consumption and addiction levels, moderate smokers should be aware of the fact that they are still at risk for developing smoking-related disorders (Trofor et al,
On the other hand, even if one could expect easier quitting smoking when smoking fewer cigarettes, it has been observed that smoking cessation outcomes can be modest even though moderately smoking or if being an occasional smoker. One possible explanation is an unexpected severe nicotine dependence found in this category of „light” smokers (Pascal et al, 2015).

The profile of smokers with respiratory disorders is often polymorphic, by adding numerous systemic comorbidities, especially in chronic obstructive pulmonary disease (COPD) or by developing a certain pattern of evolution and therapeutic response, as in pulmonary infections-mainly in tuberculosis (TB), but also in lung cancer. All such conditions impose immediate medical advice to stop tobacco use and a personalized tool to treat tobacco dependence, in a different approach for TB, lung cancer or COPD smokers.

Up to 50% of chronic smokers develop COPD and 80% to 90% of COPD mortality is caused by tobacco smoking. Worldwide, COPD is currently the fifth most common cause of death, and this trend is ascendant. Cardiovascular co-morbidity is often encountered in smokers hospitalized for respiratory disorders, especially COPD (Tønnesen et al, 2007).

Since early ’50-s, there is no doubt about tobacco exposure role in producing lung cancer. This is due mainly to tobacco smoke, which consists of vapor (gas and semi volatile compounds) and particulate matter (0.1-1.0 Gm) (Peto et al, 2000). The thousands of toxicants in tobacco smoke, among which over 50 proved as carcinogenic - particularly nitrosamines and polycyclic aromatic hydrocarbons are responsible for various types of cancers and lung localization is one of the poorest prognosis to expect, especially in continuing smokers. Carcinogenesis is a long way process beginning with damage of bronchial epithelial cells and impairment of mucous movement induced by gaseous components. Knowing the fact that the smoke produced by a single cigarette contains 1-3 mg of carcinogens, clearly, there is no other immediate benefic gesture than quitting smoking, and no other harmful attitude than continuing smoking, regarding this scientifically proved cancer risk factor (Doll et al, 1994). As well, discontinuing smoking has proved beneficial, at any moment, no matter how late in disease course. This may avoid lung cancer development, but also has an important impact on lung cancer’s treatment outcomes, here included patient’s compliance or recovery to anesthesia, surgery, chemo and radiotherapy, upon case (Nelson, 2009).

One particular situation refers to the case of infectious respiratory disorders: when occurring in tobacco smokers, there is a different clinical and evolutive pattern, with delayed recovery and frequent relapsing episodes, due to the impaired anti-microbial defense mechanisms, induced by exposure to tobacco smoke that can decrease efficacy of the normal muco-ciliary clearance of the respiratory epitelium (Wright et al, 1988). Even if standardized community infection control measures are constantly applied, one cannot ignore the negative role of tobacco use on increasing vulnerability to respiratory infections. Still, by careful consideration for screening of tobacco use in all respiratory infections cases and in particular in those chronic, relapsing forms and especially in pulmonary tuberculosis, we can optimize respiratory health of this category of patients. Moreover, the highest benefit will be obtained by prompting treatment to stop smoking.
B. Personal contributions

Scientific, professional and academic achievements in this field

One main focus of my PhD thesis was evaluation of environmental factors associated with development of congenital abnormalities, in particular small volume lungs at birth. This research direction was continued after the PhD graduation by getting further insights into this subject. Among these environmental agents, from the very beginning, my main interest was channeled to tobacco use and dependence, as tobacco is acknowledged not only as risk factor in many respiratory conditions, but is also aggravating or delaying therapeutic response in most of them. Moreover, as, at the time, one of the highest European prevalence of smoking was encountered in the Romanian population (36.7% in 1997), this fact was another „pro” towards my above described preoccupation.

The main research areas that were considered of interest at that time were categorized in six directions of study and their results were disseminated through several publications as enumerated below:

I) The context of smoking in our society and the challenges to face for changing the paradigm. (2 articles published in Tabaccologia and in BMJ-rom ed.)


II) Assessment of the specific pattern of tobacco use and dependence in various categories of the general population (women, adolescents, etc.)

a) Smoking in women (3 articles published in Pneumologia and in Revista Medico-Chirurgicala)


b) smoking in adolescents


2. Antigona Trofor, Mihăescu T, Mardare D, Sava A. ANTISMOKE EDUCATIONAL PROGRAMME FOR ADOLESCENTS BY VIDEOPROJECTION IN


SCHOOLS, presented at the “12th World Conference on Tobacco or Health”, Helsinki, Finland, 3-8 aug 2003, published in the Conference' Abstract Book, p. 638.

III) Specific risks and beliefs in other than cigarette tobacco products users (cigar smokers, “smokeless tobacco” and e-cigarettes consumers) were evaluated in two articles published in Pneumologia and one article published in the ISI indexed journal, Gaceta Sanitaria.


IV) Polyaddictions: tobacco and coffee, tobacco and alcohol (2 articles published in Pneumologia)


V) Moderate smokers (one poster presented in the ERS International congress and published in abstract in suppl of the ISI Web of Science indexed European Respiratory Journal and one article published in the Romanian Journal of Oral Rehabilitation)


VI) Particularities of respiratory diseases in relation with tobacco exposure (1 article in Revista Medico-Chirurgicala- general considerations in the field, 1 article in Pneumologia, and 1 Book chapter – COPD smokers, 1 article in ISI Web of Science indexed Proceedings Book – respiratory ill smokers at risk for cardiovascular co-morbidities, 1 article in an ISI Web of Science indexed Proceedings Book – smokers at risk for lung cancer).
a) General considerations in the field:


b) Smokers with COPD:


c) Particularities of the respiratory patients at risk for cardiovascular co-morbidities

d) Smokers at risk for lung cancer

e) Respiratory infections in smokers


More detailed description of this work is presented below:

1) *The context of smoking in our society and the challenges to face for changing the paradigm.* (2 articles published in Tabaccologia and in BMJ-rom ed.)


In summary, the main findings that reflected the 2007 „status quo“ in the Romanian society were: a high smoking rate in both general population (36%) and in doctors (43.2%),
the need for national smoking cessation and prevention programs and for developing smoking cessation services to assist smokers willing to quit, all over the country. After becoming an EU member, smoking cessation departments became available in 50 centers, in several Romanian big cities.

By providing free of charge pharmacotherapy and counselling to stop smoking, these centers had a great addressability and allowed gaining expertise in the field, ever since.

The highest impact of tobacco exposure in the early '90s, in Romania was seen among women, children and adolescents, but there were also some social categories that appeared useful to target, like doctors and media representatives, in order to counteract the offensive opened by tobacco industry and advertisement, at the time. This situation drew me the attention on the starting point to develop my research in the field, thus my early attempts to define profile of various social categories of healthy smokers have addressed pulmonologists, women, adolescents and journalists.

**II) Assessment of the specific pattern of tobacco use and dependence in various categories of the general population (women, adolescents, etc.)**

Most relevant results were published in extenso and in abstract in the IDB journal (Pneumologia) and in a supplement of Medical-Surgical Journal of the Society of Physicians and Naturalists, Iaşi. A brief description of this work is available through the list of papers here below:

a) Smoking in women (3 articles published in Pneumologia and in Revista Medico-Chirurgicala)


   In this paper, by showing data available about smoking rates and smoking precipitating factors, in a social and hormone configuration contexts pro-smoking, it was defined the pattern of smoking in female gender.


3. Smoking during pregnancy – a challenge to practitioners

   Smoking during pregnancy – a challenge to practitioners
   **Antigona Trofor**, Man M.A., Miron R.


   **Abstract of the article**

   Smoking during pregnancy is a common finding among women whose parents have been smokers, among those whose husbands are smokers, among women who smoked more than 10 cigarettes per day before they became pregnant, and women who started to smoke at
an early age. Smoking while pregnant is dangerous to both mother and child. Smoking exposure risks such as infertility (both primary and secondary), bleeding during pregnancy, abruptio placentae, placenta praevia, premature rupture of membranes, premature birth, low birth weight newborns, sudden infant death syndrome are taken into consideration. Efficient smoking cessation interventions targeting pregnancy impose, as many women are not aware of dangers of tobacco exposure. Smoking cessation medical aid consists of immediate recommendation to stop smoking, counselling, behavioural therapy and self-helping educational materials.

b) smoking in adolescents (2 studies presented in the 12th Conference on Tobacco or Health”, Helsinski, Finland, 3-8 aug 2003, published in the conference’ Abstract Book and one article published in Archives of the Balkan Medical Union.


By answering an anonymous questionnaire applied in high schools from Iasi, Romania, it was revealed that 30.5% of teenagers were regular smokers and 20% of them already severely addicted to nicotine, in the context of very deficient exposure to education for a smoke-free health life, almost inexistent in their schools.


By exposing schoolchildren to an anti-smoking educational program delivered by 20 minutes video-lessons and real-life interviews with smokers, it was proved that such interactive and attractive educational methods work in this category of population and produce a greater impact, compared to previously applied conservative educational classes.

3. Smoking behavior among teenagers in two north western Romanian cities

Milena Adina Man, Alexandra Blaga, Antigona Trofor, Camelia Ciobotaru, Simona Claudia Cambrea, Stela Halichidis, Oana Cristina Arghir

Abstract of the article

Smoking behavior is formed before the age of 18-year-old, when could appear changes in risk-taking behaviors. The aim of this study was to describe the behavior smoking of teenagers in high school, in two important cities of north-western Romania: Cluj and Oradea.
Material and methods: We conducted a cross sectional survey based on self report questionnaire administered in autumn 2011 to all high school students, who consented to participate at the study. The self reported questionnaire included demographic data and issues about smoking status, including environmental smoking exposure.

Results: The prevalence of smokers among high school students was 89.15% (n=485/544). The mean age of the participants was 15.84 ± 1.04 years (limits 15-18 years). Two thirds of ever smokers (n=201/303; 66.33%) were current smokers. A quarter of them (n=72; 3.76%) initiated smoking before the age of 10- year-old, and other 34.5% tried to abandon smoking. A half of all participants (51.1%) were exposed to second hand smoking inside their home.

Conclusions: The high rate of students who initiated smoking during high school suggests that the anti-smoking campaign should target students of primary school. Medical education against smoking must be promoted soon and constantly among primary school children and teenagers.

III) Specific risks and beliefs in other than cigarette tobacco products users (cigar smokers, „smokeless tobacco” and e-cigarettes consumers) were evaluated in two articles published in Pneumologia and one article published in the ISI indexed journal, Gaceta Sanitaria.


This paper draw conclusions about the harmful effects of toxicants in cigars (carbon monoxide, aldehydes and ammonia, arrhomatic hidrocarbures and nitrogen compounds - responsible for chronic respiratory and cardiovascular disorders, but also for oral and superior aero-digestive cancers). Special consideration was given to increasing risks due to associated alcohol consumption.


A particular category of smokers, not very frequent in our country until lately is represented by chewed or sniffed tobacco users, generic so called smokeless tobacco users, as they consume tobacco products that are not burned, so they do not generate tobacco smoke, but by chewing or nasal use, stay for long time in contact with the oral or nasal mucosa, thus can be very harmful at this level. The paper provides an overview of the health risks of the smokeless tobacco known varieties and also introduces the concept of “harm reduction” that has been advanced in the past two decades as an alternative for quitting smoking in “hard-core smokers”.

**Opinions and practices regarding electronic cigarette use among Romanian high school students**

Lucia Maria Lotrean, Bianca Varga, Monica Popa, Cornel Radu Loghin, Milena Adina Mana, Antigona Trofor

Gac Sanit. 2016; 30(5):366–369 http://dx.doi.org/10.1016/j.gaceta.2016.05.001

**Abstract**

Objective: The study assessed awareness, opinions, practices regarding electronic cigarettes (e-cigarettes) and factors associated with their use among Romanian high school students.

Methods: A cross-sectional study was conducted in 2013 in two major Romanian cities, distributing anonymous questionnaires to 342 high school students aged 16–18.

Results: 52.3% of the smokers, 29.2% of the ex-smokers and 7% of the never-smokers had tried e-cigarettes at least once in their life; 7.8% of the smokers and 4.6% of the ex-smokers had used e-cigarettes in the last month. Among smokers, e-cigarette use was associated with lower participation in school health education regarding e-cigarettes and with having parents using e-cigarettes. Among ex-smokers and never-smokers, e-cigarette use was associated with intention to use e-cigarettes in the next year and with having friends who use e-cigarettes.

Conclusion: Health education programmes and regulatory interventions addressing e-cigarettes are needed in Romania. More research is necessary on how to develop effective public health messages.

**Introduction**

Electronic cigarettes (e-cigarettes) are devices that deliver to the lung aerosols usually containing nicotine and other compounds (Schraufnagel et al, 2014).

They are promoted as an alternative to traditional tobacco cigarette smoking, but there are several concerns regarding their use: evidence about their safety and efficacy for smoking cessation remains limited, while they may increase the risk of non-smokers developing nicotine dependence and of current smokers maintaining their dependence (Schraufnagel et al, 2014; Carr, 2014; Durmowicz, 2014; Dautzenberg et al, 2013; Lotrean, 2015). Moreover, their novel nature and flavouring combined with an unrestricted marketing and sale in several countries may appeal to youth and e-cigarette experimentation might result in use of other tobacco products (Durmowicz, 2014; Gorniewicz et al, 2012; Kinnunen et al, 2013). Nevertheless, similar with other developing countries from Europe, the effect of the growing popularity and availability of e-cigarettes on Romanian adolescents is inadequately characterised.
Hence, this study has two objectives. First, it will assess awareness, opinions and practices regarding electronic cigarettes use among high school students from Romania. Second, it aims to identify correlates of experimentation with e-cigarettes among Romanian adolescents.

**Methods**

**Participants and recruitment**

A cross-sectional study was conducted in May 2013 in 6 high schools situated in 2 big cities from North-Western Romania—three high schools from Cluj-Napoca (a town with approximately 330,000 inhabitants) and three high schools from Sibiu (a town having approximately 147,000 inhabitants). The study was approved by the review committees of the management boards of the participating schools. From each high school there were randomly chosen 1-2 classes from 10th grade and 1-2 classes from 11th grade.

**Instrument**

The students were informed that their participation in the study was voluntary and were asked to fill in an anonymous questionnaire. All students agreed to participate. The questionnaire assessed socio-demographic characteristics, awareness and sources of information regarding electronic cigarettes. Opinions about e-cigarettes, their use during lifetime and in the last month, reasons for using them, intention to use them in the next year and experimentation with e-cigarettes by people from the social environment were also investigated. Smoking behaviour was also evaluated; persons who smoked traditional cigarettes in the last month were defined as smokers, those who smoked in the past but not in the last month were considered ex-smokers and students who never smoked traditional cigarettes were never-smokers. Number of cigarettes smoked per day and the intention to quit smoking in the future was also investigated among smokers.

**Data analysis**

Chi-square tests were used in order to compare smokers, ex-smokers and never-smokers with regard to the investigated issues.

Logistic regression analyses using the stepwise forward method were performed to assess the correlation of e-cigarettes experimentation and several variables among smokers (students who smoke in the last month) and non-smokers (comprised of ex-smokers and never smokers).

Data analysis was performed with the SPSS-20 statistics programme. Significant results are reported at p<0.05.

**Results**

**Study sample**

The study included 342 students aged 16-18 (mean age 17.02 years, SD = 0.68) from the 10th and 11th grade (41.2% in the 10th grade and 48.8% in the 11th grade), living in two big cities of Romania (46.8% from Cluj-Napoca and 53.2% from Sibiu). Out of these, 46.5% were girls and 53.5% were boys.

The results showed that 37.4% of the students were smokers 19% were ex-smokers, while 43.6% were never-smokers.
Table 2. Opinions and practices regarding e-cigarette use by traditional tobacco cigarette consumption. High school students aged 16-18. Romania, 2013 (Lotrean et al, 2016)

<table>
<thead>
<tr>
<th>Awareness</th>
<th>Total sample N = 252</th>
<th>Students N = 121</th>
<th>Ex-smokers N = 45</th>
<th>Never-smokers N = 140</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Awareness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever heard about e-cigarettes</td>
<td>93.9</td>
<td>91.8</td>
<td>96.6</td>
<td>91.6</td>
</tr>
<tr>
<td><strong>Sources of information about e-cigarettes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internet</td>
<td>77.6</td>
<td>77.3</td>
<td>78.7</td>
<td>75.5</td>
</tr>
<tr>
<td>Sale points</td>
<td>77.1</td>
<td>75.2</td>
<td>75.1</td>
<td>78.8</td>
</tr>
<tr>
<td>Newspapers</td>
<td>34.7</td>
<td>37.1</td>
<td>35.4</td>
<td>38.1</td>
</tr>
<tr>
<td>Friends</td>
<td>65.2</td>
<td>64.5</td>
<td>67.6</td>
<td>61.4</td>
</tr>
<tr>
<td>People from the same school year</td>
<td>35.7</td>
<td>40.5</td>
<td>26.5</td>
<td>20.6</td>
</tr>
<tr>
<td>Parents</td>
<td>14.6</td>
<td>16.9</td>
<td>15.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Brothers</td>
<td>7.2</td>
<td>7.8</td>
<td>7.6</td>
<td>7.6</td>
</tr>
<tr>
<td>School health education lessons</td>
<td>15.9</td>
<td>13.7</td>
<td>14.2</td>
<td>14.3</td>
</tr>
</tbody>
</table>

**Opinions**
- E-cigarettes are less dangerous
  - Strongly agree/agree: 35.1%
  - Disagree/slightly disagree: 14.0%
- E-cigarettes can help someone quit
  - Strongly agree/agree: 34.7%
  - Disagree/slightly disagree: 14.0%
- E-cigarettes are used only by smokers
  - Strongly agree/agree: 45.7%
  - Disagree/slightly disagree: 20.7%
- E-cigarettes are less harmful to health
  - Strongly agree/agree: 35.1%
  - Disagree/slightly disagree: 14.0%
- E-cigarettes are less dangerous
  - Strongly agree/agree: 35.1%
  - Disagree/slightly disagree: 14.0%
- People who have tried e-cigarettes among friends
  - Strongly agree/agree: 35.1%
  - Disagree/slightly disagree: 14.0%
- E-cigarettes among high school students who experimented with them
  - Strongly agree/agree: 35.1%
  - Disagree/slightly disagree: 14.0%
- To reduce the number of traditional cigarettes
  - Strongly agree/agree: 40.4%
  - Disagree/slightly disagree: 4.6%
- To quit smoking
  - Strongly agree/agree: 29.4%
  - Disagree/slightly disagree: 19.6%
- Other reasons to use e-cigarettes
  - Strongly agree/agree: 20.2%
  - Disagree/slightly disagree: 20.2%

**Intention to use e-cigarettes in the next year**
- Definitely, yes, personally yes | 12.9 | 12.9 | 12.9 | 12.9 |
- Definitely, yes, personally no | 8.1 | 16.1 | 16.1 | 16.1 |
- Definitely, yes, personally yes | 12.9 | 12.9 | 12.9 | 12.9 |
- Definitely, yes, personally no | 8.1 | 16.1 | 16.1 | 16.1 |

*Statistically significant differences (p<0.05 at chi-square test) between smokers and ex-smokers.
1 Statistically significant differences (p<0.05 at chi-square test) between smokers and never-smokers.
2 Statistically significant differences (p<0.05 at chi-square test) between smokers and ex-smokers and never-smokers.
3 The percentages are calculated for students who have tried e-cigarettes.

**Awareness, opinions and social influences regarding e-cigarettes use**

Table 2 shows that the majority of the students reported having heard about e-cigarettes. The main sources of information were friends (65.2%), internet (57.65%) and people from the same school year (39.7%); smokers were more interested to search information from these sources. One out of four students has got his information from the sale points, 14.6% from their parents and around 12% from school based health education lessons.

Half of the study sample believed that e-cigarettes were less dangerous than traditional cigarettes and considered that e-cigarettes could help in quitting smoking; 45% of the students have believed that e-cigarettes are only for smokers, with never-smoking students being statistically significant less convinced about this (Table 2).

The use of e-cigarettes perceived by students among their social environment was 67.1% among friends, 45.3% among people from the same school year, 7.3% among parents and 8.8% among their siblings.
Experimentation with e-cigarettes and its correlates

52.3% of the smokers, 29.2% of the ex-smokers and 8.7% of the never-smokers declared that they had tried e-cigarettes at least once during their lifetime, while 7.8% of the smokers and 4.6% of the ex-smokers declared having used e-cigarettes in the last month. Intention to use them in the next year was declared by 32% of the smokers, 12.3% of the ex-smokers and 7.4% of the never-smokers.

Half of the smokers declared they used e-cigarettes because of curiosity, 21% because they are less dangerous than traditional cigarettes, while less than 20% used them to quit smoking or to reduce the number of cigarettes. Ex-smokers and never smokers tried e-cigarettes mainly because of curiosity and friend influences.

The results of the logistic regression analyses show that among smokers, e-cigarette experimentation was associated with lower participation in school health education regarding e-cigarettes and having parents using e-cigarettes. Among ex-smokers and never-smokers e-cigarettes experimentation was associated with intention to use e-cigarettes in the next year and with having friends using e-cigarettes (Table 3).

Table 3. Among ex-smokers and never-smokers e-cigarettes experimentation was associated with intention to use e-cigarettes in the next year and with having friends using e-cigarettes (Lotrean et al, 2016)

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Smokers</th>
<th>Non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sources of information about e-cigarettes</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Internet</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sales person</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Newspapers</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Friends</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>People from the same school year</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Parents</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Schools</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>School health education lessons</td>
<td>0.241</td>
<td>0.078-0.747</td>
</tr>
<tr>
<td>Social influences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friends have tried e-cigarettes</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>People from the same school year have tried e-cigarettes</td>
<td>3.302</td>
<td>1.009-10.805</td>
</tr>
<tr>
<td>Parents have tried e-cigarettes</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Number of lifetime e-cigarettes</td>
<td>2.747</td>
<td>1.791-4.333</td>
</tr>
</tbody>
</table>

Discussion

This study is one of the few studies performed among adolescents from European developing countries (Durmowicz, 2014; Dautzenberg et al, 2013; Lotrean, 2015; Goniewicz et al, 2012; Kinnunen et al, 2015; Babineau et al, 2015; Camenga et al, 2014; Hanewinkel et al, 2015; Sutfin et al, 2013; Chapman et al, 2014; Wang et al, 2016; Pepper et al, 2014).

Experimentation with e-cigarettes among smokers was associated with e-cigarettes use among parents, proving, similar to other studies, 10 the importance of the family environment. Lack of school educational activities regarding e-cigarettes was also associated
with experimentation with e-cigarettes among smokers, underlying the role of school education. Experimentation with e-cigarettes was not associated with intention to quit smoking in the future. Moreover, the smokers declared the main reasons for using e-cigarettes curiosity and the fact that they are less dangerous. Hence, similar with other studies, our results underline that unlike older, more established cigarette smokers, e-cigarette use by high school students does not appear to be motivated mainly by the desire to quit cigarette smoking (Kinnunen et al, 2015; Babineau et al, 2015; Camenga et al, 2014; Hanewinkel et al, 2015; Sutfin et al, 2013).

Among ex-smokers and never-smokers, experimentation with e-cigarettes was associated with peer influence. Moreover, the main reasons declared by these adolescents for experimentation with e-cigarettes were curiosity and the peer influences. Similar with other studies, these results show that curiosity of trying these new products plays and important role, being important to further investigate if this type of experimentation is an isolated event or if it could lead to a frequent use (Lotrean, 2015; Goniewicz et al, 2012; Sutfin et al, 2013). In our study, experimentation with e-cigarettes among ex-smokers and never-smokers was associated with intention to use these types of products again in the next year.

The study has several limitations. It involved only a small sample of high school students from two big towns of Romania, which limits the generalization of the results beyond its sample, didn’t allow for the analysis of the data separately for boys and girls and might interfere with the detection of some factors associated with e-cigarette experimentation. Due to the cross-sectional design, the identification of causal relationship is not possible.

Similar with other studies from Europe (Lotrean, 2015; Goniewicz et al, 2012; Kinnunen et al, 2015; Babineau et al, 2015; Camenga et al, 2014; Hanewinkel et al, 2015; Sutfin et al, 2013; Chapman et al, 2014; Wang et al, 2016; Pepper et al, 2014; Martinez-Sanchez et al, 2014), this study shows that health education programs and regulatory interventions addressing e-cigarettes are necessary in Romania. More research is needed on how to develope effective public health messages.

_Transparency declaration_

The corresponding author on behalf of the other authors guarantee the accuracy, transparency and honesty of the data and information contained in the study, that no relevant information has been omitted and that all discrepancies between authors have been adequately resolved and described.

_What is known about the topic?_

Electronic cigarettes are devices that deliver to the lung aerosols usually containing nicotine and other compounds. Because e-cigarettes are relatively new, data on usage patterns and factors which influence them are needed, in order to shape educational and public health policies.

_What does this study add to the literature?_

This is one of the few studies performed among adolescents from European developing countries regarding e-cigarette use and presents data regarding opinions and practices with respect to this issue among Romanian high school students. The study shows that e-cigarettes are a phenomenon very present in the Romanian society and health education
programs and regulatory interventions addressing e-cigarettes are needed, while more research is necessary on how to develop effective public health messages.

Authorship contributions
L.M. Lotrean was involved in development of the study design and instrument, supervised data collection efforts, performed data analyses and writing the article. B. Varga performed data collection. M. Popa was involved in development of the study design and instrument. C.R. Loghin, M.A. Man and A. Trofor provided assistance in interpretation of results and writing the article. All authors read and approved the final manuscript.

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Conflicts of interest
None.

IV) Polyaddictions: tobacco and coffee, tobacco and alcohol (2 articles published in Pneumologia)


In summary, special consideration should be given to cumulative harmful effects of alcohol and tobacco used together (oral cancer, oesophagus cancer, cardiovascular disease, etc.) and to difficulties in treating co-dependency of alcohol and nicotine, that potentiate each other and need a personalized approach.


In brief, both nicotine in tobacco and caffeine in coffee, tea or cola drinks act through psycho-active stimulation, inducing a double dependence with high cardiovascular risk, at first. Awareness on interactions between these two drugs is raised, in order to counteract difficulties of quitting smoking in coffee drinkers, especially related to cardiovascular and neurological toxicity due to caffeine over dosage that can occur during tobacco cessation process.

V) Moderate smokers (one poster presented in the ERS International congress and published in abstract in suppl of the ISI Web of Science indexed European Respiratory Journal and one article published in the Romanian Journal of Oral Rehabilitation)

In this study, on 86 moderate smokers (37.2% men, 71% < 30 yrs old), only 32.5% had nicotine dependence scores < 3; psychiatric mild co-morbidities were met in 9.3% and 44.2% described past withdrawal history, based on validated smoking status questionnaire in use. At 6 months follow-up interview, we found 48.8% to have age of first daily smoked cigarette under 14 and 30.2% to prefer nonfiltered or menthol cigarettes brands. As 69.8% received pharmacological therapy, overall end of treatment abstinence rate was 25%. 6 months evaluation revealed a modest 11.6% abstinence rate. Conclusions: Even if low cigarette consumption, severe dependence is not uncommon and may contribute as well as specific smoking patterns to an unsatisfactory abstinence rate in moderate smokers. We must not underestimate moderate smoking, especially nowadays, when number of such smokers may increase due to tobacco control successful legislation, worldwide.


Addiction to nicotine in moderate smokers – clinical profile and smoking cessation outcomes
I.O. Pascal, L. Trofor, R. Chirita, R. Miron, Antigona Trofor

Abstract of the article
Aim of the study was to determine smoking cessation outcomes in a group of moderate smokers, based on clinical and smoking profile and on level of nicotine dependence. Material and methods Moderate smokers included in a tobacco dependence 3 months treatment program were evaluated for age, gender, smoking profile, nicotine dependence score and co-morbidities, to determine smoking cessation rates at both 3 and 6 months follow up. Results We found 124 moderate smokers, age average 31.2 yrs., in majority women (60%) and 12% had also psychiatric co-morbidities. Nicotine dependence was predominantly moderate and severe: only 31.2% subjects had a Fagerstrom score < 3. Abstinence rate at 3 and 6 months follow-up was 30%, respectively 12.5%. Conclusions: Smoking abstinence rate in moderate smokers was satisfactory, considering the complex clinical profile and the high level of nicotine dependence we have found.

VI) Particularities of respiratory diseases in relation with tobacco exposure (1 article in Revista Medico-Chirurgicala- general considerations in the field, 1 article in Pneumologia, and 1 Book chapter – COPD smokers, 1 article in ISI Web of Science indexed Proceedings Book – respiratory ill smokers at risk for cardiovascular co-morbidities, 1 article in an ISI Web of Science indexed Proceedings Book – smokers at risk for lung cancer).
These results are summarized in the followings:

a) General considerations in the field:

In the first publication: Antigona Trofor, Mihăescu T, Grigoraș C. ANTI TOBACCO USE CONSULTING. Revista Medico-Chirurgicală. 2001. 105(3):599-601, I have described the need for and all necessary steps to implement this medical gesture in all services that assist smoking patients.

b) Smokers with COPD:


c) Particularities of the respiratory patients at risk for cardiovascular co-morbidities:

Management of nicotine dependence in respiratory disorders smokers at risk for cardiovascular co-morbidity

Antigona Trofor, Milena Adina Man, Dana Alexandrescu, Ramona Miron, Elena Dantes, in the Book Proceedings of the International Conference On Risk Management, Assessment And Mitigation

Abstract of the article

We included 218 smoking patients with unique respiratory vs. double respiratory and cardiovascular disease to receive counseling +/- pharmacological smoking cessation therapy. The end point was abstinence rates at 12 months follow-up in the respiratory diseases with vs without cardiovascular comorbidity. Impact of associated cardiovascular risk on cessation outcomes in respiratory ill smokers has been evaluated to design a personalized smoking cessation approach for such subjects.

Our findings suggested that the presence of cardiovascular risk in chronic respiratory disease smokers represents a crucial point towards cessation. We believe routinely screening cardiovascular risk in current respiratory diseases practice would increase compliance to smoking cessation therapy. Also, based on this study’s results, we strongly recommend a personalized medical and psychological quit smoking approach for all smokers with chronic respiratory conditions and concomitant cardiovascular co-morbidity. As well, by adding a short motivational interview to the regular smoking cessation brief advice, we raised awareness of the individuals on unperceived co-morbid health risks and increased the efficacy of smoking cessation therapy.
d) Smokers at risk for lung cancer:

**Effectiveness of routinely approach towards smoking cessation when lung
cancer suspected in current and former smokers**

**Antigona Trofor**, Milena Adina Man, Dana Alexandrescu, Ramona Miron


**Abstract of the article**

The study was carried out on 160 patients addressed to the Smoking Cessation Center of the Clinic of Pulmonary Diseases, aiming the feasibility of achieving smoking abstinence in active or former smokers with lung cancer diagnostic presumption, whether lung cancer confirmed or not, all subjects were given brief advice to quit smoking/to maintain smoking abstinence and current smokers willing to quit were provided pharmacological and behavioral smoking cessation therapy for 3 months. The patients included were 108 current smokers (CS) and 52 former smokers (FS). Among those 108 currently smoking patients with clinic and radiologic suspicion of lung cancer, 63 (58, 3%) had bronchoscopy with bronchial aspirate +/- bronchial brushings. Smoking cessation pharmacological therapy was prescribed in 74 currently smoking patients, among who 38 cases of confirmed lung cancer and 36 with unconfirmed lung cancer suspicion. At 3 month end of treatment, 36 patients (48, 6%) had quit smoking (16 LCC and 22 LCS) and after 6 months follow-up, total abstinence rate was objectively found in 26 patients (35,1%), meaning 10 LCC and 16 LCS. Standard bronchoscopy was performed in 47 former smokers, yet bronchial biopsy in just 35, with relevant findings to confirm lung cancer (Fig. 6) in only 24 cases. Brief advice to maintain no smoking status was given to all 52 former smokers. At 6 months follow-up visit, 48 patients were still ex-smokers, while 4 patients in the LCC category relapsed to smoking. Therefore, we have concluded that a comprehensive approach of smoking behavior, to periodically assess smoking status in ex-smokers and to routinely deliver smoking cessation in all current smokers is a “must have” to manage lung cancer development.

e) Respiratory infections in smokers

To sustain my interest for this domain, later on, I have developed the subject about the infectious exacerbations of COPD smokers in the followings works in the following work:


In the same time, in order to define the pattern of respiratory tuberculosis in smokers, I have conducted several studies and disseminated their results, along time, as listed here below:

In this study, it was concluded that severe forms of TB as well as TB relapses are more frequent in heavy smokers, more severely addicted to nicotine.


In this article by assessing tobacco use and dependence status together with acquired knowledge about health risks of smoking in a TB patient population, it was revealed that 60% of the TB patients were active smokers, in majority of men (71%) with moderate-severe nicotine dependence, also that they had a very low level of knowledge about risk of continuing smoking for their respiratory health and had never been exposed to smoking cessation counseling.


In this article, it was shown that active and former smoking was associated with increased mortality among TB patients. As smoking causes damage both to the lungs and at systemic level, this could contribute to increased number of deaths due to tuberculosis. (OR=2.33 CI 95% 1.14-4.75)

1.4. Assistance in maintaining the respiratory health through improved air quality in daily life

A. State of the art

When respiratory health is affected by air pollution, community based health strategies should prevail and must be integrated into the overall disease therapeutic interventions.

In 2007, the World Health Organization has estimated that a billion people live in places with polluted air and that air pollution killed 8,000 people a day worldwide, in majority in developing countries (WHO, 2016). While we refer to air pollution, we expect to think especially to outdoor air, yet, it seems the same pollutants can be found indoor, in homes, workplaces or other indoor places. Such chemicals, some of which are called volatile organic compounds (VOC) can cause many health risks and they can be identified in carpets, walls, furniture, clothes, domestic tissues, cleaning products, toiletries, cosmetics and many other
products used in homes. It has been shown that pollution exposure at home and at work is often greater than outdoors (California Air Toxics Program, 2015). The California Air Resources Board estimates that indoor air pollutant levels are 25-62% greater than outside levels and can pose serious health problems. There are many known sources of indoor air pollution, such as: tobacco smoke, cooking, heating, vapors from building materials, paints, furniture, other materials within the home that emit unhealthy chemicals that can be inhaled or accidentally ingested (California Air Toxics Program, 2015).

B. Personal contributions

Scientific, professional and academic achievements in this field

By exploring this domain of pollutants’ impact on respiratory health, my interest was directed mainly towards measures for avoiding indoor toxicants, especially those ones derived from tobacco smoking, and at a lower extent to studying outdoor air pollutants.

So, following my research objective to highlight indoor polluting factors that can be incriminated in developing respiratory injuries, I was recruited as Romanian coordinator from behalf of the Clinical Hospital of Pulmonary Diseases Iasi, in the “IAPAH-Indoor Air Pollution and Health” grant application, a collaboration type grant call, submitted within the CE-FP7 2007 call, at topics ENV.2007.1.2.1.1, by the coordinator, Sean Semple from Occupational Medicine and Environmental Department of the Aberdeen University in UK, in May 2007. Aiming at assessing how home indoor air pollution affects health by collecting information about levels of indoor air pollution produced by burning fuel or tobacco used in homes, the application was rejected at this first stage, but accepted in the next years http://www.nuigalway.ie/iapah/iapah.html.

Even if I had not the chance to collaborate in this project, working for this grant proposal together with researchers from UK and other European countries proved an useful exercise for me in the field of respiratory health prevention and opened the door to future related research and scientific activities. Thus, by continuing my preoccupation to improving respiratory health by respiratory disease development research, I contacted other teams of health professionals interested in the field to develop new grant proposals, in the next years.

First, I started to co-work with dr. Ovidiu Petris and dr. Diana Cimpoiesu, from the Emergency Medicine and Toxicology internal Medicine Department of the University of Medicine and Pharmacy “Gr. T. Popa” Iasi, to develop a proposal about improving emergency medicine performance and visibility. I was member in the team of the grant „To Promote Research in Emergency medicine in Romania –Top Emergency”, Module III CEEX, within the CNCSIS Program „Excellence in Research”contract 203/2006-ANCS, grant director Prof. Dr. Diana Cimpoiesu, acting as a researcher responsible with COPD assessments and tobacco cessation between 2006-2008. In this position I was involved in several workshops for acquiring bronchoscopy skills for participants and producing such course materials in the project’s conferences.

Secondly, I developed another collaboration, with colleagues from Dentistry faculty of the University of Medicine and Pharmacy “Gr. T. Popa” Iasi, for the grant “National partnership in the domain of oral health regarding tobacco consumption and cessation –
premises of integrating Romanian research in the European operational area- SANFACTOR, project Nr. 42123/2008, grant director Prof. Dr. Carmen Stela Hanganu, within ANCS “Partnership” calls, acting as responsible with tobacco use and cessation research, between 2008-2011.

At a later stage, my interest in the area of chemicals induced health injuries, was reactivated and I co-authored an article about organophosphates cardiac related toxicity, published in the journal indexed in ISI Web of Science - Revista de Chimie - No 1/2015. The abstract of this original research paper is presented here below:

### The Use of Chemistry in Understanding the Pathogenic Mechanisms of Organophosphates Related Cardiac Toxicity

O. R. Petris, C. Lionte, L. Sorodoc, Antigona Trofor, E. Gazzii, M. A.
Man REV. CHIM. (Bucharest), vol. 66, No. 1, 2015, pag. 109-115

**Abstract**

Organophosphate substances, although known to exert their toxic effects mainly by inhibiting cholinesterase enzymes, associate a cardiac toxicity with pathogenic mechanisms that are not only limited to this anticholinergic effect. The aim is to discover the most reliable explanation for the late cardiac toxic effect of organophosphates in acute intoxication. The experimental research comprises evaluation of oxidative stress system, serum electrolytes levels and evidences of myocardial injury (cardiac enzymes, histological examinations) while monitoring, through gas chromatography, the presence of the toxic at cardiac level, during a period of eight days evolution of an acute intoxication with trichlorfon at two different dosages (200 and 400 mg/kg body weight). Electrolyte disorders and the intervention of oxidative stress were not documented to be involved in this type of outcome. A pathogenic mechanism of myocarditis was documented in the evolution of the acute organophosphates intoxication due to a direct action of the toxic to the heart. The late effect is associated with a dysphasic accumulation of the organophosphate at myocardial level.

1.5. A good “quality of life” of the chronic respiratory disease patients

**A. State of the art**

In 1995, the WHO recognized the importance of evaluating and improving people’s quality of life (WHO, 2005) and since then, a lot of literature on this subject has become available.

Life expectancy and causes of death have traditionally been used as key indicators of population health. While these indicators provide critical information about the health status of populations, they do not offer any information about the quality of the physical, mental, and social domains of life. Increasing life expectancy has also highlighted the need for other measures of health, especially those that capture the quality of the years lived.
The „health related quality of life (HRQoL)” is considered a multidimensional concept that includes domains related to physical, mental, emotional and social functions. It goes beyond direct measures of population health, life expectancy and causes of death, and it is focusing on the impact that health status has on quality of life of an individual.Clinicians and public health officials have implemented use of the HRQoL and well-being to measure the effects of chronic illness and of their treatments in general, in most chronic conditions (Healthy People 2020, 2010).

Quality of life encompasses more than activities of daily living, health status, disease categories, or functional ability “because it directs attention to the more complete social, psychological and spiritual being” (Albrecht et al, 1999). In other words, quality of life does not reflect people’s physical, mental, or emotional functioning or disease status, but instead expresses their ability to participate in the world around them, which is defined here as an ability to participate in activities that are common to most people in a society (Healthy People 2020, 2010).

Among all chronic respiratory diseases, there are especially two conditions that determine an important impact on patients’ quality of life: chronic obstructive pulmonary disease (COPD) and pulmonary tuberculosis. This impact is augmented when these two diseases develop in tobacco users. Among both pulmonary TB and COPD patients, smoking behaviour is very frequent as disease risk factor, but also as disease progression motor and it accelerates degradation of quality of life, in both conditions.

As regards, tuberculosis patients, it is well known that TB, a chronic specific infectious condition, requiring six months of anti-TB antibiotic therapy under direct observation, occurs in many cases in individuals with a low economic status, frequent alcohol or tobacco consumers, who may also present TB risk factors such as diabetes, gastric or hepatic disorders, or other psychiatric co-morbidities that bring a negative impact on TB evolution and treatment compliance and implicitly on patients’ quality of life.

Referring to chronic obstructive pulmonary disease (COPD), a systemic and disabling disorder, having tobacco use a major risk factor, patients face a multitude of respiratory and general symptoms, together with a psychological load in relation with their condition (Chang et al, 2011; Wagena et al, 2005) . The magnitude and diversity of these manifestations is amplified when a COPD exacerbation is intervening. Another important aspect that may have a great influence on the quality of life in respiratory disease patients, especially if they are smokers with related co-morbidities is the quality of sleep. Mostly known as the „overlap syndrome”, this condition describes coexisting obstructive sleep apnea with pulmonary disorders such as COPD or cystic fibrosis, when in time there is an aggravation of the nocturnal desaturation with progressive towards permanent hipoxemya and consequent pulmonary artery hypertension (Boisteanu et al, 2002).
B. Personal contributions

Scientific, professional and academic achievements in this field

As I started to get involved in studying the relationship between smoking and respiratory health, I realized the importance of the concept of „health related quality of life” and I began to search for its possible specific applications for the „respiratory health related quality of life”.

I have tried to extrapolate these tools for the most frequent chronic respiratory illnesses encountered in my clinical practice: chronic obstructive pulmonary disease (COPD) and pulmonary TB, in an overall approach, and later on, more particularly, when they add smoking as a coexisting disorder. The results were disseminated through several articles and a book chapter, dedicated to the following aspects:

1. The association of depression and anxiety, as well as illness perception in tuberculosis patients (one article published in Recent Advances in Modern Medicine)

<table>
<thead>
<tr>
<th>Depressive syndrome, anxiety and illness perception in Tuberculosis patients</th>
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<tr>
<td>Milena Adina Man, Octavia Luiza Negrelescu, Cosmina Bondor, Antigona Trofor, Dana Alexandrescu, Elena Dantes</td>
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<tr>
<td>in Recent Researches in Modern Medicine, ISBN: 978-960-474-278-3, p. 243-8</td>
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</table>

Short description of the results

Depression and anxiety were very high in patients with tuberculosis, in this study (6.78 % severe depression, 32.20% moderate depression and 32.20% severe anxiety, 40.68% moderate anxiety). For patients at first admission in hospital (new cases) the anxiety score was less than for chronic patients or with multiple admissions. Depression was positively correlated with anxiety (p=0.001) for patients with tuberculosis. In conclusion, evaluation and management of the mental disorders associated to Tuberculosis (significantly higher compared to the general population) may increase treatment compliance and reduce disease relapses. Overall, such an approach could significantly ameliorate the prognosis and the quality of life in patients with this chronic infectious disease.

2. The association of anxiety and depression in COPD patients (one article published in a journal indexed in ISI Web of Science)
**Introduction**

In chronic obstructive pulmonary disease (COPD), a systemic and disabling disorder, patients face a multitude of symptoms, together with a psychological load in relation with their disease (Chang et al, 2011; Wagena et al, 2005). In recent years there is increasing evidence that COPD patients often experience panic attacks, anxiety and depression symptoms, especially in severe disease stages; when anxiety and depression occur, the risk of re-hospitalization and mortality is increased (Chang et al, 2011; Wagena et al, 2005; Tetikkurt et al, 2011; Dahlen et al, 2002). Moreover there is growing recognition of the fact that patients diagnosed with depression and bipolar disorders die prematurely due to concomitant illnesses (Chang et al, 2011; Wagena et al, 2005). Explanation for this bilateral interaction lies in both symptom burden, functional impairment and psychological changes that accompany a chronic condition such as COPD for example, and in maladaptive health risk behaviors of the psychiatric patients (Chang et al, 2011; Wagena et al, 2005).

Symptoms of anxiety and depression are two of the most common co-morbidities in people with COPD (Maurer et al, 2008), leading to significantly poor health outcomes, reduced quality of life and significantly increased healthcare costs (Naylor et al, 2012). In a retrospective, observational study, Gratziou and colleagues reported that the prevalence of depression among COPD patients with severe airway obstruction (FEV1 <50%) was 25% and they had a 2.5 times greater risk of depression in comparison to healthy smokers (Gratziou et al, 2014). High prevalence of depression is independently associated with smoking (John et al, 2004) and failure to quit (Covey et al, 2006). Depression is also one of the withdrawal symptoms that predicts relapse to smoking (Smith et al, 2003). Patients with anxiety and depression often suffer from low self-confidence or self-efficacy, which may lead to worsened disease related coping (Yohannes et al, 2008) and poor self-care behaviors. Moreover, co-existing addiction and psychiatric disorders significantly decrease the cessation success rates in COPD smokers and increase mortality among these patients (Kupiainen et al, 2012).

Compared with persons without physical illness, COPD patients have impaired quality of life (McSweeney et al, 1982; Prigatano et al, 1984; Yohannes et al, 2000). That is why numerous diagnostic tools, like the COPD Assessment Test (CAT) (GSK, 2009), St George’s Respiratory Questionnaire (SGRQ) (Celli et al, 2008), Cough and Sputum Assessment Questionnaire (CASA) (Crawford et al, 2008) questionnaires, have been developed recently, to assess how daily life of the COPD patients is affected by their clinical condition.

In Romania, there are few data regarding the prevalence of COPD at national level. A study performed in 2012 estimated that 8.13% of population over 40 years had this condition...
(Magureanu et al, 2013). Even less is known about co-morbid depression, anxiety and panic in Romanian COPD patients, except for a few data available (Magureanu et al, 2013). Hence, the first objective of this study is to assess anxiety, depression and panic disorders among smoking patients diagnosed with COPD. Secondly, we will investigate their correlation with respiratory disease severity and quality of life as well as with tobacco use.

**Methods**

**Study population**

An observational study was conducted between January - September 2014, among patients diagnosed with COPD from the Clinic of Pulmonary Diseases from Iași, Romania. The study was approved by the local ethics and management boards, based on volunteer consent and permissions of participants and in respect to legislation for confidentiality of patient’s data use and publishing.

The inclusion criteria of the subjects were:
- aged > 40
- a valid diagnosis of COPD according to the ERS-ATS criteria for at least 12 months (GOLD, 2015)
- had no history of psychiatric diagnosis other than depression, anxiety, or panic attack

**Tools and Measures**

The subjects were asked to fill in a questionnaire which assessed demographic data, medical history (with special emphasis to cardiovascular co-morbidities), smoking status, COPD staging and issues related to anxiety, depression and panic attacks as well as the impact of COPD on their quality of life.

To define smoking, we used the standard Romanian Smoking Cessation Guideline brief questionnaire asking about past 12 months cigarettes consumption, number of packs-years (PY), previous quit attempts and including also nicotine dependence Fagerstrom test (Trofor et al, 2010).

The 2011 “ABCD” GOLD guideline classification, was used to stage COPD. This classification was still in use in 2015 (GOLD, 2015).

Anxiety and depression were screened by the Hospital Anxiety and Depression Scale (HAD scale), whilst the ICD 10 criteria served to confirm panic attacks. The HAD scale is a 14 item scale that generates ordinal data. Seven of the items relate to anxiety and seven to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0-21 for either anxiety or depression, with scores categorized as follows: normal (0-7), mild (8-10), moderate (11-14) and severe (15-21) (Zigmond et al, 2003).

Impact of COPD on patients’ quality of life was determined by means of the COPD Assessment Test (CAT), a patient-completed instrument, designed to provide a simple and reliable measure of health status in COPD, to both physician and patient (GSK, 2009). CAT is a simple 8 item questionnaire that measures the general impact of COPD on a patient’s health and how this is changing over time; it is recommended for use at any COPD visit. It contains questions about COPD symptoms-cough, phlegm, tight chest - exercise capacity and quality of sleep. It has a scoring range of 0-40 and implications of the score need to be evaluated in
relation to a patient’s disease severity. Each patient gets a score at each visit. Any difference or change of 2 or more is considered meaningful for interpretation of changes in COPD status.

Dyspnea was evaluated through Modified Medical Research Council Dyspnea Scale (mMRC), a 0-4 gradually assessing dyspnea index.

**Statistical Analysis**

Descriptive analysis were performed, while Pearson bivariate correlations were used to assess the relationship between several variables. A statistically significant threshold was considered a $p < 0.05$. Data were analyzed using SPSS 17 (SPSS Inc.).

**Results**

A total of 60 COPD patients (52 men and 8 women) were enrolled in the study. Mean age was 62.2 years of age. A percentage of 38.3% were smokers and 61.7% were ex-smokers in the last 12 months). Among smokers, the medium packs-years was 34.3 and the medium Fagerstrom score was 7.5.

Cardiovascular co-morbidity (hypertension, coronary heart disease, acute myocardial infarction, heart failure) was identified in a large proportion (43.3%) of subjects.

In terms of COPD severity, as classified by the GOLD 2011 criteria, 23.3% were in stage B, 41.7% in stage C and 35% in stage D. The medium number of COPD exacerbations/year was 1.9 and the medium number of severe exacerbations was 0.8 per year. Overall, mean mMRC was $2.86 \pm 0.92$ SD, mean CAT score was $21.75 \pm 8.24$ SD. Panic attacks, as judged by the ICD 10 criteria were recognized in 43.3% of patients. Anxiety and depression symptoms among COPD subjects were identified (10.65±3.54 SD anxiety score, to 9.93±3.80 SD depression score respectively). A percentage of 16.7% of participants had a normal score with regard to anxiety (score 0-7), 40% had mild anxiety (score 8-10), 30% moderate anxiety (score 11-14) and 13.3% severe anxiety (score 15-21). With regard to depression 23.3% had a normal (score 0-7), 31.7% had mild depression (score 8-10), 35% moderate anxiety (score 11-14) and 10% severe anxiety (score 15-21).

The results of the bivariate correlation analyses showed no significant correlations between smoking status (smokers vs ex-smokers) and either severity of COPD, depression, anxiety, or panic attack. Heavy smoking was not associated with COPD, depression, anxiety, or panic attack, in our sample, while cardiovascular co-morbidity history also did not influence HAD scale scores or any panic event as no significant correlation was distinguished.

On the other side, our results indicated that mMRC and CAT scores had a significant correlation ($r=0.63$, $p \leq 0.001$), while anxiety and depression (assessed by HAD scale) were found to correlate significantly ($r=0.54$, $p \leq 0.001$). Moreover, mMRC scores also obtained significant correlations with the score for anxiety ($r=0.71$, $p \leq 0.001$), score for depression ($r=0.34$, $p=0.019$), and panic events ($r=0.551$, $p \leq 0.001$). Similarly, CAT’s scores had significant correlations with: the: score for anxiety ($r=0.63$, $p \leq 0.001$), score for depression ($r=0.45$, $p=0.002$), respectively with panic attacks ($r=0.386$, $p=0.008$). Finally, COPD Gold stages were correlated significantly with scores obtained for anxiety ($r=0.307$, $p=0.001$).
Discussions

Our results indicated that anxiety and depression were constant findings among our COPD patients, however this was unrelated to tobacco use within this population.

In COPD, depression & anxiety prevalence estimates vary widely, due either to the use of varied measurement tools, or to the different degrees of illness severity across studies. In stable COPD, the prevalence of clinical depression ranges between 10% and 42%, while that of anxiety ranges between 10% and 19%. The risk of depression is higher in patients with severe COPD compared to control subjects and especially in oxygen-dependent patients, as well as in patients who have recently recovered from an acute COPD exacerbation (Maurer et al, 2008). In another systematic review of 64 studies focusing on patients with severe COPD, it was concluded that the prevalence of depression ranged from 37 to 71%, and that of anxiety from 50 to 75%, figures comparable to or higher than prevalence rates in other severe somatic conditions, such as cancer, AIDS, heart disease, and renal disease (Lacasse et al, 2001; Kunik et al, 2005).

Many patients with COPD experience panic attacks, defined as episodes of intense anxiety accompanied by symptoms of physical arousal. In this respect, consideration needs to be given to differentiate a real panic disorder from a panic attack precipitated by exercise in severe COPD patients, with a limited physical effort capacity. To be diagnosed with a pure panic disorder, patients must experience recurrent panic attacks, anticipatory anxiety about future attacks and some unexpected and unpredictable attacks (not always in situations inevitably causing dyspnea in COPD). The prevalence of panic disorder in COPD has been estimated as up to 10-times greater than the population prevalence of 1.5–3.5% (American Psychiatric Association, 1994; Smoller et al, 1996).

In our study, statistic outcomes revealed significant correlations of anxiety, depression and panic disorders with COPD symptoms intensity and with related quality of life, as assessed by mMRC and CAT. According to data published in 2011, by Salerno and Carone (Salerno et al, 2011), there is a clear association between dyspnea and anxiety or depression in COPD, and these symptoms are correlated with and contribute to the severity of the chronic obstructive pulmonary disease. Authors concluded further studies are needed to better understand the relationship between psychological abnormalities and the physiopathology of COPD and how this may be further influenced by concurrent tobacco use.

Anxiety and depression are very often diagnosed in COPD, even in the same time, with a significant impact on patients’ quality of life and disease evolution. The reason for developing these symptoms is not very well known, but researchers have identified some frequently associated factors, like: low body mass index, physical disability, severe dyspnea, % of predicted FEV<50%, co-morbidities, poor quality of life, female gender, current smoking, living alone and low social status (Kunik et al, 2005). Within the current study, all patients were smokers or ex-smokers and the scores for anxiety, depression and panic attacks were similar for both categories.

Studies from other countries show that even though health professionals are aware of the fact that symptoms of anxiety and depression are two of the most common co-morbidities in people with chronic obstructive pulmonary disease (Ng et al, 2007), in fact, it seems, these COPD co-morbidities are not routinely managed in all pulmonary diseases services, which
leads to significantly poor health outcomes, reduced quality of life and increased healthcare costs (Naylor et al, 2012).

Similar with other studies, our results recommend that clinicians caring for patients with COPD should screen for psychological distress and manage this co-morbidity appropriately (Baraniak et al, 2011). According to current UK guidelines for the management of anxiety and depression, psychological treatment, pharmacological treatment or both in combination, are recommended as best practices (National Institute of Clinical Excellence, 2009; National Institute of Clinical Excellence, 2011).

The limitations of the study are related to the relatively small sample size which was over represented by man participants, however this reflects the situation of the hospitalized patients with COPD. Moreover, the study did not include a control sample of people without COPD in order to compare the score for anxiety, depression and panic attacks between the groups, so the comparisons are possible only with data obtained by other studies.

**Conclusions**

In conclusion, the results of this study indicate that anxiety, depression and panic attacks were constant characteristics among COPD patients, regardless of their current tobacco use. These findings underline the necessity to routinely screen anxiety, depression and panic in COPD patients. Further research is needed to assess the potential role of other tobacco related indexes with depression, anxiety, panic attacks among tobacco users with COPD.

3. Increasing quality of life in COPD exacerbations through supplemental antiinflammatory therapy addressing chronic airway inflammation described in COPD (one article published in *Medicina Interna*):

<table>
<thead>
<tr>
<th>The role of Fenspiride for antiinflammatory therapy in COPD: review</th>
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<tr>
<td><strong>Antigona Trofor</strong></td>
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<td><em>Medicina Interna</em>, 2014, vol. XI, nr.1, pag. 77-90</td>
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**Abstract**

Overview of available data in the literature about fenspiride clorhidrate has been done. Based on general characteristics of fenspiride (a medication with anti-inflammatory, anti-coughing and bronchodilator action), an analysis of the evidences published until 2012, including 2012, is provided about: efficacy and safety of the substance as anti-inflammatory therapy in acute and chronic respiratory diseases, overall, but also in particular for acute and chronic bronchitis and COPD. More in depth details are given on fenspiride’ role in reducing number and severity of COPD exacerbations, as well as in its favorable influence on COPD evolution and quality of life, thus recommending prescription of fenspiride as a basic anti-inflammatory treatment, in II\textsuperscript{nd} stage COPD patients, in context of constant administration of specific therapies such as bronchodilators, anticholinergic and glucocorticoids.
4. **Overall quality of life in smoking COPD patients** (one book chapter published by the University of Medicine and Pharmacy „Gr. T. Popa” Iasi)

I have contributed to an educational material dedicated to the subject, with focus on survival and quality of life benefits of precocious smoking cessation in this category of high risk individuals: „Management of nicotine dependence – a mandatory component of the care for COPD smoking patient“, Antigona Trofor, R. Miron, published by the University of Medicine and Pharmacy „Gr. T.Popà” Iasi, in sept 2016, ISBN 978-606-544-410-2.

5. **The quality of sleep in COPD patients**

A more in depth analysis of the association between smoking, co-morbidities and sleep apnea syndrome was presented at the American College of Chest Physicians (ACCP) world congress and published in abstract in Am. J. Crit. Care. Med, in 2010:

Smoking and co morbidities analysis at sleep apnea syndrome in a sleep population from Romania

Mihaiacuta S., Deleanu O., Ursoniu S., Mihaltan F., Antigona Trofor, Nedelcu R., Hotea C., Tudorache V.


**Abstract**

**Rationale:** Obstructive Sleep Apnea Syndrome (OSAS) represents an under-diagnosed disorder in Romania. In most cases, the cardiovascular comorbidities are present. One third of the population smokes. We analyzed particularities of the association of co morbidities and smoking as a dependent variable in patients with OSAS from 2 sleep labs (M. Nasta Bucharest and V. Babes Timisoara, Romania) **Material and methods:** 2441 consecutive patients with suspected OSAS (November 2003 - January 2009) were evaluated with sleep questionnaires, anthropometric measurements, polysomnography for apnea-hypopnea index (AHI normal 0-4, mild 5-14, moderate 15-29, severe over 30). We measured differences (Pearson χ2 test) between two groups, without OSAS (AHI 0-4) and with OSAS (AHI ≥5) regarding diabetes, obesity, dyslipidemia, chronic obstructive pulmonary disease (COPD), endocrine disease, arrhythmia, coronary artery disease (CAD), heart failure, arterial hypertension (HTA) and smoking habit (active, passive, ex-smokers). **Results:** 1899 (77, 99%) males, 542 (22, 01%) females (p<0.001 between groups without OSAS and with OSAS); smoking status: non-smokers 987 (40, 57%), active smokers - 1092 (44, 88%), ex-smokers - 354 (14, 55%) (p=0.308 for difference between ever smoker and non smoker) with much fewer women as ex-smokers (9, 84% vs. 90,16% in men); mean age 50, 72 ±11, 66 years; AHI distribution: 453 patients (19.57%) AHI 0-4, 429 (17, 51%) mild SAS, 500 (19.88%) moderate SAS, 1053 (43, 05%) severe SAS; obesity in 2063 patients (84, 93% (p<0.001). Presence of co morbidities: 1173 patients (48,23%) with HTA (p<0.001), 683 (28,06%) with CAD (p<0.001), 438 (18%) with arrhythmia (p=0.640), 336 (13,83%) with COPD (p=0.821), 166 (6,82%) with left heart failure (p=0.001), 675 (43,95%) with dyslipidemia (p=0.887), 417 (23,95%) from 1741 patients with diabetes (p=0.001), 21
from 637 with cor pulmonale (p=0.633). Severe desaturation were found in non-smokers versus active smoker (52.5% vs. 34.42%). Mean BMI and Epworth Sleepiness Score were similar for smokers, former smokers and never smokers. **Conclusion:** In a sleep population, the confirmation rate for OSAS is very high (91, 40%), severe disease (43, 24%). Patients with and without OSAS are not significantly different regarding smoking status, but they are significantly different regarding cardiovascular diseases. There are no significant differences between the presence of CAD or HTA in patients with OSAS that are smokers vs. never smokers.

### 1.6. Developing skills that help reducing the risk for tobacco induced respiratory disorders

**A. Background**

Once identified the main action areas to implement strategies for smoking prevention and cessation in current clinical practice of physicians in charge with respiratory illnesses, the next stage in my research activity was to orientate towards acquiring skills for this purpose and in the same time to identify the means by which my skills could be disseminated and applied among other categories of specialists interested to develop such skills. Practically, I attended several trainings and specialty courses to obtain the competence for providing smoking cessation (pharmacotherapy and behavioural-cognitive counseling) to smokers willing to quit addressed to a respiratory disease clinic. Then, I got involved in several European educational programs and national treatment programs aiming at quitting smoking.

To increase visibility of my work and to attract researchers from abroad in our research activities developed within Clinic of Pulmonary Diseases Iasi, I have implemented, in 2010, a project for improving administrative capacities of the Clinical Hospital of Pulmonary Diseases Iasi, in relation with research and development activities run by researchers in our hospital. The major goals of the IPAS Iasi project (improving administrative capacities of the Hospital of Pulmonary Diseases Iasi) - ID SMIS 749/13054, was to attract national and international research partnerships with our hospital, to improve management of research activities and to increase valorisation of results obtained from research.

In parallel, I developed a specialized curricula for graduate and postgraduate trainings in the field of smoking cessation and I shared my expertise with other categories of specialists in charge with smoking patients, as part of an overall plan to develop and implement smoking cessation methods in Romania. All these activities were done mainly under the umbrellas of the Romanian Society of Pulmonologists (www.srp.ro), of the NGO „Aer Pur Romania” (www.aerpur.ro), of the European Respiratory Society (ERS) (www.ersnet.org) and various other governmental and nongovernmental bodies that will be mentioned, in context.
B. Personal contributions

**Scientific, professional and academic achievements in this field**

**a) Professional training in this field:**

- “Central and Eastern European Tobacco Control Institute” (7-12 May 2000, Warsaw, Poland)

- “Effective Advocacy and Movement Building for Tobacco Control” (23-25 April 2003, Bucharest, Romania)

- “Framework Convention Alliance (FCA) awareness Raising and Capacity Building Workshop on Tobacco Control and the WHO Framework Convention on Tobacco Control” (20-23 May 2004, Sinaia, Romania)

- European Respiratory Society School Course on “Smoking cessation” (10-12 Dec 2004, Bucharest, Romania)

- Spring school regarding smoking prevention among young people organized by European Network for Young People and Tobacco (14-18 March 2005, Helsinki, Finland)

- Competence in the field of “Treatment of tobacco use and dependence” (Certificate series E, Nr. 07505/14.12.2004) and “Cognitive-behavioral techniques for treating tobacco use and dependence” (Certificate series E, Nr. 07816/27.01.2005), provided by Health Ministry-National Center for Post-university studies training development for Health Professionals - Bucharest. These two certificates were equivalent for specialized competence in smoking cessation, at the time.

**b) Developing the sub-specialty of Tobaccology in Romania**

In 2007, I took the initiative, inside the Romanian Society of Pulmonology, to develop a new section dedicated to specialized assistance of smokers and to producing educational resources available in Romanian language, to train specialists in this new domain of medical activity, none legitimized at the time, in our country. This new Tobaccology section, that I chaired (2007-2011) has raised awareness on the need to develop a standardized approach in tobacco induced respiratory diseases, among pulmonologists. Also, it has contributed to publication of the first Romanian smoking cessation guideline (GREFA) in 2008. This document was produced by a large board of specialists from the most important Medicine universities in Romania and thus, it has served as support for implementing the basic notions about tobacco use and dependence in the medical curricula (www.srp.ro).

Ever since, I have participated and organized numerous dissemination activities to implement the smoking cessation skills at both national and local level, inside Romanian Society of Pulmonology, in parallel plans, addressing to postgraduate medical curricula level and also to graduating medicine students, as described in section 1.2. (Academic activity)
c) Director of the project „IPAS Iasi (Improving Administrative Performance of the Hospital of Pulmonary Diseases Iasi)” - ID SMIS 749/13054, (2010-2011) financing contract nr 138/11/06/2010, co-financed by European Fund for Regional Development, in basis of the financing contract with the National Authority for Scientific Research, as Intermediary Body (IB), in the name and for Economy and Commerce Ministry in his quality of Management Authority (MA) for „Programul Operaţional „Crescerea Competitivităţii Economice”(POS CCE)”-Rom. (Beneficiary: SPITALUL CLINIC de PNEUMOFTIZIOLOGIE IASI , Total value: 398.300,00 RON).

d) Research projects and publications in this field: “Adolescents smoking Cessation” - European project for smoking cessation in young people

As from 2003 a sum of European projects aiming smoking prevention and cessation in youth were started by the European Network for Young People and Tobacco, under the umbrella of the European Commission, Public Health Programme-Strand III, Health Determinants (http://ec.europa.eu/health/ph_projects/2003/action3/action3_2003_05_en.htm), the Welsh Assembly Government developed a programme of work on smoking cessation for adolescents and young people between 2003 and 2006. This work was part of the wider European Community Grant, ENYPAT Framework Project, Agreement number 2003306, which was run by the coordinating organisation, National Public Health Institute of Finland (KTL).

I was acting as the Adolescent Smoking Cessation project coordinator for Romania and led the development and evaluation of the programme in Romania.

Results from this European project have been disseminated by an article published in 2010 and are presented here below:

Approaching tobacco dependence in youngsters: impact of an interactive smoking cessation program in a population of Romanian adolescents

Antigona Trofor, Stefan Mihaicuta, Milena Adina Man, Ramona Miron, Valentina Esanu, Letitia Trofor


Introduction

Although most people are aware about deleterious effects of smoking over 30% of the world’s population is made of smokers. Nicotine, an alkaloid component of tobacco that has addictive capacities 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 (Benowitz et al, 2008; Benowitz et al, 2009). 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 and caffeine 5. Therefore, defined as a chronic addictive disease, chronic tobacco consumption or simply “smoking” has been recognized by psychologists as a disease by itself, inducing physical, psychological and behavioral disorders. This disease is named “tobacco dependence” or “nicotine dependence” and it is caused by dependence to nicotine, a highly addictive drug present in any tobacco product (Trofor et al, 2008). Moreover, in long term continuing smokers, chronic tobacco exposure has been proved to develop a wide variety of diseases, due to the numerous toxic compounds in tobacco.

*Problem formulation*

Statistics show high prevalence of smoking among young people. According to CDC data in 2005, 23% of high school students report smoking in the last month, compared to 21.3% in 2003 and 36.4% in 1997. The prevalence of any form of tobacco use among 14-18 years old students in us was 28% (Giovino, 2007). In Romania, espad study in 1999 showed 21% of romanians over 15 to be daily smokers (Trofor et al, 2009), and 34.8% of young people 15-24 years old were found current smokers (Romanian National Center for Health Politics and Services, 2007).

Among the 5 millions romanians to smoke, more than half began smoking before the age of 18. From these ones: 10.5% began in gymnasium (11-14 yrs old), 36.9% in high school (15-18 yrs old) and 37.7% when 19-24 years old (Romanian National Center for Health Politics and Services, 2007). Also, cumulative probability to initiate smoking under 15 has increased between 2003-2007 from 4% to 12.8% in girls and from 19% to 20.2% in boys (Trofor et al, 2009).

Several approaches have been used to approach adolescents: programs to prevent smoking initiation, developing intrapersonal and social competencies to avoid smoking in vulnerable circumstances like peer smoking, developing skills to resist social pressure to smoke. The most efficient programs are multi componential interventions to combine school based and local society interventions (Tonnensen, 2002).

In Romania, standard interactive smoking cessation interventions targeting adolescents became available only in 2005 by “adolescent smoking cessation” (ASC), a program designed by the welsh government assembly in collaboration with enypat (European Network For Young People And Tobacco) experts. ASC was successfully delivered in several European countries (United Kingdom, Sweden, Belgium, Spain, Greece, and Denmark) for the first time in 2004. In Romania, it was implemented in pilot phase in 2005, from behalf of the nongovernmental association “aer pur romania” when it was run in two cities: Iasi and Timisoara.

*Aim*

Asc program’s primary objective was to provide smoking cessation to smoking adolescents. The secondary objective of ASC was to raise awareness of both no smokers and smokers’ adolescents against tobacco use hazards and to promote a smoke free life style inside high school communities. This was done by assessing youngsters’ attitudes and beliefs towards tobacco dependence, compliance to smoking cessation interventions and success rate
of a standard smoking cessation program, when first implemented in a naive population of Romanian adolescents.

Participants and methods
The study was carried out on 231 subjects that participated in (ASC) program, in its pilot phase in Romania, in 2005. Prior to beginning the project’s sessions, program coordinators have contacted schools principals, to advertise asc and to invite schools to take part to it. In a second phase, schools included in asc had to inform teachers, students and parents about the program and to form mixed (smokers, ex smokers and no smokers altogether) groups of adolescents willing to be in ASC.

Subjects were recruited and evaluated based on the asc questionnaire, a validated set of questions about personal data, smoking and cessation profile, willingness to involve in asc whether current smoker or not. Smoking status (current, former or no smoker) was validated at inclusion on basis of carbon monoxide determination in exhaled air.

To preview nicotine dependence profile in adolescents, we applied a set of 3 questions (“would you like to give up smoking?”, “if smoker, do you find difficult to stop smoking when willing to?”, “did you ever try to stop smoking?”) (Statistics on smoking, 2008).

ASC program description
Along 3 months, study population was delivered 6 interactive asc sessions. In the first session, asc questionnaire was collected and smoking status was checked by carbon monoxide measurement in exhaled air. Also, subjects were explained what the program will consist of and the health benefits of quitting smoking. Interactivity between smokers, no smokers and facilitators was encouraged and the final (6th) session with prizes to reward quitting smoking was advertised. In sessions 2-5, students were given information on: different types of tobacco products and noxious tobacco components, dependence to nicotine in tobacco, active and passive smoking related diseases, smoking risk to pregnancy and motherhood, benefits of stopping smoking and methods to quit smoking. This was done in an interactive manner, with video-lessons and role-playing scenario. Such approach aimed to induce cigarette refusal skills and self esteem capacities in order to resist temptation to smoke in challenging situations as school or leisure time environment.

The 6th session was dedicated to a final evaluation, as impact of asc participation. Again, smoking status (smoking abstinence validated by carbon monoxide in exhaled air) and adolescents’ beliefs towards smoking & cessation were assessed by the asc questionnaire distributed for the second time at the end of the program. Also, in this final session, participants that were found quitters and reducers were rewarded by prizes.

During all 6 sessions, children received small incentives, snacks and refreshments to stimulate participation and, where possible, a festive session (smoke-free disco) was organized as a practical lesson to test adolescents’ readiness to stay smoke free.

Follow-up of participation rates/session was done in order to assess compliance to asc. Success rate of the asc program was appreciated by: a) primary outcomes (quitters and reducers ratio at the end of the program), b) secondary outcomes (compliance into asc reflected in participation rate/session and impact of asc on personal beliefs about smoking and
cessation). In interpretation of results, special consideration was given to the initial level of knowledge /acceptability of smoking and to predicted nicotine dependence, as impact factors on program outcomes.

**Results**

Eight high schools (4000 pupils in 9-12\textsuperscript{th} grade) were invited to subscribe asc. Study inclusion criteria were: parents and teachers agreement letter, scholar agenda and facilities, pupils’consent to take part in asc, carbon monoxide validation test, asc sessions participation rate > 66%. Thus, 231 adolescents 14-19 years old were selected to be enrolled in the asc project. Study population characteristics at inclusion were defined by asc questionnaire, which provided data about: gender and age distribution, smoking profile and cessation profile. 57.1% of study population were girls and 42.9% boys.

![Figure 1. ASC study group distribution by age (Trofor et al, 2010)](image)

As shown in Figure 1, girls and boys were almost equally represented in the study population and the same when compared by age, except 17 years old teenagers where girls were much more numerous.

**Smoking profile**

Smoking status defined by the five categories: every day smokers, at least once a week but not every day smokers, less than once a week smokers, used to smoke - actually stopped smoking and never smokers, with dynamics of these categories during the 6 weeks ASC project is shown in Figure 2.

This alows calculation of quitters and reducers rates, as the program’s primary goal was to determine adolescents to decline smoking.

![Figure 2. Smoking status dynamics during ASC program (Trofor et al, 2010)](image)
Cessation rate was 12.3% (15 among 121) in every day smokers and 16.6% (4 among 24) in at least once a week but not every day smokers. Also, 5 (4.1%) every day smokers and 8 (30%) at least once/week, not every day smokers reduced cigarettes.

Other smoking characteristics, considered useful in data interpretation are listed below:

1. Intensity of cigarette consumption ranged between 8 - 40 cigarettes/day in every day smokers and from 2 to 10 cigarettes in at least once/week but not every day smokers. Less than once a week smokers were mostly occasional experimenters to smoke at parties, in weekends and leisure time, between 1-5 cigarettes/month. Former smokers were not exceeding 10 cigarettes/day in the past, when they used to smoke.

2. Duration of smoking ranged between: 4 months – 3 years in every day smokers, 6-12 months in at least once/week but not every day smokers, 4-15 months in less than once a week smokers and 12 - 30 months in ex smokers.

3. Mean age of starting smoking was 12.6 years in every day smokers, 13.2 years in at least once/week but not every day smokers and 14 years in less than once a week smokers.

4. Indices to predict nicotine dependence in smoking adolescents: among every day smokers we found 37.2% to answer positively to all 3 questions in item III of the ASC questionnaire. Only 5 such smokers succeeded to quit.

Personal beliefs about smoking were evaluated both at the beginning and at the end of ASC sessions and the overall picture can be seen in Table 4.

**Table 4.** Personal beliefs about smoking at start (S) and end (E) of ASC. Response to question: “How far do you agree or disagree with these statements about smoking?” (Trofor et al, 2010)

<table>
<thead>
<tr>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Not sure</th>
<th>Agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Young people who smoke harm their health</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>E</td>
<td>S</td>
<td>E</td>
<td>S</td>
</tr>
<tr>
<td>22</td>
<td>4</td>
<td>31</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>(9.5%)</td>
<td>(1.7%)</td>
<td>(13.4%)</td>
<td>(2.6%)</td>
<td>(6.9%)</td>
</tr>
<tr>
<td><strong>Smoking increases your risk of heart attack</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>E</td>
<td>S</td>
<td>E</td>
<td>S</td>
</tr>
<tr>
<td>20</td>
<td>11</td>
<td>34</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>(8.7%)</td>
<td>(4.8%)</td>
<td>(14.7%)</td>
<td>(8.7%)</td>
<td>(8.2%)</td>
</tr>
<tr>
<td><strong>Smoking increases your risk of getting cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>E</td>
<td>S</td>
<td>E</td>
<td>S</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>35</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>(8.7%)</td>
<td>(1%)</td>
<td>(15.2%)</td>
<td>(1.2%)</td>
<td>(8.2%)</td>
</tr>
<tr>
<td><strong>Smoking makes you feel grown up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>S</td>
<td>E</td>
<td>S</td>
<td>E</td>
<td>S</td>
</tr>
<tr>
<td>56</td>
<td>81</td>
<td>34</td>
<td>72</td>
<td>8</td>
</tr>
<tr>
<td>(24.2%)</td>
<td>(35%)</td>
<td>(14.7%)</td>
<td>(31.2%)</td>
<td>(3.5%)</td>
</tr>
<tr>
<td><strong>Smoking is harmful to others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>E</td>
<td>S</td>
<td>E</td>
<td>S</td>
</tr>
<tr>
<td>80</td>
<td>3</td>
<td>67</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>(34.8%)</td>
<td>(1%)</td>
<td>(29%)</td>
<td>(4.8%)</td>
<td>(5.2%)</td>
</tr>
<tr>
<td><strong>Smoking is</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>E</td>
<td>S</td>
<td>E</td>
<td>S</td>
</tr>
<tr>
<td>74</td>
<td>28</td>
<td>56</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>(32%)</td>
<td>(12.1%)</td>
<td>(24.3%)</td>
<td>(14.7%)</td>
<td>(10%)</td>
</tr>
</tbody>
</table>
Most young people smoke | 18 (7.8%) | 73 (31.6%) | 24 (10.4%) | 89 (38.5%) | 18 (7.8%) | 4 (1.7%) | 92 (39.8%) | 54 (23.4%) | 79 (34.2%) | 11 (4.8%)

I don't mind if my friend smoke | 19 (8.3%) | 90 (39%) | 16 (6.9%) | 98 (42.4%) | 10 (4.3%) | 3 (1.3%) | 110 (47.6%) | 18 (7.8%) | 76 (32.9%) | 22 (9.5%)

Smoking helps you keep slim | 23 (10%) | 96 (41.6%) | 22 (9.6%) | 88 (38%) | 56 (24.2%) | 13 (5.6%) | 62 (26.8%) | 22 (9.5%) | 68 (29.4%) | 12 (5.3%)

Most adults smoke | 20 (8.7%) | 68 (29.4%) | 34 (14.6%) | 85 (36.8%) | 0 (0%) | 6 (2.6%) | 87 (37.7%) | 35 (15.2%) | 90 (39%) | 37 (16%)

**Cessation profile**

Own beliefs and attitudes towards cessation were evaluated both at the start of ASC and at the end. In the final session, program’s impact was appreciated also by a set of questions to preview future attitude of adolescents towards smoking. At the start of ASC, only 78 adolescents were very much motivated to quit smoking while 29 were less motivated and the rest of 42 not at all motivated. As regards personal beliefs about cessation, the following pattern was registered at project’s start:

- If deciding to quit: 65 (43.6%) subjects were very sure to be able to succeed, 47 (31.5%) quite sure and 48 not at all sure.

- A high ratio (64.2%) of smokers admitted they need professional help to quit smoking.

A second positive outcome of ASC was a high number of participants that have attempted to stop smoking for short time (one to several days) at least once, during the program. Thus, we have found the following data:

- 103 (66.9%) subjects among 154 still smoking at the end of ASC have stopped smoking at any time during the project, even if only temporarily (36 once, 42 twice and 25 three times).

- The longest period they managed to stay smoke-free was more than 3 weeks, up to 4 weeks in 8 subjects.

To appreciate ASC’ impact on participants we reviewed their answers when asked about:

- To what extent did the program help them to quit/attempt quit/cut down? (77.8 % answered “yes”).

- How confident are you that you would not be smoking cigarettes this time next year? This question was focusing on those that had attempted to quit and were still stopped at the end of the project - (12 subjects answered „very confident”, 6 as „fairly confident”, while just one as „non confident”)

- By the end of the program, how aware are you about smoking cessation and where to go for support? (Table 5, for answers).
Table 5. How aware were participants about smoking cessation at the end of the ASC program? (Trofor et al, 2010)

<table>
<thead>
<tr>
<th>Strongly disagree n (%)</th>
<th>Disagree n (%)</th>
<th>Not sure n (%)</th>
<th>Agree n (%)</th>
<th>Strongly agree n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I now have better understanding of how to quit smoking</td>
<td>8 (3.5%)</td>
<td>6 (2.6%)</td>
<td>3 (1.3%)</td>
<td>97 (42%)</td>
</tr>
<tr>
<td>I now have better understanding about where to go for help about quitting</td>
<td>3 (1.3%)</td>
<td>6 (2.7%)</td>
<td>9 (3.9%)</td>
<td>132 (57.1%)</td>
</tr>
<tr>
<td>I now have better understanding of why it is important to quit smoking</td>
<td>2 (0.8%)</td>
<td>1 (0.4%)</td>
<td>0 (0%)</td>
<td>117 (50.6%)</td>
</tr>
<tr>
<td>I now have better understanding of the effects of smoking</td>
<td>3 (1.3%)</td>
<td>1 (0.5%)</td>
<td>2 (1%)</td>
<td>131 (56.6%)</td>
</tr>
</tbody>
</table>

Another parameter useful to assess program’s impact was compliance of participants, appreciated by participation rate/session, as in Figure 3. Here it is revealed the project benefited a high interest, with optimal attendance rate/sessions, over 85.2%. Moreover, all participants in sessions 1 and 6 had carbon monoxide tests, for study data validation.

Discussion

ASC results provide strong support for the efficacy of interactive smoking cessation programs in adolescents, particularly within a naive population. Overview of literature in the field showed comparable 6.8 to 12.3% smoking cessation rate in young daily smokers of 1-9 to >10 cigarettes/day (Sargent et al, 1998). Also, comparison between data in Romanian ASC and ASC in other European countries showed great variability: 14% quitters in Denmark, 9% in Slovakia, 0% in Netherlands and 35% in Wales (the ASC mother country) (Trofor et al, 2009).

Pilot ASC results need to be analyzed within context of ASC study group structure (small sample of teenagers, being part of a pilot European project delivered by volunteers, low funding), and weak legislation at the time (tobacco advertising and smoking in public places was still allowed in 2005). Yet, the program was very welcomed in Romania, especially when compared to other countries where ASC was delivered (and where only 57%
of participants attended all sessions - ranging from 100% in Netherlands to 18% in Denmark) (Trofor et al, 2009). When questioned in the first session about hazards of smoking, subjects agreed smoking harms young people’s health in 70.1 %, increases risk of heart attack and cancer in 68.4 %. By the end of ASC, perception about health risks of smoking changed: 95.7 % agreed smoking ‘health risks, 86.6% were aware that smoking induces heart attack and 97.8% linked smoking to cancers. Acceptability of smoking decreased due to ASC from 80.5 to 17.3 %, as a good impact of the program. Similar analysis from a survey when subjects asked whether “smoking was OK for someone their age just to try to see how it is”, revealed 38 % of pupils to answer “yes” in 2007 (General Household Survey, 2006). Immediate benefit of ASC was appreciated based on: high ratio (66.9%) of attempts to stop smoking, majority of quitters to be confident in a successful quit attempt and perceived support given by ASC for quit attempts in 77.8%.

Better understanding (over 90% in average) of how to quit smoking, where to go for help about quitting, why is it better to stop smoking and increased awareness about effects of smoking, as shown in table II allows optimistic estimates of the long term impact of the program. As it worked by peers, young facilitators, by putting together active and former smokers with never smokers, by interactive sessions, incentives and prizes, ASC provided insights into what works and what does not work in delivering smoking cessation in adolescents (Fiore et al, 2008).

Conclusions
ASC pilot project run in 2005 was the first expert smoking cessation program delivered to Romanian adolescents. 12.3% of every day smokers and 16.6% of at least once a week but not every day smokers succeeded to quit smoking. Impact of ASC program on smoking and cessation beliefs and attitudes was positive in 90 % of participants. As Romanian ASC in 2005 was successful for both adolescents and facilitators, it became a national program run in 2007-2008 in partnership between Aer Pur Romania and Romanian Health Ministry. Lessons from ASC sustain recommendations to approach smoking cessation in teenagers by always asking about tobacco use, routinely advice to quit, provide accessible and appropriate therapy focusing on peers, incentives and interactivity and in respect to this age category smoking profile.

1.7. Assessing the impact of active and passive smoking on the respiratory system

1.7.1. Biomarkers of tobacco exposure in current clinical

use A. State of the art

It is well known that cigarette smoke contains approximately 4000 chemicals including 50 proven carcinogens that are delivered either actively, via inhaled tobacco smoke into the lungs, through active smoking, or passively from the environment where exhaled smoke exists.
Biological assessment of smoking effects refers to some specific biomarkers, allowing objective proof of tobacco exposure, like carbon monoxide (CO) in exhaled air, cotinine (a nicotine metabolite that can be measured in plasma, saliva, urine, hair and intranasally) but also anatabine, anabasine, thiocyanate, uric acid and nitric oxide (NO), identified by more recent research (Lisko et al, 2013).

Carbon monoxide can be most easily monitored and represents an indicator of sure tobacco consumption. CO concentration in a smoker’s body is determined if the patient exhales in a CO analyzer. The CO unit is ppm (parts per million), a parameter that can be converted to equivalent % carboxyhemoglobin reading, by a micro smokerlyzer device (Figure 4). The toxicity of CO is influenced by blood saturation, CO level in the air and breath air volume. Additional factors like environmental pollution (exhaust gas), passive smoking, professional exposure or smoke from biomass/coal burning may induce confusion in interpretation of CO values, yet active smoking remains the major cause to increase CO levels. In normal conditions, in non-smokers, exhaled CO is < 4 ppm. Careful interpretation of CO is required in some special situations, when CO levels may register higher than estimated values, such as in COPD smokers, for example. In these patients, a higher CO ratio is either explained by the production of CO as a result of the chronic airway inflammatory processes in COPD, or it is simply due to the more intense smoking described by this category of patients (Behrakis, 2012). Jimenez Ruiz and colleagues reported higher CO levels in COPD versus non-COPD smokers: 19,7 ± 16,3 vs. 15,4 ± 12,1 ppm (p<0.0001) (Jiménez-Ruiz et al, 2001). The measurement of exhaled CO and NO may represent a new method for the noninvasive monitoring of airway inflammation and oxidant stress in COPD ex-smokers. Exhaled CO and NO are strongly affected by cigarette smoking, which limits their usefulness in tobacco exposed COPD patients (Montuschi et al, 2001).

CO measurement has also been used as a tool to enhance patient motivation to quit. The fast conversion of CO to normal values encourages the smoker to be abstinent and thus demonstrates lower CO values at each follow-up visit, which supports the quitting attempt. Given its value, as a motivational tool it is recommended that specialized smoking cessation centers should be equipped with a CO analyzer (ENSP, 2016).

![Figure 4. Expiratory carbon monoxide (CO) monitoring device (micro smokerlyzer)](https://covita.net/comonitors.html)
Cotinine is another biomarker for tobacco use. Cotinine is the main metabolite of nicotine and is a biomarker of exposure to tobacco smoke. By monitoring the concentration of cotinine in the body, one can assess an individual’s tobacco smoke exposure. Cotinine can be measured in blood, hair, saliva and urine. The half-life of nicotine is about two hours; however nicotine concentration can vary depending on the time of the day when the last cigarette was smoked (Benowitz, 2002). Cotinine has a half-life of 15-20 hours and as such can be used to measure 24-48 hour smoking abstinence. In smokers, plasma cotinine is about 200 ng/ml, but may reach up to 1000 ng/ml depending on the intensity of smoking (West et al, 2005). There is considerable variation among individual smokers in levels of cotinine and daily intake of cigarettes (Benowitz, 2002; West et al, 2005; Jarvis et al, 2003). Rates of nicotine metabolism are genetically determined and can influence cotinine levels. A cut-off of < 15 ng/ml for saliva and of 50 ng/ml for urine is recommended (Benowitz, 2002; West et al, 2005; Jarvis et al, 2003). In situations where the patient is using nicotine replacement therapy, measurement of cotinine is not recommended. In these cases CO monitoring is the preferred method of validation (ENSP, 2016). As such, cotinine assessment is not at the present time recommended as a tool for guiding clinical practice, but is most valuable in clinical research units (ENSP, 2016).

The passive smoking or second hand smoking (SHS) contains respiratory irritants, thus it may adversely influence the clinical course of respiratory conditions, especially in COPD. In an analysis of cross-sectional data from the UK’s annual health survey, based on self-declared passive smoking, Jordan and colleagues have shown a significant dose-response correlation between hours of exposure and increased COPD risk, in terms of clinically significant airway obstruction and symptoms and a two-fold increase COPD risk among never smokers, when exposed > 20 hours per week (Jordan et al, 2011). Exposure to SHS can be measured by: self-reported indicators of exposure through interviews or questionnaires, measuring tobacco smoke components in the air to which subjects are exposed (environmental measurements) or by measuring concentration of tobacco smoke compounds in the body of the exposed subjects (biomarkers) (Florescu et al, 2009). Such biomarkers for current use in clinical practice are carbon monoxide (CO) concentration in exhaled air, to certify recent, 4-5 hours exposure and cotinine (a metabolite of nicotine) for past, no longer than 3 days exposure. Cotinine is considered the preferred biomarker of SHS exposure, as shown in Table 6.

Table 6. Published values of cotinine in plasma, urine, and saliva* by exposure level

<table>
<thead>
<tr>
<th>Matrix (ng/mL)</th>
<th>Unexposed non smokers</th>
<th>Passive smokers</th>
<th>Active smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>0.09-0.7</td>
<td>2-10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Urine</td>
<td>&lt;10</td>
<td>10-100</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Saliva</td>
<td>0-5, 0.182</td>
<td>5-10</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Source: Florescu A. et.al., Values reported by the California EPA Report (2004) and Bramer and Kallungal
B. Personal contributions

**Scientific, professional and academic achievements in this field**

a) Professional training in this field:

- training in carbon monoxide in exhaled air assessment techniques: Bucharest, 2000

- training in the field of “Treatment of tobacco use and dependence” (Certificate series E, Nr. 07505/14.12.2004) and “Cognitive-behavioral techniques for treating tobacco use and dependence” (Certificate series E, Nr.07816/27.01.2005), provided by Health Ministry - National Center for Post-university studies training development for Health Professionals - Bucharest.

b) Research and publications in this field:

My early research in this broad, new domain has materialized in two publications about the assessment of carbon monoxide in exhaled air of smokers with respiratory diseases addressed to the Clinic of Pulmonary Diseases and of smokers with COPD enrolled in a smoking cessation program.

<table>
<thead>
<tr>
<th>Efficacy of assessing carbon monoxide in a smoking cessation programme for patients with pulmonary disorders</th>
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**Brief summary**

Smoking status was validated by carbon monoxide (CO) measurement in exhaled air in 88 smokers with pulmonary tuberculosis (TB) and in 32 smokers with COPD (all patients were hospitalized). In 2 weeks follow up, there was a discrepancy between self declared non smoking status (51.9% ) and validated exhaled CO abstinence (29.4%) among the TB smoking patients. In the COPD group, data were comparable. **Conclusion:** Introducing CO validation for smoking abstinence adds value to smoking cessation counseling in patients hospitalized for pulmonary disorders, by objective proof of patients’ smoking status.
Efficacy of monitoring carbon monoxide during a smoking cessation program for COPD patients with chronic tobacco consumption

Antigona Trofor, Cristina-Elena Danciu

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Iasi, 4-6 March 2005, p. 634-6, ISBN 973-7906-62-4

Abstract

Aim: to improve the clinical status of COPD patients by smoking cessation. To obtain objective data during quitting smoking and to demonstrate test’s feasibility. Material and method: 32 smoking patients hospitalized for COPD were evaluated for COPD severity in relation with their smoking status. Smokers willing to quit were assessed carbon monoxide (CO) in exhaled air in follow up. Results: in the target group of COPD heavy smokers (59.5%), with severe nicotine dependence (41%), only 34.3% agreed to receive smoking cessation treatment. High levels of exhaled CO were found in 2 weeks follow up in 39.3% of the cases, respectively in 28% at the final CO test. Conclusion: smoking cessation is beneficial in COPD patients and monitoring CO during smoking cessation process has increased efficacy of the smoking cessation therapy.

Remaining in the same area of study of the biomarkers of tobacco exposure and their usefulness in managing respiratory diseases in smokers versus non-smokers, later in developing this research area, I was preoccupied in identification of a more reliable and practical application of these diagnostic and treatment monitorization tools. In the same time, I tried to define those biomarkers that are the most relevant, but also inexpensive and easy to use in clinical practice of a respiratory disease service in charge with smoking patients.

The results are available in an article published in the IDB (International Data Base) indexed journal Romanian Journal of Oral Rehabilitation in 2014, detailed here below:

Biomarkers of tobacco exposure-relevant diagnostic implications in daily practice

 Ramona Miron, Letitia Trofor, Daniela Bucur, Milena Adina Man, Roberta Cernat, Antigona Trofor


Abstract

Aim of the study was to present available data on biomarkers of tobacco exposure and to inform about their utility in daily practice, focusing on expertise in the field in the Clinic of Pulmonary Diseases of Iasi, Romania.
Data overview. Smoking status declared by patients must be objectively validated by biochemical tests to determine biomarkers of tobacco exposure. The main biomarkers utilized by practitioners are: carbon monoxide in expired air and plasma, saliva, urine, hair and intranasal cotinine. More recently, researchers have studied also the role of some new biomarkers: anatabine, anabasine, thyocianate, serum uric acid and nitric oxide in expired air. We present up to date data about advantages and disadvantages of each such biomarker and practical details on clinical use, as some of them are also markers of chronic airway inflammation.

Conclusions. Laboratory tests for tobacco biomarkers offer the opportunity to measure constituents of tobacco smoke and to show exposing to toxicants in tobacco, regardless smoking behavior. In daily clinical practice of the Clinic of Pulmonary Diseases of Iasi have been successfully introduced carbon monoxide and nitric oxide in exhaled air, serum uric acid and urinary cotinine determinations.

Introduction

Tobacco smoking is the single greatest cause of preventable premature death worldwide. Well known as the main risk factor for lung cancer, tobacco use also promotes the development of vascular disease and, thus, is at the origin of ischemic and peripheral heart disease and stroke. Epidemiological studies have confirmed the contribution of active smoking to cardiovascular risk, by finding an odds ratio (OR) for acute myocardial infarction of 2.87 for current versus never smokers (Yusuf et al, 2004). Moreover, exposure to passive smoking has been found to increase the risk of cardiovascular disease by approximately 30%, more than would be expected based on comparable amounts of active exposure to tobacco smoke (Barnoya et al, 2005).

Nowadays, despite scientific evidence about harmful effects of tobacco, almost one-third of the global adult population currently smokes. Even if strong expert decision exist to eliminate smoking for reducing cardiovascular disease, the World Health Organization estimates that worldwide, the number of smokers is expected to increase from 1.3 billion to 1.7 billion by the year 2025 (Guindon et al, 2003).

Whether so called usually as smoking or its synonym - tobacco use and dependence -, this is considered by all current manuals and guidelines as a chronic relapsing disease, due to nicotine, an addictive component present in any tobacco product. Thus, it is unanimously recommended to mandatory identify and treat any smoker to quit (Behrakis et al, 2012). Diagnosis of tobacco dependence takes into account both clinical and biological evaluation of smoking/tobacco use, together with a psycho-behavioral evaluation. Biological (laboratory diagnosis) refers to some specific biomarkers, allowing objective proof of active or passive tobacco exposure, such as: carbon monoxide in exhaled air, cotinine (a nicotine metabolite that can be measured in plasma, saliva, urine, hair and intranasally), but also the more recently identified anatabine, anabasine, thiocyanate, uric acid and nitric oxide (Lisko et al, 2013).

Clinical diagnosis of tobacco use and dependence

Before more in depth approach of the biomarkers importance for daily practice of assisting smoking patients, we shall briefly describe below the criteria for clinical diagnosis of tobacco (nicotine) dependence, as defined by the most recently agreed European smoking
cessation guideline, published in 2012 (Behrakis et al, 2012). So, basic clinical evaluation should consider:

- **Smoking status** (smoker/ex-smoker/non smoker); smokers are defined as at least 6 months daily consumers, while ex-smoker have quit since 6 months minimum.

- **Type of tobacco product** (knowing that certain products are more harmful than others, for example risk of oral cancer is higher in cigars and pipes vs cigarette smokers [Trofor et al, 2005]).

- **Intensity of tobacco consumption**, as quantified by *number of packs-years* for cigarette smokers, respectively number of pipes, cigars, amount of tobacco chewed –in grams-, etc. Number of packs-years (PY) is calculated as number of cigarettes smoked daily/ 20 (a standard cigarettes pack has 20 cigarettes) x number of years of smoking.

- **Nicotine dependence score** is resulting from the Fagerstrom nicotine dependence test - a sum of 6 items questionnaire, most importantly querying about time of first cigarette smoked at awakening. The dependence score is calculated based on answers to all 6 questions, like mild (0-3), moderate (4-6) or severe (>7) addiction to nicotine.

- **Medical history** of a smoker is relevant generally, but especially for any tobacco related disorder imposing immediate cessation or any concomitant disorder like anxiety, depression, myocardial infarct, stroke, anorexia, skull and brain injury, dermatological affections, etc., that might ask cautions of the tobacco cessation pharmacotherapy.

- **Analysis of previous attempts to stop smoking** is crucial to prevent smoking relapse and to identify risk factors for a severe nicotine dependence or to find explanations for unsuccessful treatment. In this view, one should expect smokers feel more difficult to quit during the first 6-8 weeks after stopping tobacco use. Due to absence of nicotine provided to the body via tobacco smoke, patients might describe a “nicotine withdrawal syndrome”, consisting of: acute/uncontrollable need to smoke (craving), irritability, restlessness, depressive mood, increased appetite (especially for sweets), trouble to concentrate and focus memory, headaches, insomnia and sometimes dizziness.

When available, clinical evaluation of smokers should be supplemented with a psychological evaluation, aiming diagnosis of behaviour disorders, but also an inventory of depressive symptoms and a motivational interview about personal perception of the quitting smoking process.

**Laboratory diagnosis of tobacco exposure**

Smoking status established on basis of the above mentioned clinical criteria, when also declared by the patient, must be objectively validated by biochemical tests to determine biomarkers of tobacco exposure. These ones were developed as specific tools to assess human body exposure to tobacco products. They offer a possibility to measure components and toxicants inside tobacco smoke, independently of smoking behaviour, which means even if a subject is not a smoker, but is passively exposed to smoking by others, tobacco traces can be detected into the body of the non smoker. It seems use of only one such biomarker won’t completely satisfy the smokers’evaluation, thus several biological assessments are recommended, in current clinical practice. The main biomarkers utilized by practitioners are: carbon monoxide in expired air and cotinine (a metabolite of nicotine) that can be measured in plasma, saliva, urine, hair and intranasally. Actually, researchers have studied also the role of
some new biomarkers: anatabine, anabasine, thyocianate, uric acid and nitric oxide. Same time, biomarkers of tobacco carcinogenesis, like: 1-hydroxypyrene (1-HOP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides (NNAL-Gluc), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and 8-Oxo-7′,8′-dihydro-2′-deoxyguanosine (8-oxo-dG) in urine, were approached in various studies (Hecht et al, 2003; Boffetta et al, 2009; Hecht et al, 2010).

Further, we shall detail most used biomarkers in daily clinical practice of assisting smokers-patients and their implications for clinical diagnosis. We shall insist on these ones available in the Clinic of Pulmonary Diseases of Iasi, at present.

**Carbon monoxide (CO)** can be most easily monitored and represents an indicator of certain tobacco consumption. CO concentration in a smoker’s body is determined if the patient exhales in a carbon monoxide analyzer. The CO unit is ppm (parts per million), a parameter that can be converted to equivalent % CO Hb carboxyhemoglobin reading, by a micro smokerlyzer device. Toxicity of CO is influenced by blood saturation, CO level in the air and breath air volume. Additional factors like environmental pollution (exhaust gas), passive smoking, professional exposure or smoke from biomass/coal burning may induce confusion in interpreting CO values, yet active smoking remains the major cause to increase CO levels. In normal conditions, in non-smokers, exhaled CO is < 4 ppm.

The European Smoking Cessation guideline of the European Network for Smoking Prevention (Behrakis et al, 2012) has stated the 7 ppm limit of CO level to distinguish active smokers from non-smokers (Behrakis et al, 2012). Also, cautious interpretation of CO is required in some special situations, when CO levels may register higher than estimated values, such as in smokers with COPD, for example. This is due to either greater CO production resulting from more intensive inflammatory process of the chronic obstructive pulmonary disease, or from more intensive smoking usually is seen in this category of patients (Susumu et al, 2003).

**Figure. 5.** Micro Smokerlyzer – Smoking cessation center of the Clinic of Pulmonary Diseases Iasi (Miron et al, 2014)

In the tobacco cessation center of the Clinic of Pulmonary Diseases of Iasi, routinely determination of CO in exhaled air of smokers attending our unit has been introduced since 2000, with various equipments, continuously improving our technique and resources until nowadays (Figure 5). Usually, in our current practice of assisting smokers to quit, we correlate CO assessments with “lung life”small instrument results. This is an easy to manipulate device, very useful for an interactive manner to involve patients in the process of stopping smoking. After blowing into the “lung life” device, it will display lung function
(FEV) values, together with estimated age of the patient’s lung, adjusted with age, gender, race and height. If a patient smokes, his/her age will appear older, in a dose-relationship with number of packs-years of cigarette consumption. This diagnostic tool is currently in use in the practice of our smoking cessation center, since 2009 (Figure 6).

![Image of "lung-life" device](image)

**Figure 6.** The “lung-life” device - Smoking cessation center of the Clinic of Pulmonary Diseases Iasi (Miron et al, 2014)

*Thiocyanate* is another marker of tobacco exposure as tobacco smoke contains significant amounts of hydrocyanic acid (hydrogen cyanide), which will be converted in the body into thiocyanate; it can be measured in serum, urine and saliva. Thiocyanate lacks specificity as a marker of involuntary smoking, primarily because of dietary contributions from cyanide-containing foods, such as almonds, or from the presence of thiocyanate itself in certain cruciferous vegetables such as cabbage, broccoli, cauliflower, horseradish, garlic and also in beer. Still, it is good to know that much smaller amounts are found in food compared to tobacco smoke. Serum level of thiocyanate is also influenced by industrial exposure to cyanides in metallurgy, by electrolysis, precious metal refining, case hardening of steel and gas and in the chemical industry, also by processing of the photos.

Although most recent research reported significantly increased levels of thiocyanate in active vs. passive smokers, respectively vs. non smokers, yet, its lack of specificity limits routine use of this lab test for detecting aggression from tobacco smoke (Bottoms et al, 1982). It is unanimously recommended a threshold of $> 60\mu\text{mol} / \text{L}$ for distinguishing smokers from non smokers (Morabia et al, 2001).

*Cotinine* is considered the „gold standard” biomarker to prove contact with tobacco products and the most useful in dividing smokers from non smokers, also to check level of inhaled nicotine and any passive („second-hand”) tobacco smoke presence. Nicotine enters the body at skin level, also by respiratory and by digestive way. Besides tobacco, another source of nicotine may be delivered in some vegetables (potatoes, tomatoes, cauliflower and cabbage, as well as black tea and coffee). So, confusion may intervene with false tobacco exposure; it was estimated that a medium daily consumption of tomatoes, potatoes, cauliflower together with black tea could bring 8.8 $\mu\text{g}$ nicotine/day, which equals 0.7 ng/ml, thus less than the recognized level of exposure to nicotine from tobacco (Davis et al, 1991).
Cotinine is a metabolite of nicotine, to be used as an indicator of exposing to the drug delivery via tobacco, because it stays more than 24 hours in the blood. While nicotine has a half-life of approximately 2 hours, in turn, cotinine has 15-20 hours (Fagerstrom, 2008). Cotinine can be determined in blood, saliva, hair and urine (Trofior et al, 2010).

a) **Hair cotinine** is a good, cheap, non-invasive indicator of long term tobacco use, in both smokers and non-smokers. Benefits and disadvantages of using hair versus salivary cotinine or salivary versus urinary cotinine were compared in various studies. When it comes to hair versus salivary cotinine, researchers have shown superior long term outcomes for hair samples: allowing 1-3 months exposure estimates, it is easier to collect and manipulate the hair samples, it needs only 30 mg of hair to detect cotinine as 0.05 ng/mg hair. In exchange, it takes 0.5 ml of saliva to evidentiate cotinine in 0.05 ng/ml, but salivary test of cotinine is interpretating a short term (1-2 days) exposure and saliva samples are more difficult to handle. Yet, some cautions should be taken in relation to any hair treatment or colour (Kim et al, 2009; Florescu et al, 2007).

b) **Salivary cotinine** was studied to link cigarette smoking to cotinine levels in saliva. A Romanian study done in Constanta analyzed correlation between concentration of salivary cotinine and parodontal health status in smokers of 15 to 19 years old. By using the NicAlert™ Saliva tests, saliva samples from 362 active smokers were tested to evaluate cotinine fraction, based on last 48 hours tobacco consumption. This was a significant determination of the salivary cotinine. The “cut-off” level for the NicAlert™ assessment is of 10 ng/mL. It is a rapid method; interpretation of results is done after 20 minutes, but quite expensive (39$ for only two determinations). A subject is considered as a non smoker or passive smoker if salivary cotinine ranges 0-10 ng/ml; as an occasional/moderate smoker when a 10-100 ng/ml salivary cotinine range and as an active smoker if saliva cotinine concentration is 100-1000 ng/ml (Nuca et al, 2010).

In a previous study published in 2000, salivary cotinine varied between 0 to 838 ng/ml (with a mean of 166 ng/ml). Every supplemental cigarette/day was associated to an increase of 14 ng/ml in salivary cotinine and established limit to distinguish between smokers and non smokers was 7-13 ng/ml, somehow below other already recognized “cut-off-s” such as 10, 44, or even 100 ng/ml (Etter et al, 2000).

c) **Urinary cotinine** determination allows few advantages, compared to serum quantification of cotinine: is not so invasive and shows a significant difference between smokers and non smokers. But, there are also some shortfalls; for instance, during smoking cessation with nicotine substitutes, cotinine from nicotinic pharmacotherapies may add to cotinine provenient from tobacco, so overlapping levels may induce confusion in interpretation of results. As well, collecting and storage of urine sample is more costly and laborious; also lab results are not so immediate as for carbon monoxide, for instance, a fact that might delay therapeutic interventions (Stevens et al, 2004).

Optimal proposed limit to differentiate active smokers from non smokers was 100 μg/g for cotinine in urine (Stevens et al, 2004). Heinrich-Ramm et al. have demonstrated that urinary cotinine is accumulating in a dose-relationship with number of cigarettes smoked daily (p < 0.0001). Each cigarette is supplementing with approximately 41μg/g of creatinine the level of cotinine in urine. These authors have found a mean urine cotinine in non smokers
200 folds lower, compared to active smokers found with 5.0 μg/g of creatinine (Heinrich-Ramm et al, 2002).

Concentration of urinary cotinine in relation to plasma cotinine may be affected by several factors like urinary flow rate, urine ph and renal function. So, in 2009, Benowitz demonstrates that measuring urine cotinine, after adjustment with creatinine levels, seems to be the best predictor for plasma cotinine correct values (Benowitz et al, 2009).

On the market, there are also available qualitative tests of cotinine in urine, less expensive and more rapid, resembling to pregnancy tests, by also displaying a positive or negative result (read after only 5 minutes) (Figure 7).

![NicCheck®]

**Figure 7.** Urinary cotinine test- qualitative determination method applied in the Smoking cessation center of the Clinic of Pulmonary Diseases Iasi (Miron et al, 2014)

d) **Plasma cotinine** can be measured by a quantitative method, yet invasive and sometimes difficult to apply, especially when collecting samples in children. A plasmatic cotinine of less than 15 ng/ml is considered probative for a non-smoking status. In smokers, cotinine level is around 200 ng/ml, but it can reach to 1000 ng/ml, depending on smoking intensity (Trofor et al, 2010).

Numerous studies have tried to find correlations among levels of cotinine in plasma and other tobacco impregnation biomarkers. One of these studies has analyzed CO comparatively to cotinine from plasma in 207 participants and found that it is preferably to use cotinine when assessing long term tobacco abstinence, except in patients treated with nicotine substitution therapy (Jatlow et al, 2008). In a study showing for the first time a significant correlation between plasma cotinine levels and risk of pancreatic cancer (PC), it was observed an increasing risk of PC in subjects with serum cotinine > 1187.8 nmol/L (level corresponding to a number of 17 cigarettes smoked daily), by comparison to subjects with serum cotinine having < 55 nmol/L (OR: 3.66, 95% CI: 1.44-9.26). The highest PC risk was revealed in smokers of more than 30 cigarettes/day versus non smokers (OR: 4.15, 95% CI: 1.02-16.42) (Leenders et al, 2012).

e) **Cotinine determined in nasal lavage fluid**

Nasal mucosa is directly exposed to cigarette smoke in both active and passive smokers. Agression from tobacco smoke manifests through reduced olfactory function; on the other hand, in smokers treated by nasal spray with nicotine for quitting smoking, side effects like nasal irritation or burning and impaired smell were also described. Only one study exists that determined levels of cotinine in nasal lavage, to estimate exposure to tobacco smoke. It
resulted that cotinine levels in nasal lavage were significantly higher in smokers versus non-smokers. Optimal "cut-off" limit used by these researchers was of 1.0 ng/ml for distinguishing smokers from non-smokers, with a sensibility of 91% and a 99% specificity. Yet, it is to keep in mind that this method of quantifying nasal cotinine concentration indicates furthermore direct injury of smoking on the nasal mucosa (Ozdener et al, 2009).

**Serum uric acid**

Uric acid is a degradation product from nucleic acids and the final result of the purine oxidation process. Uric acid is transported by the blood plasma from the liver to the kidneys, where it is filtered and then excreted in a percentage of 70%. The rest of uric acid is eliminated and degraded into the gastrointestinal tract. Its normal value in the human body is influenced by food, gender, age, genetic factors, physical effort and physiology (Ames et al, 1981). It acts like a valuable antioxidant, including against oxidative stress caused by chronic tobacco smoking.

Literature in the field described a significant low level of uric acid in smokers, in a dose-relationship with cigarette consumption; also, a higher uric acid level was demonstrated in former smokers (6.18 mg/dL vs. 5.98 mg/dL in current smokers) (Hanna et al, 2008; Tomita et al, 2008). In a study in 2010, to examine the effect of cigarette smoking on plasma uric acid concentration and to determine the correlation between this parameter and the biological tobacco markers like plasma thiocyanate and urinary cotinine, plasma uric acid concentration was significantly lower in smokers than in nonsmokers. As well, among smokers, authors noted a negative correlation between uric acid and both plasma thiocyanates (r = -0.437; p < 0.05) and urinary cotinine (r = -0.580; p < 0.05). The significant low plasmatic uric acid in smokers was attributed to a reduction of the endogenous production as a result of the chronic exposure to cigarette smoke (a significant source of oxidative stress). Considering these data, it is recommended to stop or to reduce smoking and to introduce plasma uric acid estimation as a routine test, since it is cheap and simple to reflect the antioxidant level (Haj et al, 2011). This determination is currently available in the Clinic of Respiratory Diseases of Iasi.

Other data showed increased values of uric acid and reactive protein C in active smokers towards passive smokers and non-smokers (Boshtam et al, 2006). Such conflicting evidence suggests more research is needed to define the role of uric acid as a useful biomarker for tobacco use and cessation.

**Expired nitric oxide (NO)**

NO or the endothelium derived relaxing factor is produced in endothelial cells and it is synthesized by the oxidative process of the guanidine of the amino acid L-arginine by a family of enzymes named NO synthases (NOS’s). NO is a potent vasodilator of the smooth muscle. NO diffuses from the alveoli to vascular smooth muscles, it stimulates guanylate cyclase leading to increased intracellular $cGMP$, which triggers smooth muscle relaxation and vasodilation. Chronic smoking influences endothelial function, reduces formation of nitric oxide and increases degradation of nitric monoxide by generating reactive oxygen species (Toda et al, 2010).
Inhaled tobacco smoke has chronic and acute effects on nitric oxide values. Researchers have signaled lower NO levels in smokers (Kharitonov et al, 1995). NO level is increasing after stopping smoking (Hogman et al, 2002). Cigarette smoke has been shown to induce deterioration of the respiratory epithelium (which is responsible for NO production); so decline in NO level can represent a sign of respiratory destruction. Alternatively, cigarette smoke can inhibit NO production by unidentified yet genetic mechanisms. Another proposed explanation is that the existing high CO level in smokers’airways can determine a fall in exhaled NO, as NO synthases is a cytochrome P450 hemoprotein, possibly inhibited by a great CO concentration (White et al, 1992).

Many studies have demonstrated low levels of NO in smokers and high levels of NO after smoking cessation. Travers et al., in 2007, found NO levels with 1.18 (95% CI, 0.92–1.51; p = 0.20) higher in non smokers than in current smokers and with 1.13 (95% CI, 0.97–1.31; p = 0.11) higher than in former smokers. They established as reference NO value in normal subjects a limit of 7.8 - 41.1 ppb (Travers et al, 2007). In 2010, Tramontini et al. described twice more high levels of the expired NO in non smokers: 20.1 ppb (17.7-27.8) (p<0.001), towards smokers: 10.8 ppb (7.8-15.3) (Tramontini et al, 2010).

Exhaled NO is also a well-studied marker of airway inflammation and of oxidative stress and is increased in lung diseases such as asthma (Kharitonov et al, 1996) and bronchiectasis (Kharitonov et al, 1995). In contrast, exhaled NO is decreased in healthy chronic smokers (Kharitonov et al, 1995). Exhaled NO is also increased during COPD exacerbations (Maziak et al, 1998), whereas conflicting results have been reported in stable COPD patients. One study (Corradi et al, 1999) showed higher NO levels in ex-smokers with COPD, compared to healthy nonsmokers and in current smokers with COPD, compared to healthy current smokers. Two studies did not show any difference in NO concentrations between subjects with COPD and healthy subjects (Rutgers et al, 1998).

NO is easy to measure and is very useful for clinical assessment of the smoking status, as well in evaluating of the above mentioned chronic airway disorders, by monitoring airway inflamation. Exhaled NO values are more stable to monitor, as they modify every few days, unlike the CO monitorization, as CO values are more dynamic, changing every few hours. NO determination in exhaled breath has been introduced since last decade in the routine practice of the Clinic of the Pulmonary Diseases Iasi, as a valuable biomarker of the airway inflammatory process in asthma and COPD, in particular and for showing effects of chronic exposure to tobacco smoke. The NIOX MINO (Figure 8) is provided with a filter free of NO and with a sensor especially designed to provide electronic signals to NIOX about exhaled breath samples. Measurements are done by a deep inhalation to total lung capacity through the special filter, followed by an exhalation through the filter, done for 10 seconds. To wait for results, it takes 1:40 min.
Biomarkers of exposure to tobacco smoke involved in carcinogenesis

Among many known carcinogenic agents in tobacco smoke, the most important are considered: polycyclic aromatic hydrocarbons (PAH), N-nitrosamines, metals, aromatic amines, heterocyclic amines and aldehydes. Those ones more involved in carcinogenesis, being also approached in various studies dedicated to this topic are the followings: 1-hydroxypyrene (1-HOP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides (NNAL-Gluc), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane (NNK) N'-nitrosonornicotine (NNN) and 8-Oxo-7′-dihydro-2′-deoxyguanosine (8-oxo-dG) in urine (Hecht et al, 2003). Their use in current practice was rapidly extended abroad in the past few years and so, new data are now available. These are sensible, quantitative and reliable tests, but also costly, unfortunately not available in daily practice in our smoking cessation center; anyway such biomarkers are almost constantly increased in smokers, as majority of study reports. A panel of biomarkers alike was elaborated for routinely evaluation of risk for cancer in both active and passive smokers, here including: NNAL, NNK, NNN, 1-HOP, MHBMA (monohydroxybutyl mercapturic acid), SPMA for S-phenyl mercapturic acid (a metabolite of benzene), HPMA for 3-hydroxypropyl mercapturic acid (a metabolite of acrolein), HBMA for 4-hydroxybut-2-yl mercapturic acid (a metabolite of crotonaldehyde), HEMA for 2-hydroxyethyl mercapturic acid (a metabolite of ethylene oxide), 8-epi-PGF (prostaglandins growth factor) 2αd, cyclooxygenase-derived prostaglandin E2 (PGE2) etc. (Hecht et al, 2003)

Hecht et al. have found considerable differences, by gender (p = 0,003) and race (p = 0.022) in smokers, when studying two such composed biomarkers, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butano (NNK) and N-Nitrosonornicotine involved as causal agents in lung, oral, oesophagus and pancreas cancers (Hecht et al, 2003). These cancers are well known as certified to develop due to chronic tobacco consumption (Trofor et al, 2005). 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronides (NNAL-Gluc) were identified and quantified in the urine samples from patients in Hecht’s study (Hecht et al, 2003). Hence, non-hispanics smoking women were found with increased levels of urinary NNAL (353 and respectively 336 pg/mL) (Hecht et al, 2003).

Acrylonitrile is a class 2B carcinogen present in cigarette smoke. Urinary 2-cyanoethyl mercapturic acid (CEMA) is an acrylonitrile metabolite and a potential biomarker for acrylonitrile exposure. Actuality research has shown much greater urinary CEMA levels in smokers versus non smokers (Minet et al, 2011).
Conclusions

There are many recognized and still developing biomarkers for tobacco exposure assessment. There is a great amount of literature in the field, useful to clarify the multitude of questions arising about role of such biological markers and their concrete utility for daily clinical practice. Indeed, these lab tests offer the opportunity to measure constituents of tobacco smoke and to show exposing to toxicants in tobacco, regardless smoking behavior. More exactly, by the help of tools like this, we can objectively confirm if a person, either active smoker, or non smoker but passively exposed to smoking, was affected by noxious tobacco components.

Only one such biomarker is not enough to validate tobacco exposure, thus associating several tests is more reliable. Among all these biomarkers outlined above, we have been successfully introduced in daily clinical practice of the Clinic of Pulmonary Diseases of Iasi carbon monoxide and nitric oxide in exhaled air, serum uric acid and urinary cotinine determinations. These ones are in use since almost a decade already and are in particular aimed for smoking cessation monitoring and for assessing asthma and COPD status, in our patients, either active, passive or never smokers.

1.7.2. Active and passive smoking pathological findings and their correlations useful for clinical practice

A. State of the art

There are many scientific proves about the harmful effects of smoking for the respiratory system, as a target organ of tobacco aggressions. The most feared relate to the 50 recognized carcinogens in tobacco smoke, responsible for lung cancer development.

Chronic exposure to cigarette smoke leads to lung inflammation with an increase of inflammatory cells such as macrophages (Retamales et al, 2001; Shapiro et al, 1999), neutrophils (Finkelstein et al, 1995; Lacoste et al, 1993), dendritic cells (DCs) (Casolaro et al, 1988; Soler et al, 1989), and CD8_T lymphocytes (O'Shaughnessy et al, 1997). These cells are capable of releasing inflammatory mediators and proteinases, such as matrix metalloproteinase (MMPs) or neutrophil elastase, which are believed to play a role in the progressive lung destruction in COPD (Shapiro et al, 2003; Shapiro et al, 1999).

According to a systematic review of the literature for detailed information on chemical components in tobacco smoke, lung function and other harmful respiratory effects were attributed to acrylonitrile, ammonia, chromium, cobalt, copper, nickel and m-xylene. Aldehydes and small organic compounds resulting from combustion of organic material are the most responsible for respiratory irritation (Fowles et al, 2003). Tobacco use is associated with very large rates of exposure to oxidants like peroxy organic free radicals, N2O, nitric oxide, etc. that trigger inflammatory responses and lead to airway inflammation (Tuder et al, 2012).

Some constituents of cigarette smoke are not yet well studied in experimental research, such as styrene, acetamide, methyl-chloride, etc. or additives that are added to cigarettes in order to increase tobacco addiction.
The respiratory epithelium is the first line of defence against inhaled noxious agents, such as tobacco smoke. Smokers are vulnerable to changes, increasing goblet cells and appearance of bronchial squamous metaplasia (Tuder et al, 2012). It also has been described a rarefaction of ciliated and non-ciliated bronchial cells (Betsuyaku et al, 2004) associated with inflammation and parietal bronchial fibrosis and alteration of surfactant proteins (synthesized glycoprotein’s in distal respiratory epithelium) of smokers. All these modifications can occur in smokers without any known respiratory disorder and they are easy to evidentiate into bronchial aspirate and bronchoalveolar lavage fluid done within fibrobronchoscopy (Lumsden et al, 1984).

B. Personal contributions

Scientific, professional and academic achievements in this field

Publications in the field


b) Articles published: one article presenting an overview of bronchial mucosa modifications in patients with tobacco exposure.

Bronchoscopic findings related to tobacco smoke exposure

Antigona Trofor, Ramona Miron, Mihaela Sandu, Letitia Trofor,

In summary, the most useful aspects revealed by this paper are described in the followings:

I) Bronchoscopic diagnosis in chronic tobacco consumption non-associated to a respiratory disease

The practical aim of endoscopic observation remains histological examination of bronchial epithelium for identification of premalignant lesions. The recently revised World Health Organization (Chhajed et al, 2005) classification includes hyperplasia, squamous metaplasia, mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma in situ and normal histology. In addition to alterations in the microscopic appearances of the bronchial epithelium, we can add neo-angiogenesis known as angiogenic squamous dysplasia and changes in the stromal support tissues of the epithelial cells. Furthermore, smokers are
considered susceptible of premalignant changes in relation with the intensity of tobacco use (>30 pack-years of cigarette smoking), bronchial obstruction (FEV1<70% predicted) and moderate dysplasia or worse in sputum cytology.

II) *Role of bronchoscopy in biological markers of tobacco exposure*

Assay of biological material with bronchoscope (bronchial biopsies, bronchoalveolar lavage fluid, bronchial aspirate and brushing) allows finding of cells modifications and biological constants at healthy smokers. The most importants are reviewed below:

1. **Smoking per se induces inflammation**, there are effects on the bone marrow, resulting in peripheral blood leukocytosis, and, in heavy smokers, there is a shift in the balance of peripheral blood lymphocytes from CD4 (T-helper) to CD8 (T-suppressor) predominance (Gamble et al, 2007). This altered balance is also seen in bronchoalveolar lavage fluid, bronchial biopsy specimens and airway tissue from resections in smokers with lung cancer. In BAL, total number of cells and alveolar concentrate of macrophages, lymphocytes, neutrophils and eosinophils is bigger to smokers and this come to normal after nine months of smoking cessation (Thomson et al, 2004). Nicotine in cigarette smoke will have a secondary immune modulatory effect on eosinophils function, by inhibition of pro inflammatory cytokines deliverance’s macrophages (Neurohr et al, 2003).

2. **Increasing of the antioxidant glutathione in the bronchial epithelium:**

Glutathione is a tripeptide (GSH; L-glutamyl-L-cysteinyl-glycine), key intra- and extracellular reducing agent protecting against oxidative stresses. Cigarette smoke contains $10^{14} - 10^{16}$ free radicals per puff and exposes the lung to an excessive oxidative burden. More studies (10) concluded that smoking does increase smokers’ glutathione levels comparative with non-smokers, because GSH serves as one of the fundamental anti oxidative defence mechanisms in the control of inflammatory processes in lung injury. In this way, epithelial permeability decrease and alveolar epithelium cells are protected (Neurohr et al, 2003). This data suggest that the intracellular glutathione concentration of bronchoalveolar washings cells (alveolar macrophages) decrease, even if it is well known that alveolar macrophages’ level is increased (Sopori et al, 1998; Li et al, 1994).

3. **Increasing the expression of nuclear factor (NF)-kB in epithelial bronchial cells**

It has been shown that the total amount of p65, expression of nuclear factor-kB, as assessed by Western blotting, is increased in bronchial biopsies of smokers with normal lung function (Stefano et al, 2002). Some authors suggested that smoking per se is an inductor agent of epithelial cells activation (Christman et al, 2000). It is concluded that increasing expression of nuclear factor-kB and epithelial cells activation become potential able to produce proinflammatory cytokines. Ultimately, immunohistochemistry determination revealed increasing number of CD3, CD4 and CD8 in bronchial sub-mucosa layer at healthy smokers, comparative to no-smokers (Christman et al, 2000).

4. **Cells modification in the induced sputum**

Examination of induced sputum and bronchial aspirate at healthy smokers revealed increased levels of neutrophils and macrophages comparative with persons who never smoke
(Kinnula et al, 2007). The levels of 8-isoprostane in the induced sputum were higher in healthy smokers than in no-smokers, 8-isoprostane has been suggested to be the most reliable approach to monitor oxidative stress. However, they do not appear to differentiate healthy smokers from those who are at risk of developing chronic obstructive pulmonary disease (stage 0 GOLD classifications) (Kinnula et al, 2007).

5. Increasing bacterial adhesion to oropharyngeal and bronchial epithelial cells

Study of bronchial brushing to the carina level and subsegmental level of right inferior lobe from healthy smokers (Riise et al, 1994) revealed a higher bacterial adhesion of S. Pneumoniae to bronchial epithelial cells. Also, there was a significantly higher adhesion of H. influenza to ciliated columnar epithelial cells from the carina level and the sub-segmental level.

6. Alteration of pulmonary permeability

Acute exposure to cigarette smoke may decrease pulmonary blood/air barrier (Ward et al, 2000). An increasing body of literature suggests that the integrity of the pulmonary blood/air barrier is altered in a diverse range of circumstances: intense exercise in elite athletes and smoking in otherwise normal subjects. As well as airway and parenchyma inflammatory disease, authors tried to evaluate pulmonary permeability to urea, use as dilution marker for bronchoalveolar lavage (BAL). Unfortunately, the above mentioned study is difficult to interpret, because of the heterogeneity of the smoking group and some variables such as: the timing of the last cigarette relative to bronchoscopy that was not stated, passive exposure to cigarette smoke, this last one being cited as an independent factor of decreasing pulmonary permeability (Kaplan et al, 1992). Until new searches will clarify these aspects, we can affirm certainly that integrity of pulmonary blood/air barrier is aggressed by smoking (Ward et al, 2000).

7. Increasing manganese superoxide dismutase

Manganese superoxide dismutase (SOD) is elevated in the alveolar epithelium of cigarette smokers, probably due to the increased oxidant burden in smokers’ lungs. The researchers go to this conclusion from study of tissue samples from the lungs of no-smokers, smokers and COPD patients. Superoxide dismutase (SOD) is the only enzyme capable of consuming superoxide radicals, as results by immunohistochemistry techniques (Harju et al, 2004).

III) Bronchoscopic diagnosis in chronic tobacco consumption associated to a respiratory disease

1. Asthma in smokers

Induced sputum eosinophil counts are reduced in smokers, compared with no-smokers, with mild asthma (Chalmers et al, 2001). The reasons for a reduction in sputum eosinophil counts in asthmatic smokers have not been elucidated, but could be explained by exogenous nitric oxide (NO) in cigarette smoke increasing the apoptosis of activated eosinophils (Zhang et al, 2003). Cigarette smoking may modify inflammation that is associated with asthma, although there is limited published data on airway pathology in
smokers with asthma (Thomson et al, 2004). To date, the evidence points towards a combination of both heightened and suppressed inflammatory responses in smokers compared with no-smokers with asthma but also a corticosteroid resistance in asthmatic smokers. The mechanisms of this resistance are unexplained, but could be as a result of alterations in airway inflammatory cell phenotypes (increased neutrophils or reduced eosinophils), changes in the glucocorticoid receptor $\alpha$ and $\beta$ ratio, over expression of glucocorticoid receptor $\beta$, increased activation of pro-inflammatory transcription nuclear factors (factor- kB) or reduced histone deacetylase activity (Thomson et al, 2004).

2. Smokers with COPD

Bronchial biopsy specimens from chronic obstructive pulmonary disease (COPD) patients demonstrate increased numbers of eosinophils and macrophages, and also CD8+ T lymphocytes, mastocytes, neutrophils, going to inflammatory infiltrate cells of bronchial mucosa. Cell count data from current smokers and ex-smokers, were analysed for the following cell types: CD4+ and CD8+ T lymphocytes, CD68+ (monocytes/macrophages), neutrophil elastase + (neutrophils), EG2 + (eosinophils), mast cell tryptase+ and cells mRNApositive for tumour necrosis factor $\alpha$. The results demonstrate that there were no significant differences between smokers and ex-smokers in the numbers of any of the inflammatory cell types or markers analysed (Gamble et al, 2007). In interpretation of these results, we must mention a variability of inflammatory cells distribution in COPD bronchial tissue. So, there are necessary more biopsies for CD8+ lymphocytes evidence, as these are key-cells of described inflammation in COPD. Data correlate to age, generation of bronchus biopsied, examined sections and the interval between biopsies (Gamble et al, 2006).

3. Lung cancer and smoking

Beside classic aspects of bronchoscopic diagnosis in cancer, to be treated in specific chapter of pathology, we want to point out the opportunity of vigilant endo bronchial examination in smokers, to catch early diagnosis. Auto-fluorescence bronchoscopy (AFB) when used as an adjunct to standard white light bronchoscopy (WLB) enhances the bronchoscopist’s ability to localize small neoplastic lesions, especially intraepithelial lesions. In former smokers, pre-cancerous changes were influenced by number of packs-years. Recent smoking intensity (the number of cigarettes smoked per day in the year before undergoing bronchoscopy) did not influence the occurrence of pre-invase lesions, in a study published in CHEST 2008 (Moro-Sibilot et al, 2002). Authors point out that tobacco use questionnaires were sometimes difficult to complete. Thus, the term age of initiation of smoking was often misunderstood, with some patients answering by giving the age at which they smoked their very first cigarette and some patients answering by giving the age at which their daily tobacco use began. So, there are necessary additional studies in this field.

4. Respiratory infections in smokers

Acute tobacco exposure increases mucociliary clearance in healthy smokers, described by scintigraphic visualization of the bronchi (bronchoscintigraphy) (Mortensen et al, 1989). Smokers with no-obstructive chronic bronchitis had significantly more goblet cells and less ciliated epithelial cells. Authors observed the profile study of airways infections from
carinal and subsegmental levels of the bronchial tree with a standard cytological brush (Riise et al, 1992). The issue can be approached reversely: short-term smoking reduction studies using bronchoscopy and bronchoalveolar lavage revealed benefits or reduced tobacco exposure: bronchial inflammation, as assessed by direct inspection, neutrophilia in bronchial lavage fluid, number of alveolar macrophages, alveolar neutrophils as well as concentration of neutrophil elastase alpha 1-antiprotease complex in alveolar lavage fluid, had improved significantly (Rennard et al, 1990).

5. Bronchoscopic findings associated to flavoured additives in tobacco products

Cigarette smoking has been recognized to cause AEP (acute eosinophilic pneumonia), and association of cigarette smoking-induced AEP with menthol-flavored cigarettes. Acute eosinophilic pneumonia (AEP) is characterized by eosinophilic infiltration in the lungs, respiratory distress, and a rapid therapeutic response to corticosteroids. Based on review of two cases of AEP following flavoured cigar smoking, we believe that the flavouring component may have a major role in precipitating the illness. The bronchoscopic exam is an important piece of diagnosis, from BAL (eosinophilia >25%), lung biopsy evidence of eosinophilic infiltrates, hypoxemic respiratory failure, diffuse pulmonary opacities on chest radiograph and absence of known causes of eosinophilic pneumonia, including drugs, infections, or asthma (Al-Saieg et al, 2007).

6. Bronchoscopic aspects in smoking-related interstitial lung disease

Recently, cigarette smoke has been incriminated as a cause of interstitial lung diseases represented by desquamative interstitial pneumonia, respiratory bronchiolitis associated with interstitial lung disease, pulmonary Langerhans’ cells histiocytosis and pulmonary idiopathic fibrosis (Ryu et al, 2001). The effect of cigarette smoking in the development of interstitial lung diseases is poorly understood. Due to the rarity of these diseases, it is difficult to firmly establish a direct causative role of smoking in the pathogenesis of these conditions. Bronchoscopic examination, in these cases, brings more information about inflammation and interstitial fibrosis from diffuse infiltrative interstitial lung disease by trans-bronchial biopsy and at the same time, exclude granulomatosis like sarcoidosis, hypersensitivity pneumonia, lymphangitis carcinomatosis, lymphomas, infections or other diffuse diseases, that can be diagnosed by usual bronchial biopsies. It is well known that aspects like fibrosis and interstitial infiltrate of tissue are not specific for usual bronchial biopsies but also do not exclude categorically a commune interstitial pneumonia (Wall et al, 1981).

1.8. Tobacco use and dependence defined as a chronic relapsing disease: basis of its approach for current clinical practice

A. State of the art

In medical terms, chronic smoking is defined as: tobacco dependence, nicotine dependence, tobacco addiction or nicotine addiction.
Tobacco dependence is a disease, in the category of addictions, as classified by the World Health Organization (WHO) in the International Classification of Diseases, where it is included in: „Mental and behavioural disorders due to tobacco use” and has the disease code „F17” (Behrakis et al, 2012). Tobacco dependence is associated with the long-term, daily use of tobacco-based products (cigarettes, pipes, cigars, narguile, smokeless tobacco, etc.). Doctors and health professionals must therefore take into account that tobacco dependence is a medical condition and not a habit, vice, pleasure, or life-style choice. As well, all doctors must assist their tobacco users patients, regardless of their specialty, according to international tobacco control legislation.

The main etiological factor of the tobacco dependence disease is nicotine. Nicotine is a highly addictive drug which is contained in tobacco and which determines dependence in those who use tobacco products chronically. By smoking tobacco, individuals not only introduce nicotine into their own bodies and maintain or increase tobacco dependence, thus developing an addictive disorder per se, but also expose themselves to numerous severe tobacco consumption induced illnesses, caused by the numerous chemicals contained in tobacco. That’s why, it is compulsory to provide smoking cessation advice to all smokers. The earlier tobacco dependence is treated, the earlier the patients will quit using tobacco and the higher will be their health benefits (Behrakis et al, 2012).

As tobacco dependence is a disease, more exactly a chronic relapsing disease, it must be diagnosed and treated in the same way as other chronic diseases at risk to relapse.

Routine identification of smokers is mandatory in current medical practice. The best opportunities for this purpose are occasional or annual medical visits, as most citizens visit their own family doctor or general practitioner at least once a year, or regularly/occasionally visit a dentist or another health professional for various health reasons. All doctors, no matter what their specialty, should use these occasions to identify patients who are tobacco users. This is a mandatory medical gesture, legitimized in all EU countries as a routine intervention and patients’ smoking status should be recorded in the patient’s medical records: e.g. hospital admission or discharge papers, referrals, laboratory reports etc. This recommendation is based on a meta-analysis of nine randomized studies about the impact of tobacco use screening on cessation rates (Fiore et al, 2008).

Clinical diagnosis of tobacco use and dependence is based on:
- smoking status (non-smoker, occasional smoker, daily smoker, ex-smoker),
- the type of tobacco product used (gives an idea about the level of addiction, since nicotine dependence is more severe in cigarette consumers, compared to those who use cigars, pipes, water pipes, e-cigarettes or oral tobacco),
- tobacco consumption defined as: number of cigarettes smoked per day; number of cigarette packs-years (no. of PY). The number of pack/years is calculated by multiplying the number of cigarettes packs smoked/day by the number of years of smoking (e.g. if someone smokes 15 cigarettes per day for 15 years, this equals 15x15/20 = 11.2 PY).
- tobacco/nicotine dependence score, assessed using the Fagerström nicotine dependence test (Table 7), FTND that provides not only a yes/no answer but also a final score, which
categorizes tobacco users as having either low, medium, or high levels of nicotine dependence.

Table 7. Fagerström Test for nicotine dependence (FTND) (Fagerstrom et al, 1989)

1. How soon after you wake up do you smoke the first cigarette?
   - Under 5 minutes (3)
   - 6-30 minutes (2)
   - 31-60 minutes (1)
   - More than 60 minutes (0)

2. Does it feel difficult for you to abstain from smoking in places where smoking is banned (e.g. church, cinema, train, restaurant etc.)?
   - Yes (1)
   - No (0)

3. Which cigarette would it be the most difficult for you to give up?
   - The first cigarette in the morning (1)
   - All the others (0)

4. How many cigarettes/day do you smoke?
   - 10 or fewer (0)
   - 11-20 (1)
   - 21-50 (2)
   - 51 or more (3)

5. Do you smoke more frequently in the first hours after you wake up than in the rest of the day?
   - Yes (1)
   - No (0)

6. Do you also smoke if you are so ill that you are immobilized in bed most of the day?
   - Yes (1)
   - No (0)

The key questions are questions 1 and 4: the number of cigarettes smoked daily and the time of the first cigarette after waking up in the morning. These questions may be asked by a doctor during consultation and constitute the short version test, scored from 0 to 6, with the same score values as the 10 questions version of FTND. In specialized smoking cessation clinics the use of additional assessment tools to profile tobacco users level of dependence is optional. Such an evaluation is possible using several instruments, i.e. the Nicotine Dependence Syndrome Scale (NDSS) and the Wisconsin Inventory of Smoking Dependence Motives (WISDM) (Behrakis, 2012; Kawakami et al, 1999).

- analysis of previous quit smoking attempts

It is recommended that clinician’s assess: the number of past quit attempts, longest smoking abstinence period, any previous cessation treatment and what the treatment consisted of, any history of withdrawal symptoms, any relapsing risk factors, positive aspects described during abstinence. These features are important to anticipate treatment success or failure risk factors, as well as treatment compliance and patient’s capacity to overcome withdrawal.
- motivation to quit smoking:

According to J.O. Prochaska and C.C. DiClemente’s well known Transtheoretical model (TTM) of Behaviour Change (Behrakis, 2012) the psychological process of smoking cessation goes through five stages (Figure 9).

Pre-contemplation: the patient is fully satisfied by his/her smoking behaviour and he/she does not feel any need for a change;

Contemplation: the patient feels the need for a change, but this is not strong enough to push himself/herself to action or to make an action plan;

Preparation: the patient has decided to try to change his/her smoking behaviour and is ready for this change in the near future;

Action: the patient starts the smoking cessation attempt.

Maintenance: abstinence for 6-months or longer.

Figure 9. Stages of change for smoking cessation according to Prochaska model (Behrakis, 2012)

Simple scales, in which clinicians ask patients to rank on a scale from 1 to 10, their motivation to quit smoking, can also be useful in busy clinical practice (Figure 10).

Figure 10. Easy to use scale of motivation (Behrakis, 2012)

Regardless of the patient’s readiness to quit or motivation, smoking cessation treatment should be initiated by a physician for all patients who report tobacco use. In the case of smokers with co-morbidities and patients with tobacco dependence the health professional has to communicate to the patient the risk of continued tobacco use and the need to quit immediately. As is the case with all medical decisions, the patient remains free to
refuse treatment, but the specialist has to propose smoking cessation treatment and thus have the same conviction as when proposing a treatment for diabetes or for hypertension.

- **patient’s medical history**

  The patient’s medical history is relevant in the choice of therapeutic option, with regard to any drug interaction or any incompatibility required by a concurrent disorder/comorbidity. Acute cardiovascular events, history of seizure, kidney disease, current or history of addiction etc. may also impose caution in prescribing some pharmacological treatments; thus the need to note them in the smoker’s medical records.

- **pregnancy/breast feeding / contraception**

  It is also very important to check the physiological status in women (pregnancy, breast-feeding, contraception methods etc.) to organize smoking cessation effectively. Pregnancy is associated with significant increases in the rate of nicotine metabolism (Behrakis, 2012).

- **patient’s anxiety and depression history**

  Generally, depression and anxiety are the most frequent conditions described in heavy smokers. Very often such syndromes impose caution or raise awareness about the side effects of cessation medication. Two simple questions from the Primary Care are recommended as a screening tool for depression (Behrakis, 2012).

  - Have you felt sad, depressed, desperate in the past month?
  - Have you had the feeling that you do things with neither pleasure nor interest in the past month?

  A positive answer to both questions may be interpreted as a strong sign of depression. Another faster way to quantify depression can be just one question:

  - Have you felt sad on most of the days over the past two weeks?

  If the answer is yes, again we can consider this a strong indication that the patients may be suffering from depression.

  All patients responding yes to this question should be screened for suicidal ideation using simple screening tools or validated assessment tools.

  - Have you had any thoughts of death? (This requirement applies especially in those patients undergoing pharmacological non nicotinic therapies)

  **Laboratory diagnosis of tobacco dependence**

  Smoking status as defined based on clinical criteria may be also evaluated by biochemical laboratory tests to assess biomarkers of tobacco smoke exposure, such as carbon monoxide concentration in exhaled air and level of cotinine (a metabolite of nicotine).

  Biochemical validation is generally used in research to confirm self-reported rates of smoking abstinence and as such is not recommended as standard practice in all clinical settings for routine identification of smokers. Yet, it is highly recommended to monitor smoking cessation treatments in specialized smoking cessation services.

  After careful complete clinical and laboratory evaluation of smokers, the specialist can proceed to organize cessation therapy, if the patient is willing and motivated to receive it.
Therapeutic interventions for tobacco use and tobacco dependence

Therapeutic intervention to stop smoking is mandatory!

Article 14 of the Framework Convention on Tobacco Control states that every country should provide smoking cessation assistance, and implementation of this approach is now being considered by many countries (Behrakis, 2012). Assistance with quitting tobacco use should be a major part of every European country’s tobacco control strategy.

Standard approach to quitting smoking

Five strategies are recommended for addressing tobacco use in clinical settings. Known as the 5As these strategies are (Behrakis, 2012):

- **Ask** all patients about smoking status;
- **Advise** patients who smoke to quit;
- **Assess** readiness to quit;
- **Assist** with making a quit attempt, including providing behavioral counseling and prescribing first-line smoking cessation medications; and
- **Arrange** follow-up.

The 5As model is an evidence-based approach to increasing smoking cessation. The 5As methodology has been used in a variety of smoking cessation intervention programs.

![The 5As algorithm for tobacco treatment delivery in clinical settings](image)

**Figure 11** The 5As algorithm for tobacco treatment delivery in clinical settings (Behrakis 2012)

In current practice, there are two major types of cessation interventions: minimal intervention and specialized cessation treatment.

**Brief advice** represents “a sum of verbal indications to stop smoking, given in medical terms and by adding information about harmful effects of smoking”. When routinely administered to all patients, as a basic, systematic intervention, followed by referral to a specialized centre, it becomes a very strong therapeutic tool. Minimum advice is
recommended to all categories of smokers, ex-smokers, as well as to those who have never smoked.

As a level 2 intervention, tobacco users should receive specialized individual treatment consisting of medication that has been proven to be effective in treating nicotine addiction (varenicline, bupropion, nicotine substitutes, etc.) and a series of cognitive-behavioral counseling sessions delivered individually. Specialists use the term “counseling” to define the specific cognitive-behavioral assistance given to patients under treatment to quit smoking. The counseling sessions have the role to provide smokers with knowledge about the smoking cessation process and with solutions for overcoming obstacles during the quit attempt. Usual format intervention consists of several (minimum four) sessions lasting 20-45 minutes through 9-12 treatment weeks.

In the first consultation, the patient is clinically and biologically evaluated his/her smoking status and then, briefly introduced to the available treatments, warned about nicotine withdrawal symptoms and agrees on the most suitable solutions.

During the 9-12 week standard treatment, regardless of therapy indicated, it is recommended to follow up all patients (at least two visits) in order to be certain that the patient follows the correct treatment, in standard doses in the case of pharmacotherapy, to address psycho-behavioral difficulties or withdrawal symptoms and that there are no adverse effects of medication. Follow-up visits allow the doctor to obtain an update of the smoking status, to monitor biomarkers of tobacco use and to prevent lapses or relapses. These visits offer an opportunity to provide prompt support – the doctor can intervene right on time in case the smoker is discouraged or has a slip after a short temporary abstinence. The most important visit is the first one – it is recommended to schedule it immediately after the target-quit day.

Counseling and medication are effective when used by themselves, but the combination of counseling and medication is more effective than either used alone and increases abstinence rates (Fiore et al, 2008). The clinician providing medication does not need to be the clinician providing the counseling. It may be that a physician, a dentist, physician’s assistant or nursing practitioner could prescribe medicines, and counseling could be provided by another tobacco treatment specialist (doctor, nurse, psychologist, quit lines worker etc.).

Meta-analysis of nine studies in 2008 indicated that providing medication in addition to counseling significantly increases treatment outcomes (22.1% when medication is added to counseling vs. 14.6% when medication alone) (Fiore et al, 2008). In an open-label, pragmatic, randomized trial that compared two models of a pharmacist-led behavioral intervention [Group A (3-sessions) vs. Group B (1-session)] combined with five weeks of NRT, delivered in 98 pharmacies in Ontario, Canada, cessation outcomes were higher among participants completing three intervention sessions compared to one session (Costello et al, 2011).
B. Personal contributions

Scientific, professional and academic achievements in this field

a) Educational materials and tobacco use and dependence assistance guidelines for both patients and health professionals

1. Author of the educational DVD “Smoking cessation counseling- educational material for specialists in the field” (Iasi, 2009)

2. Author of the educational DVD “Smoking cessation - educational material for patients who smoke” (Iasi, 2009)


4. Coordinator of the first Romanian smoking cessation guideline (GREFA) for health professionals (Tehnopres Publishing House, Iasi, 2008), www.srp.ro


b) Articles published

In relation with my teaching activity in the Dentistry Faculty I have dedicated an article to put the basis of the correct definition for the tobacco use and dependence disease for this category of the undergraduates target audience.

Smoking cessation – a „must have of good oral health status”

Antigona Trofor, Ramona Miron


Abstract

Chronic tobacco consumption is a disease per se and it is defined as nicotine dependence. Furthermore, smoking is known to induce many diseases such as cancers, cardiovascular disorders, chronic obstructive lung diseases, etc., to seriously affect pregnancy and delivery in smokers as well as infant and foetus, to be an unaesthetic condition and to generally damage anyone actively or passively exposed to this major risk factor. From dental medicine practitioner’s point of view, we can say for sure smoking has a negative impact on oral health and on evolution towards healing of oral pathology in smokers. By such perspectives, we propose an analysis of best pattern to make dentists willing to involve in smoking cessation interventions. Therefore, best examples to enable dentists to preserve beneficial smoke-free stage in their patients and to avoid negative consequences of tobacco on oral health status are looked for. Despite scientific evidence based incriminatory effects of
tobacco on human health, tobacco products continue to be legally sold everywhere in the world. Dentists have the opportunity to periodically assist smoking patients in their practice. So, if current or former smokers, such occasions should be frutified towards smoking abstinence or to create motivation to maintain smoke-free status in never smokers. Dentists should routinely evaluate smoking status of their patients, assess willingness to quit smoking and send motivated smokers to specialized smoking cessation centres which are now available in many cities in Romania. Swiss expertise on motivational interview to stop smoking is quoted, by giving example a team of Swiss dentists that have successfully implemented in their country a model of dentists units team trained to specifically assist smokers to quit in dentistry.
CHAPTER 2. RESEARCH CONTRIBUTIONS TO DEVELOPING TREATMENT AND PREVENTION HEALTH STRATEGIES FOR TOBACCO USE AND DEPENDENCE

2.1. Research within pilot programs for prevention and treatment of tobacco use and dependence

A. Background

As my interest in the field of tobacco use and dependence management became more and more consistent with my acquired training and skills in this domain and as the new advances in the tobacco control health policy became available in Romania, by signing and ratifying international regulatory documents for assisting tobacco users, this favourable context allowed me to involve in the development of a new smoking cessation department in the Clinic of Pulmonary Diseases Iasi, in 2000. Ever since, until 2007, our center has gained expertise based on 100% volunteer activity. Also, due to Medicine University affiliation, the center had attracted trained personnel and built a team able to provide treatment for tobacco dependence disease, mainly for respiratory ill patients, at a first stage.

In the same direction, we conducted a phase IV clinical trial (the first smoking cessation clinical trial in our clinic) for the treatment of tobacco dependence in healthy smokers, with Bupropion Hydrochloride versus placebo, on 15 volunteer smokers. This clinical trial required 4 clinical visits to allocate medication and for follow up. Smoking abstinence was monitored by carbon-monoxide measurements in exhaled air, thus introducing this technique in our clinic, by this occasion.

Outcomes of the study showed a 28% abstinence rate in the Bupropion group.

These results were disseminated in the XV-th annual congress of the European Respiratory Society, Copenhagen, Denmark, in 2005, as shown below:

<table>
<thead>
<tr>
<th>Smoking cessation with bupropion—is it succesful enough?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigona Trofor, Mihaescu T, Esanu V. Grigoras C.,</td>
</tr>
</tbody>
</table>

Relevance of results

In 68 patients (42 males, 26 females, age average 38 years, nicotine dependence score 7± 2) treated with Bupropion for 2 months and followed for 6 months post treatment, treatment completion was achieved in 64%. The rate of continuous abstinence among completers was 28 %, while reducers were 14.2%

To summarize our smoking cessation center’s experience between 2000-2007: with a demand of 5-10 patients appointed/ week, smokers could find 2 trained doctors and 2 trainees to assist quit attempts, they had to buy medication for a complete cure and no follow-up
resources were provided, except the carbon monoxide measurements in exhaled air, as a private equipment available from a clinical research project developed in our center.

Becoming an EU member in 2007 brought important changes into the Romanian tobacco control picture with a positive impact on smoking cessation development.

Some relevant aspects to define the status quo, at the time of pilot smoking cessation programs development:

• smoking ban in progress: tobacco advertising was fully forbidden, enforced legislation against smoking in public places, public debates to prepare cigarettes packs pictorials to issue in 2008 and new cigarette packs warnings.
• new pharmacological therapies for smoking cessation (such as Varenicline and nicotine gum and patches) became available (Bupropion as cessation medication was available since 2001).
• Health Ministry allocated funds for smoking cessation pilot programs both for adults and teenagers.

Following all these advances in tobacco control in Romania, a pilot program for stopping smoking in adults was set at once in our country: the 2007 “Stop smoking” pilot program for adults, to reimburse smoking cessation activity, a green-line phone and cost of medication was an experimental 3 months (October-December 2007) first phase of a national program run in several Romanian smoking cessation centers. As an experimental program, the project was developed with small amount of funds, aiming to identify its feasibility and future best pattern of a likely national program to be further implemented in the next year, 2008.

In parallel, health policy responsibles were looking for a pilot smoking cessation and prevention program feasible in youngsters, too.

B. Personal contributions

Scientific, professional and academic achievements in this field

a. Coordinator of pilot smoking cessation programs

I have been the local level coordinator of the pilot “Stop smoking” national program, implemented in the Smoking Cessation centre from the Clinic of Pulmonary Diseases Iasi, in 2007. The pilot program was successfully implemented, so it became a regular smoking cessation program in 2008 and it is running ever since.

Pilot testing programs for smoking prevention and cessation in youngsters was another research direction I followed starting with 2004-2005, and I acted as coordinator of the European project „Adolescent smoking cessation”, from behalf of the Romanian NGO Aer Pur Romania, under the umbrella of the EU Health Programme 2008-2013.

„Adolescent Smoking Cessation (ASC)” is a program that was designed by Welsh Government Assembly in collaboration with ENYPAT* experts and was successfully delivered in several European countries (United Kingdom, Sweden, Belgium, Spain, Greece, Denmark) for the first time in 2004. The program provided cognitive-behavioural techniques, aiming smoking cessation in adolescents. In Romania, ASC was implemented in pilot phase in 2005, from behalf of the Nongovernmental association “Aer Pur Romania” when it was run
in two cities: Iasi and Timisoara, on volunteer activity basis given by young facilitators. In 2005, 231 adolescents were included in this pilot phase.

b. Articles published

- **Outcomes of the “Stop smoking” pilot program**
  


- **Outcomes and lessons from the pilot program for smoking cessation in adolescents**
  


  *Early smoking cessation results in our center were disseminated in 2 articles published in abstract in supplements of the ERJ ISI Web of Science indexed journal, as follows:*


Outcomes and lessons from the pilot program for smoking cessation in adolescents were disseminated in the following 3 articles published in abstract in supplements of the ERJ ISI Web of Science indexed journal and of the European Psychiatry ISI Web of Science indexed journal:


Most relevant outcomes of the “Stop smoking” pilot program were disseminated in an article providing results from a big database of the smoking cessation centers from Iasi. The article was published in 2015, at distance from the first pilot studies in the field:

<table>
<thead>
<tr>
<th>Treatment of nicotine dependence—early positive outcomes of a reimbursed smoking cessation pilot program in Iasi, Romania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letitia Trofor, <strong>Antigona Trofor</strong>, Rodica Gherghesanu, and Roxana Chirita</td>
</tr>
<tr>
<td><em>Bulletin of Integrative Psychiatry</em>, vol. 21, no. 3(66), 2015, p. 43-49</td>
</tr>
</tbody>
</table>

**Abstract**

*Background and Aims:* In 2007, Romanian Health Ministry implemented in pilot phase a national program, designed to pay smoking cessation experts and to reimburse cost of three types of pharmacological therapies for nicotine dependence induced by tobacco smoking. The aim of the study was to evaluate the impact of the first totally reimbursed smoking cessation program run in our center, to debate the role of reimbursement on success rate of quitting tobacco use and to identify the gaps and the values of the program, based on a first 3 months expertise.

*Material and methods:* Patients were sent by G.P.-s, or addressed by media to the smoking cessation center in October-December 2007, in a first phase of the pilot program designed to cover expenses for 3 months pharmacological treatment and counseling for nicotine dependent smokers. The patients received one initial evaluation visit, two follow-up visits and a final visit. The smoking abstinence was assessed by the carbon monoxide measurement in exhaled air and by urinary cotinine tests.
Results: Among 100 initial consults appointed, 46 subjects were found eligible to receive nicotine dependence therapy. The treatment was completed by 54.3% of the subjects, with 8.7% lost in follow-up and 15.2% side-effects requesting to abandon the therapy. Overall success rate was 34.7%, higher than prior 28% established in our center before this program.

Conclusions: Tobacco smoking is defined as a chronic relapsing disease which determines dependence to nicotine, a drug contained in any tobacco product. Reimbursement of therapy for nicotine dependence and providing qualified personnel for smoking cessation activity has increased patients‘ compliance to quitting tobacco use.

2.2. Design and implementation of smoking cessation national health programs and policies

A. Background

Successfull implementation of the pilot smoking cessation programs for both adults and adolescents revealed the need for designing national programs to prevent and stop tobacco use. These programs were run by the Romanian Health Ministry, with governmental funds and in a first stage, I was invited by national program responsible to partner my research experience in the Adolescent smoking cessation pilot project, as author of this program in Romania from behalf of Aer Pur Romania NGO organization. By sharing my adolescents’ smoking cessation experience, I contributed to the design of the national program „Adolescents stop smoking” 2007-2008, as author and coordinator in Romania of this national program, run in partnership by the Romanian Health Ministry, NGO Aer Pur Romania and the Clinical Hospital of Pulmonary Diseases Iasi, with approval from the European coordinator.

In a second stage, I was asked to coordinate the newly developed „Stop Smoking” national program for smoking cessation in adults, based on my previous experience and positive results gathered in its 2007 pilot phase. As such, I became the local coordinator of the „Stop smoking” national program, since 2008, by ensuring good coordination of the specialized smoking cessation activity in the smoking cessation center of the Clinic of Pulmonary Diseases Iasi and by contributing to development of two other similar centers in Iasi, located at Rehabilitation Medicine Hospital Iasi – coordinated by Assoc.Prof.dr. Paraschiva Postolache - and at the Emergency Internal Medicine Clinic in Iasi – coordinated by Assoc. Prof. dr. Ovidiu Petris, as my center’s addressability became more and more high, in the next 2 years.
B. Personal contributions

Scientific, professional and academic achievements in this field

a) Research and professional achievements in the field

• Based on my research experience with design and implementation of the Adolescents Smoking Cessation pilot European project in Romania, in 2005, I became author and national coordinator of the “Adolescents stop smoking - 2007-2008” national public health program in Romania. The program was funded by the Romanian Health Ministry, within the national program III “Tobacco Control through encouraging smoking cessation” – in the sub-programme III.2. of public health (funding: 125 000 RON in 2007, 200 000 RON in 2008).

• Based on my experience acquired in the pilot „Stop Smoking” program for adults in 2007, I became the local coordinator of this programme in Iasi between 2008-2010.

b) Publications in this field:


The following three studies pointing out programs’ evaluations and lessons learnt were published as abstracts, in supplements of the European Respiratory Journal, indexed in ISI Web of Science.

1. Antigona Trofor, Mihaltan Fl, Lotrean L, Trofor L, Mardare A, CR Loghin. SMOKING CESSATION AND PREVENTION NATIONAL PROGRAMS FOR YOUNG


The most relevant results accumulated in both these smoking cessation programs were disseminated in 1 article about the expertise with young people, published in Pneumologia and in one article about the long term expertise with smoking cessation for free in adults, published in the Open Medicine journal, indexed in ISI Web of Science, as shown here below. All these 2 articles are presented here below:

Smoking cessation and prevention for young people - Romanian expertise

Antigona Trofor, Florin Mihaltan, Stefan Mihaicuta, Lucia Lotrean
Pneumologia, vol. 58, nr. 1, 2009, 72-78

Background
Tobacco is the first drug young people come in contact with, as it is the most accessible and its use is not affecting social integration. On the contrary, smoking is often associated by teenagers with a fast way to facilitate socialization, in a population category for which social accept and adult models are important goals. Several Romanian smoking prevention programs have concluded, in 2003, age average of smoking initiation was 13.8 yrs (Holm et al, 2003). Approaching adolescents to discuss their smoking habit is a delicate task for health professionals and educators, taking into consideration specific behavioral and personality changes of this age group.

One cannot develop a dialogue with adolescents on this matter, without understanding their motivation to start smoking. And the answer is unanimously accepted by experts: smoking begins due to psychological factors such as: desire to have an adult, mature look, to be more easily socially accepted by their friends, idols, models, especially when these ones are smokers.

Very often children smoke by curiosity, imitation, the need to experience new things, or to be in trend. Otherwise, by lighting a cigarette, they “feel more strong” to face sentimental or exams emotions, they believe tobacco gives them the power to confront conflictive situations or may be, their own anxiety. Thus, decision to smoke at this age is a consequence of complexity of factors involving attitudes, social norms, social pressure and own adolescents perception about themselves.
Smoking rate among young people is hard to determine, both because few studies, on small groups, have been achieved in Romania and also, it is a general belief that adolescents fear to declare tobacco use, when interviewed. Lifestyle study of adolescents 18-19 years old, showed increasing smoking rates between 1993-1999, from 9% to 24% in girls, respectively from 20% to 38% in boys (Bucur, 1999; Smoking and public health in Romania, 2004; Mihaltan, 2001). More recently, in 2003, according to a National Study about Alcohol, Drugs and Tobacco Consumption inside The European School Survey Project on Alcohol and other Drugs (ESPAD), 64% of schoolchildren aged 16 in Romania have ever smoked at least one cigarette, meaning 11% more, compared to 1999 (Smoking and public health in Romania, 2004).

Finally, ESPAD 1999 found 12.4% of Romanian boys and 5.2% of Romanian girls under 15 to be already daily smokers (Smoking and public health in Romania, 2004).

To prevent and decrease smoking among young people, specialists in the field all over the world, have tried:

- Mass media campaigns
- School based programs (have the advantage to reach wide audiences, to develop opportunities for interpersonal communication and are easy to accept as health education is already in school curriculum; nevertheless disadvantage of limited time and insufficiently trained personnel cannot be ignored).
- Community programs
- Measures which limit exposure and accessibility of tobacco products to young people.

Nationally implemented strategies for smoking prevention and cessation in young people were practically absent in our country until 2005. Some action taken in this field occurred mainly around National or International No-Tobacco Days, when education to prevent smoking induced harm was provided in schools, youth centers, by public contests or media events.

Situation changed in 2005 when volunteer members of Romanian NGO “Aer Pur Romania” have become involved in several European projects targeting smoke free schoolchildren and adolescents.

The first approach to school-based programs for smoking prevention was done with “Smoke-free class” competition project, to be brought in Romania (Figure 12).

The program co-funded by The European Union, was carried out in several European countries since 1997. In Romania the program was implemented for the first time in the school year 2004/2005 by the non-governmental organization Pure Air and Romanian National Anti drug Agency and was ran annually ever since. The objective of this program is smoking prevention among secondary school children aged 11-15 years old. Classes decide to be a non-smoking class for a period of four months (at least 90% of class students decide to be non smokers during the program). The program is carried out as a class activity. Pupils sign a class contract and an individual contract promising not to smoke during the competition. The contracts serve to underline their commitment. The responsibility for the control of smoking lies mainly with the pupils themselves: pupils monitor their smoking status and report regularly, whether they have smoked or not. During the competition the
classes are encouraged to perform several antismoking activities. Classes, which refrain from smoking during the competition and participate in the recommended educational activities are rewarded. This is done by participation in a national, as well as a European prize draw, in which they can win a number of attractive prizes. The main prize in the European prize draw is a trip to one of the other participating countries.

The program was implemented in Romania in 5 counties of the country in 2004/2005 and starting with the next year was implemented at national level (Figure 13). Moreover, the number of the participating classes also increased from 355 in 2004/2005 to 999 in the following school year. In 2005 the European draw prize was won by a Romanian class and was represented by a trip for the whole class to Venice, Italy, where the pupils met Italian colleagues, participants as well in the Smoke Free Class competition in Italy.

Following this European partnership, Romanian tobacco control team with expertise in this field launched, in 2005, joint action to help adolescents prevent or stop smoking. The target group - adolescents 15-19 years old - benefited two European initiatives to provide them a smoke-free status. First European program to start in 2005 was Adolescent Smoking
Cessation (ASC-Figure 14). The Romanian partners were: Aer Pur Romania NGO, Romanian National Anti Drug Agency, Public Health Departments, Clinic of Pulmonary Diseases of Iasi and Clinic of Pulmonary Diseases of Timisoara.

The program was designed by Welsh Government Assembly in collaboration with ENYPAT* experts and provided cognitive-behavioural techniques aiming smoking cessation and prevention in young people. Before implemented in the two Romanian cities: Iasi and Timisoara, ASC was successfully delivered in several European countries: United Kingdom, Sweden, Belgium, Spain, Greece, Denmark, etc.

Project’s goal was assessment of adolescents willingness to receive smoking cessation and this was achieved by recruiting smokers aged 15-20 to be offered smoking cessation, in a group program, aiming to provide education for a smoke-free life and putting together active smokers, former smokers and non smokers. Target group of ASC was adolescents from IX-XII grade.

Who is included in ASC?
Smokers that want to quit and agree to participate all 6 sessions of the program, never smokers, former smokers and experimental smokers that are willing to get involved as support group, but only if they have parents and teachers approval.

Adolescents smoking cessation program design
Adolescents were recruited for ASC after filling in a registration questionnaire for standard selection of participants (Trofor et al, 2005). Work groups of 20-25 participants were given 6 classes about smoking induced harm, general aspects of tobacco use influence both on individuals and society, and benefits of quitting smoking. Smoking status was determined in the first session by carbon monoxide (CO) measurement in exhaled air, than quitting smoking was encouraged and supported along sessions 2-5 and finally, in session 6 smoking status was again confirmed by carbon monoxide. Six sessions were delivered:
**Course 1**: General information - a 17 minutes documentary film
   Interviews, introducing facilitators and group members Assessing CO in exhaled air

**Course 2**: What do you know about cigarettes/tobacco – interactive session
   Evaluation of actual smoking status
   Feed-back questionnaires

**Course 3**: What do you know about smoking? – interactive session
   Practical activity: Smoke-free disco (Figure 15)

![Figure 15. (Trofor et al, 2009)](image)

**Course 4**: Tobacco smoking and health consequences– interactive session
   Evaluation of actual smoking behavior and attempts to quit

**Course 5**: Smoking cessation techniques- interactive session
   Passive smoking’s risks
   Health benefits of smoking cessation

**Course 6**: Evaluation of final smoking status
   Identifying quitters and reducers
   Final festivity: prizes, outcomes, media event (Figure 15)

Subjects that quit smoking as a result of program’s impact received prizes, as well as reducers and support group participants.

**Results**: 231 adolescents from 8 high schools in Iasi and Timisoara graduated the program in 2005 (132 girls and 99 boys), their smoking status being shown in Table 8.

**Table 8. (Trofor et al, 2009)**

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every day smokers</td>
<td>125</td>
</tr>
<tr>
<td>At least once a week, but not every day</td>
<td>12</td>
</tr>
<tr>
<td>Less than once a week</td>
<td>24</td>
</tr>
<tr>
<td>Used to smoke but stopped</td>
<td>23</td>
</tr>
<tr>
<td>Never smoked</td>
<td>47</td>
</tr>
</tbody>
</table>
Main outcomes of ASC were: 19 quitters (8.2%) 20 reducers and 48 participants tried to stop smoking at least once during the project. Six months evaluation showed 10 adolescents still abstinent and 4 still reducers (Trofor, 2006).

Other positive outcomes were: increasing in tobacco use related knowledge, increasing self-esteem; positive comments about organizers; they enjoyed, had fun and experienced something very different from regular school classes; easily accepted future collaboration in other projects.

Even if percentage of quitters looks rather modest, being well known difficulty to address adolescents in a smoking cessation program, we may consider results as encouraging, both because of good participation rate of Romanian adolescents and because of satisfactory participation rate, when compared to similar results in other countries where the program was delivered by our European partners.

The second program to target schoolchildren was “Quit and Win” (Q&W) contest, aiming to encourage young smokers to stop smoking. Subjects who refrained from smoking during entire contest duration (one month) were rewarded with prizes.

**Short history**

Q&W was adapted by WHO in 1986 from the initial Heart Health Program of the Minnesota University running since 1980. In 1994 it becomes an international phenomena, each 2 years, under patronage of WHO and EUROCINDI (*Countrywide Integrated Non-Communicable Disease Intervention*). The contest has an adult and adolescent variant design.

In 2005, Q&W for young people was brought in Romania (Figure 16) for the first time, among other 10 participant countries as Finland, Sweden, Check Republic, England, Slovakia, Germany, Spain, Greece, Iceland.

![Figure 16. (Trofor et al, 2009)](image-url)
What meant Q&W in Romania?

Main objectives were: motivation of both smokers and non smokers adolescents to adopt a smoke-free life-style, decreasing smoking rates in youth and assessing smoking prevalence to this age group. Target group was 14-18 years old high school pupils, in 5 big towns of Romania, which made a 6000 subjects project inclusion group (Figure 16).

Between 1 October – 30 November 2005, 6000 registration forms were distributed in 35 high schools from cities of Bucharest, Iasi, Cluj, Constanta and Timisoara. 67.3% of interviewed subjects registered for the contest, meaning 4038 persons, 24% current smokers and 76% never smokers.

They had to remain or become no smokers for 30 days (one month). By the end of the abstinence month, among those who succeeded to fulfill the smoke-free criteria, winners, selected by drawn, were offered 26 prizes (for 13 smokers who quit and 13 constant never smokers) consisting of two PC-s (prize I), 4 mobile phones (prize II) and 20 sport equipments (prize III). Winners of prize I, II and III were checked if no smoking status by assessing carbon monoxide concentration in the exhaled air.

Carbon monoxide as a result of cigarette combustion is inhaled into the lungs. Its half-life time in exhaled air is 6 hours. Carbon monoxide (CO) concentration measured at the end of an expiration is directly reflecting CO blood concentration. Thus, CO in exhaled air is a good indicator of tobacco consumption within past 5-6 hours (except other situations as CO intoxication by fires, underground parking exposure, etc.).

Differentiated questionnaires for smokers and never smokers were distributed at the end of the contest to appreciate impact of the program. 2774 subjects (68.7% of the 4038 who took part) agreed to answer.

Smoking profile of participants

Overall smoking rate was 32.6%. Never smokers were 61.9% girls under 16, while smokers, defined as those who consumed cigarettes at least 30 days prior to registration for the contest, were divided into two groups: occasional smokers (14.3%) and daily smokers (18.3%).

Program’s impact

The following questions were addressed to smokers/never smokers

- What determined you to quit smoking?

![Figure 17. (Trofor et al, 2009)](image)

Occasional smokers stop smoking easier (64, 3%) and health concerns were main reasons for their decision to quit (Figure 17).
- *Did you relapse smoking?*

  23.1% of occasional smokers came back to smoking (Figure 18) after variable abstinence interval during initial days of the contest.

![Figure 18. (Trofor et al, 2009)](image)

Abstinence duration during the 30 days contest is drew bellow (Figure 19):

![Figure 19. (Trofor et al, 2009)](image)

Never smokers were asked if tempted to start smoking during the contest (Figure 20):

![Figure 20. (Trofor et al, 2009)](image)

Smokers’ reasons to register for the contest were (Figure 21):

![Figure 21. (Trofor et al, 2009)](image)
When asked if the competition helped them to think about giving up smoking, affirmative answer was more relevant in the occasional smokers’ category (Figure 22):

![Bar chart showing percentage of occasional and daily smokers](image)

**Figure 22.** (Trofor et al, 2009)

Finally, another program of smoking prevention among Romanian secondary school children was *I do not smoke*. The program was funded by the Royal Embassy of Netherlands in Romania and was implemented by nongovernmental organization, Pure Air Romania in partnership with National Anti Drug Agency, Romanian Ministry of Education and University of Medicine and Pharmacy of Cluj-Napoca (Figure 23). The program was implemented in 2006 among 27 classes of pupils aged 13/14 years old from Cluj-Napoca, another big city situated in the North Western part of Romania.

![Image of a cartoon hand with the text: Nu, multumesc, eu am decis si nu fumez](image)

**Figure 23.** (Trofor et al, 2009)

The program embraced the social influence approach and focused on development of cigarette refusal skills. It consisted of five weekly sessions of forty-five minutes each, and was translated from a Dutch version that was tested earlier (De Vries et al, 1994) and adapted to the Romanian social and cultural context.

Structure and content of each session, presented by adolescents on video, can be summarized as follows:

- a) introduction of the theme in a class, on video,
- b) activities in small groups, peer-led,
- c) return to one group and continuation of the lesson on video,
- d) activities in small groups, peer-led,
- e) (sometimes) home activities.
The video consisted of an introduction made by three volunteer adolescents with real life situation role-played by them, interviews with adolescents and an introductory part to explain the activities also performed by young people.

The activities, focusing on the theme of the lessons, were realized in groups of four or five students and were led by a peer leader. The peer leaders were students from the same class as the participants students. They did not present information about the program, but served as chairmen of the small activity groups. They summarized the activities, stimulated the group to work and presented the outcomes of group work.

The teachers coordinated the lessons, assisted the peer leaders and stimulated the students to participate. Both teachers and peer leaders received a one-hour training before the beginning of the program. For the training of peer leaders and teachers, a special training video was developed to explain everybody’s task.

Students, peer leaders and teachers had their own manuals, summarizing content of the video by cartoons, as well as the description of activities and instructions to achieve it.

Each lesson had a different theme, thus program made overall approach of: consequences of smoking, direct, indirect or peer pressure of smoking, effects of active and passive smoking, and indirect pressure from advertisement and adults. Several methods of skills training were modeled on video and were practiced afterwards during activities by role-plays in small groups in order to enhance self-efficacy and the acquisition of refusal skills. The last lesson provided a summary; the activities centered on skills training and decision making.

To increase commitment, students were asked to conclude a non-smoking contract and to write their name on a non-smoking poster that could be clearly seen in the class.

All the four programs for young people described above were extremely useful and very much appreciated by participants, as our feedback in follow-up showed. But in order to obtain fruitful results, reflected in low smoking rates in youth and promotion of healthy smoke free life-style among this population category, we need to provide permanent action in the field.

The impact of a health education program is determined not only by the effectiveness of the interventions, but also by the quality of program implementation, by the proportion of intended participants exposed to the program and by dissemination following outcomes.

As these European programs proved successful, in 2007, financed by Romanian Health Ministry and by partnership of public health institutions with "Pure Air Romania" Association, two of the above mentioned school based programs have become national governmental objectives.

_Adolescent smoking cessation_ is to be implemented in 2007-2008, as a first step in 20 Romanian counties (half of the country) and we expect to have an overall extension for the next years and permanent it, as a successful way to determine adolescents to avoid smoking.

Secondly, _I do not smoke_ will follow, beginning with 2008, to be delivered in as many Romanian schools as possible, covering the secondary school age group.

**Conclusions**

Considering actual smoking rates in Romania, we are aware of the fact that youngsters tobacco use prevention will claim for sustained and long term tobacco control measures, but having joint governmental, non governmental and academic institutions
initiatives, represents a good start to assist this age-group, especially when strong smoking intake policies will add in the future.

Also, relevant results about long term evaluation of the reimbursed „Stop Smoking” program for adults treated in three big cities in Romania (Iasi, Cluj, Tg. Mures), were published recently in Open Medicine:

<table>
<thead>
<tr>
<th>Smoking cessation for free: outcomes of a study of three Romanian clinics</th>
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<tbody>
<tr>
<td><strong>Antigona Carmen Trofor</strong>, Milena Adina Man, Corina Marginean, Filipeanu Dumitru, Letitia Trofor</td>
</tr>
</tbody>
</table>

**Introduction**

There is enough available evidence to advocate for the higher effectiveness of free of charge smoking cessation. For example, both the groups of Doescher et al. and Kaper et al. demonstrated over 10 years ago a beneficial impact of medical insurance contributions on using medication to stop tobacco use and on smoking cessation success rates (Doescher et al, 2002; Kaper et al, 2005). Harris and collaborators showed that medical systems completely covering the costs for tobacco dependence treatment ensure increased self-reported tobacco abstinence rate and duration, with a relatively low price, as compared to the partial or absent benefits of non-compensation (Harris et al, 2001).

Several studies have shown that different factors such as the type of cessation treatment as well as individual characteristics (age, gender, socio-economical level, length of smoking exposure, nicotine addiction) may influence the smoking cessation process both in terms of uptake and of short or long term abstinence rates (Khati et al, 2015; Stead et al, 2016; Trofor et al, 2009). Co-morbidities have been found to impact the cessation process and sometimes to cause discontinuation of the cessation treatment (Trofor et al, 2010).

In 2007, when smoking prevalence in the general Romanian population was 30% (Trofor et al, 2009), Romania implemented a national program (“Stop Smoking”), providing medication and counselling, entirely for free. At that time, the initiative was very welcomed by smokers, specialists in the field and policy makers, as pharmacological treatment and qualified aid to quit smoking were practically unavailable in a standardized manner and many low income individuals could not afford the treatment costs. Patients were directed to the tobacco treatment centers by a free phone advice line, being offered pharmacotherapy (varenicline, bupropion or nicotine patch) and 4-6 counseling sessions, for three months. However, even if designed as a national and free of charge intervention, over the next six years, numerous difficulties were encountered such as high call volume the need for more full-time qualified personnel/auxiliary staff, insufficient centers available in small cities and rural areas, administrative deficiencies in providing cessation medication supplies and finally, progressively decreasing governmental funding. Program coordinators struggled annually to maintain the program, so by continuing efforts and introducing patients’ co-payment, they
succeeded program survival until 2014, by keeping governmental financial support at an acceptable level.

The present study focused on the results of the program among participating smokers treated in three smoking cessation centers from three big cities of Romania-Iasi, Targu Mures and Cluj. It had three objectives. First, to report the smoking cessation rate at the end of the program at 3 months after the enrolment in the program (T1) for different types of treatment. Second, to investigate the individual factors associated with smoking cessation among smokers who received different types of treatment. Third, the abstinence rate at 12 months after the quitting date (T2) was also assessed, giving special attention to the changes of the smoking status from T1 to T2.

**Methods**

**Sampling procedure**

The study is part of a national program which received the approval and funding of the Romanian Ministry of Health. It was implemented in smoking cessation centers from three hospitals; the patients who were enrolled were coming on a voluntary basis to the hospitals in order to receive smoking cessation support and were agreeing that they accept the medical procedures offered by the smoking cessation centers accessed by them, in respect to the national program protocol participation.

Data collection was performed in two phases. First, an analysis of the databases that included smokers who participated in the “Stop smoking” program between 2007 and 2010 in three tobacco treatment centers in Romania (Clinic of Pulmonary Diseases Iasi, Clinic of Pulmonary Diseases Cluj and Clinic of Pulmonary Diseases Targu Mures) was conducted. These databases contained information about demographics, medical history, smoking characteristics, abstinence rate at the end of the program (3 months after the enrolment of the participants) and cessation therapy and program compliance. Second, all program participants were contacted by telephone for a long term telephone follow-up (LTFU) at 12 months after the quitting date (as recorded in patients’ files) in order to assess long term abstinence rate. Follow-up was conducted as a short telephone interview done by volunteer pulmonologists or psychiatrists in training. It used a standard follow-up questionnaire, based on recommendations in the Romanian Smoking Cessation Guideline (GREFA) (Trofor et al, 2008; Trofor et al, 2008*), which investigated present smoking status, abstinence duration, difficulties to staying abstinent and willingness to receive relapse prevention counseling.

**Statistical analysis**

The prevalence of several individual characteristics and smoking and cessation profiles at 3 months and 12 months follow-up were assessed. Pearson bivariate correlation analyses were used to highlight interrelations between abstinence rate at three months and several individual and smoking related characteristics such as: gender, presence of respiratory co-morbidities, presence of cardiovascular co-morbidities, number of cigarette packs/years, nicotine dependence score, quit attempts, and the presence of severe withdrawal syndrome. The Pearson bivariate correlation analyses were performed separately for each treatment regimen (nicotine patch, bupropion, or varenicline). Data were analyzed using the SPSS 17 statistical program (SPSS Inc.). A statistically significant threshold was considered at p < 0.05.
Results

Sample characteristics and abstinence rate at three months follow-up.

The study included 832 smokers who participated in the smoking cessation program. The overall abstinence rate at three months follow-up was 53.4%, while 28.6% were still smokers and 18% were registered as unrated.

The sample characteristics and their smoking profile by treatment regimen are described in Table 9 (Factors associated with smoking cessation at three months).

The results of Pearson bivariate correlation analyses show that among subjects treated with nicotine patch, no statistical significant correlations were found with individual and smoking characteristics. Among subjects receiving bupropion, fewer quitters were found among those with respiratory co-morbidities \((r=-0.76, p=0.02)\), with a high nicotine dependence score \((r=-0.82, p=0.019)\) and with \(\geq 2\) quit attempts \((r=-0.13, p\leq 0.001)\) or with a severe withdrawal syndrome \((r=-0.29, p\leq 0.001)\), respectively.

In smokers treated with varenicline, there were statistically significant increased quit rates in more severely addicted smokers \((r=0.23, p\leq 0.001)\), and in patients with \(\geq 2\) quit attempts \((r=0.30, p\leq 0.001)\). Also, significantly more women than men have stopped smoking with varenicline \((r=0.113, p=0.001)\). On the contrary, significantly fewer smokers with respiratory disorders \((r=-0.10, p=0.003)\) and fewer heavy smokers \((r=-0.23, p\leq 0.001)\) became abstinent under varenicline.

Abstinence rate at 12 months follow-up

The results show that at 12 months post quit date, 39.3% of the participants were still smokers, 18.6% were still abstinent and 42.1% were unrated patients. Even if at 3 months follow-up the smoking status could not be rated (no exhaled CO validation) in 18% of subjects, at 12 months follow-up 46.7% of these patients could be contacted and it was found that 40% of the people from the unrated group were continuing smokers, while 6.7% declared themselves non-smokers. A further 53.3% subjects could not be contacted and rated at 12 months follow-up.

Among patients evaluated at 3 months follow-up as non-smokers, 35.4% declared themselves as relapsing smokers, 28.6% declared themselves as no-smokers, while 36% could not be rated at 12 months follow-up. Among smokers at 3 months follow-up, they had the following status at 12 months: 46.2% continued to be smokers, 7.6% were no-smokers, while 46.2% could not be rated. Table 10 provides an overall summary of the characteristics and smoking status of the participants at 12 months follow-up.

Discussions

Tobacco use is detrimental to health and all health professionals have the duty to intervene and initiate tobacco cessation (Behrakis et al, 2012). Successful pharmacotherapy and counseling of patients to stop smoking is the most cost-efficient approach to prevent death and disease due to tobacco smoking. Discount or free of charge cessation medication (compensated in advance) has been proved to increase both the number of medical prescriptions and the abstinence rates (Hughes et al, 1991). It seems when compensated, patients have a higher probability to receive treatment and to try to quit and to refrain from smoking (Kaper et al, 2005). It is in the interest of insurance companies, medical services, governmental departments and pharmaceutical companies to collaborate, in order to ensure
compensation of tobacco dependence interventions and to inform smokers about the existence of such a strategy (Behrakis et al, 2012).

Smoking cessation expertise is rather recent in Romania, as tobacco treatment units were created in 2000, at first only in 3 big cities (Bucuresti, Iasi, Timisoara). Until 2007, free counseling was offered by trained specialists, but the only pharmacotherapy available was bupropion and its cost had to be entirely supported by the patient. Because of this, very little data about smoking cessation outcomes in this period are available. However, due to lack of any medication compensation and to previous low accessibility of centers, such data refer mainly to bupropion or counseling cessation results in small groups of patients and other data come from European projects developed by Romanian NGO “Aer Pur” (Trofor et al, 2010). For example, in the cessation centre of the Clinic of Pulmonary Diseases Iasi, bupropion abstinence rate was 28%, at 6 months post quit date (Trofor et al, 2005).

Prior to 2007, most Romanian studies were based on results from reimbursed smoking cessation centers; despite this, there is a small amount of Romanian literature in this field. In the Clinic of Pulmonary Diseases Iasi, such end of treatment abstinence rate ranged from 38.3% to 50.7% (Trofor et al, 2008**).

The study presented here was performed in three smoking cessation centers in Romania. It shows that the overall abstinence rate at three months was 53.4 % and this was due mainly to the fact that pharmacotherapy and counseling have been offered for free. Despite such fruitful abstinence outcomes at three months (T1), at 12 months follow up (T2), an abstinence rate of only 18.6% was found. Post-treatment abstinence should be a strong predictor for abstinence at the 12 months follow-up. One possible explanation of the observed versus estimated difference between the T1 and T2 abstinence rates is that program funding covered only 3 months treatment phase.

Looking for comparison with similar data in the field, a wide range of results can be found, varying from 12 months abstinence of 14% in a Swedish study (Nohlert et al, 2013) to 34% in a study performed in Australia (Richmond et al, 2003). As well, in an intensive 8 days residential smoking cessation program, a significantly higher 6 months abstinence rate for residential patients compared to outpatients (52% vs. 27%) was found (Hays et al, 2011).

Abstinence rate at three months follow up by treatment regimen appears highest in the Varenicline group. Nevertheless, as due to different market costs of cessation therapies (varenicline cost was three times higher than both costs of nicotine patch and of bupropion), and to the program regulatory request that all 3 medications had to fit the same budget equal shares; thus, unequal amounts of varenicline, bupropion and nicotine gum were provided to the centers. This represents a weak point of the program, but without jeopardizing scientific research criteria for smoking cessation validation, as they are described by literature in the field (Hughes et al, 2003).

Also, the individual characteristics described a random cessation pattern: more women, more heavy smokers, and more frequent previous withdrawal syndrome were described among subjects in the Bupropion group, while the highest nicotine dependence scores and most numerous cases of previous quit failures were seen in the Varenicline group. In the nicotine patch group, there were 50% of subjects with co-morbidities, but no other specific features.
There was a similar age average between the treatment regimens. Special emphasis should be placed on the positive impact generated by the reimbursed program, as was observed during the telephone investigation. This was suggested by the great number of respondents at the 12 months follow-up, even in the still smoker and unrated groups and by considerable willingness for relapse prevention counseling, in the majority of interviewed participants. As well, even if relapsed to smoking, many subjects achieved a long duration of partial abstinence (154 days ± 180 SD abstinence days), as revealed by the “longest stop smoking period” at 12 months follow-up.

There are multiple unexplored facets of the problem under discussion. For instance one could be validated at three months follow-up as non-smoker, but could relapse to smoking until long term evaluation. As 12 months follow-up was conducted by telephone interview, there was no possibility to objectively check self declared smoking status by exhaled air CO validation. In return, some smokers who did not manage to quit by the end of the 3 months treatment program were found to be non-smokers at 12 months. Thus, there is a possibility that, by 12 months, patients have succeeded in stopping smoking by their own will, based on program’s long term impact. We may name this an educational “post-effect”, as besides free medication, they also received several counseling sessions during clinic visits.

**Conclusions**

This is the first study in our smoking cessation centers to analyze long term impact of fully reimbursed smoking cessation, covering three months pharmacotherapy and counseling. By analyzing data coming from a smoking cessation database in three Romanian centers from respiratory disease clinics of the medicine universities of Iasi, Cluj and Targu Mures, we have found 18.6% abstinent among respondents to a telephone contact visit, 12 months post quit date. Providing smoking cessation for free had a positive long term impact on program participants, even if there was no intermediary contact between the 3 months and the 12 months follow-up. Thus, for the majority of respondents declared willing to receive relapse prevention counseling, a total of 154 days ± 180 SD abstinence days was recorded among still smokers and some of the smokers at three months follow-up continued to quit even after program’s end, probably due to an educational “post-effect” of the program.

Further research could be useful for cessation practitioners worldwide and for designing a standardized reimbursement approach to ease implementation of such programs at national level.
### Table 9. Individual characteristics, smoking and cessation profile, by treatment regimen at three months follow–up (Trofor et al, 2016)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nicotine patch</th>
<th>Bupropion</th>
<th>Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>130</td>
<td>489</td>
<td>213</td>
</tr>
<tr>
<td>Age(years) (mean)</td>
<td>43.65±12.2SD</td>
<td>43.09±12.5SD</td>
<td>44.9±12.45SD</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>42.3</td>
<td>48.3</td>
<td>36.2</td>
</tr>
<tr>
<td>Cigarettes/day (average) in the last 12 months</td>
<td>23.91±11.1SD</td>
<td>20.14±7.8SD</td>
<td>23.4±7.9SD</td>
</tr>
<tr>
<td>Nicotine dependence score (≥7)(%)</td>
<td>42.1</td>
<td>29.9</td>
<td>55.9</td>
</tr>
<tr>
<td>Packs-years (average)</td>
<td>24.7±16.6SD</td>
<td>27.2±11.01SD</td>
<td>21.6±10.12SD</td>
</tr>
<tr>
<td>Co-morbidities (n)</td>
<td>65</td>
<td>206</td>
<td>57</td>
</tr>
<tr>
<td>≥1quit attempt (%)</td>
<td>23.1</td>
<td>13.3</td>
<td>51.2</td>
</tr>
<tr>
<td>Withdrawal syndrome (%)</td>
<td>14.6</td>
<td>27.4</td>
<td>17.4</td>
</tr>
<tr>
<td>Exhaled air carbon monoxide level (ppm)-Initial status (average)</td>
<td>14.9±4.2SD</td>
<td>16.08±4.7SD</td>
<td>15.33±2.5SD</td>
</tr>
<tr>
<td>Exhaled air carbon monoxide level (ppm)-Final status (average)</td>
<td>0.12±0.7SD</td>
<td>0.04±0.2SD</td>
<td>0.24±0.7SD</td>
</tr>
<tr>
<td>End of treatment abstinence (%)</td>
<td>10.8</td>
<td>15.5</td>
<td>30.5</td>
</tr>
</tbody>
</table>

### Table 10. Characteristics and smoking status at 12 months follow-up (= at enrollment, **=at 3 months after enrollment) (Trofor et al, 2016)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Smokers</th>
<th>Non-smokers</th>
<th>Unrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>327</td>
<td>155</td>
<td>350</td>
</tr>
<tr>
<td>Age *(years) (mean)</td>
<td>42.09±11.8SD</td>
<td>45.5±11.48SD</td>
<td>44.07±13.3SD</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>38.3</td>
<td>16.6</td>
<td>45.1</td>
</tr>
<tr>
<td>Cigarettes/day (average) in the last 12 months*</td>
<td>23.6±9.03SD</td>
<td>22.6±7.3SD</td>
<td>21.6±9.3SD</td>
</tr>
<tr>
<td>Nicotine dependence score (≥7)* (%)</td>
<td>41.4</td>
<td>53.4</td>
<td>28.7</td>
</tr>
<tr>
<td>Packs-years *(average)</td>
<td>23.8±15.41SD</td>
<td>27.2±16.3SD</td>
<td>27.1±17.9SD</td>
</tr>
<tr>
<td>Co-morbidities* (n)</td>
<td>117</td>
<td>51</td>
<td>160</td>
</tr>
<tr>
<td>≥1quit attempt *(%)</td>
<td>26.3</td>
<td>38.1</td>
<td>17.1</td>
</tr>
<tr>
<td>Withdrawal syndrome history *(%)</td>
<td>19</td>
<td>24.5</td>
<td>25.7</td>
</tr>
<tr>
<td>Expired air carbon monoxide level* (ppm) - Initial status (average)</td>
<td>15.82±3.9SD</td>
<td>15.7±4.2SD</td>
<td>15.8±4.8SD</td>
</tr>
</tbody>
</table>
Expired air carbon monoxide level **(ppm) - Final status 0.14±0.5SD 0.06±0.2SD 0.09±0.5SD (average)

End of treatment abstinence**(%)

<table>
<thead>
<tr>
<th></th>
<th>33.6</th>
<th>11.6</th>
<th>31.4</th>
</tr>
</thead>
</table>

Maximum abstinence duration (mean) evaluated at 12 months follow up

<table>
<thead>
<tr>
<th></th>
<th>154 days ±180.1SD</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
</table>

Willingness for relapse prevention counselling (%)

evaluated at 12 months follow up

<table>
<thead>
<tr>
<th></th>
<th>61.5</th>
<th>97.2</th>
<th>0</th>
</tr>
</thead>
</table>

2.3. Research for development of skills in the field of specialized assistance for tobacco use and dependence

A. Background

My previous research about the level of knowledge and skills among doctors and other health professionals has revealed a huge gap between the need for assisting smokers at risk for various tobacco related disorders and the availability of specialists in treating tobacco use and dependence in all Romanian medical services. Moreover, my research about smoking prevalence among medical personnel has identified another great educational deficiency: a high rate of tobacco users among medical staff; in fact this rate was higher than in the general population, in 2000, being well known that such situation is a reliable epidemiological indicator of bad tobacco control measures in the respective country (Munteanu et al, 2005).

It appeared obvious that, at the time, most doctors (many being themselves tobacco consumers) lacked basic notions about tobacco use hazards, about health benefits of quitting and the methods to achieve tobacco abstinence, so an urgent action imposed to fill this gap. That’s why, by the occasion of investigating smoking behavior in medical doctors, nurses, etc., I took numerous initiatives to „advertise” opportunities for acquiring training in the field of treatment of tobacco use and dependence. At first these actions were directed towards pulmonologists and internal medicine specialists and later on to nurses, dentists, G.P.-s and other health professionals willing to get involved in assisting smoking patients.

In order to have an overal view of the magnitude of this deficiency, I have also investigated prevalence of smoking among medicine students, as they represent an important future potential of smoking cessation specialists.
B. Personal contributions

Scientific, professional and academic achievements in this field

a) Professional and academic achievements in this field:

- I have chaired the first national conference „Tobacco and Health” (Iasi, 2006) with international participation of 10 foreign experts, followed by other 2 similar events in 2009 and 2011, conference with international participation of the Tobaccology Section of Romanian Society of Pulmonology (www.srp.ro), with the purpose to offer access to best quality education in the field, to participants, through pre-conferences courses and workshops.


b) Publications in the field

The main area of research considered for this study direction referred to smoking among doctors and medicine students (2 articles in abstract in supplement of the ISI Web of Science indexed European Respiratory Journal and two articles published in extenso in Tabaccologia and in Pneumologia). Most relevant conclusions are described here below:


In this study, performed among my colleagues, specialists in pulmonary diseases, it was found that even doctors who treat respiratory disease patients, including smokers had a high smoking rate of 57.1%, and overall, smoking behavior was present among 49.3% of the personnel, inducing a negative influence on patients.


In this study conducted on the 2-nd year Dentistry students in the University of Medicine and Pharmacy “Gr. T. Popa” Iasi, it was found that 24.4% of respondents were active smokers and 13.3% were former smokers. The level of knowledge about tobacco induced diseases proved very low (13.6% were aware of the cardiovascular risk of tobacco and only 36.2% knew that nicotine substitutes are used for smoking cessation treatments) The lack of knowledge about oral disorders due to tobacco exposure served as basis to introduce basic notions about tobacco use and dependence treatment in the medical graduates and postgraduates curricula.
3. Self-reported tobacco exposure and knowledge in the field in medical students. A cross-sectional observational study.

**Abstract of the article**

Introduction: A cross-sectional observational study about self-reported tobacco exposure and level of knowledge about approaching tobacco use and cessation was made among medical students of the University of Medicine in Cluj Napoca, Romania.

Methods: A self-reported, anonymous and validated questionnaire (with 21 questions) was administered to collect data about age, gender, rural/urban area, active and passive smoking exposure; secondly, students were evaluated their level of knowledge regarding tobacco use and cessation by calculating a total score of knowledge.

Results: Of 300 respondents, 28.33% were current and 5.67% were former smokers. 71.76% among current smokers reported being passively exposed to tobacco smoke in their homes. The total score of knowledge of the questionnaire was 60.05%. 83.33% of the interviewed students (n=250) thought they should receive training for counseling patients to quit using tobacco, respectively to be provided a tobacco use and cessation course, by curricula.

Conclusions: Medical students had a low, unsatisfactory level of knowledge about harmful effects of smoking on human health. This reflected also in their own smoking behavior. A specialized smoking cessation course should be mandatory introduced in the medicine universities curricula.

4. One article published in *Pneumologia*, for advocating and giving useful examples of successfully introducing smoking cessation curricula into current clinical activity of practitioners with their smoking patients.

**Abstract**

Smoking cessation – a “must have” in medical curricula. HERMES project – a “pro”

Antigona Trofor, Tr. Mihaescu

*Pneumologia*, Vol. 58 – Nr. 3/2009, pag. 159-162, ISSN 1223-3056

**Abstract**

Smoking cessation – a „must have“ in medical curricula. HERMES project – a supportive initiative Respiratory Medicine is a complex domain of activity, moreover has enlarged its content in last decades by numerous areas of expertise, among which also smoking cessation, a field aiming to assist individuals to quit or prevent tobacco use.
Introducing routinely this preoccupation in Romanian doctors’ work is supposed to legitimate nicotine dependence as a disease, as already classified by world medical organizations. In agreement with HERMES project, an European Respiratory Society initiative to harmonize education in respiratory medicine across Europe, we recommend smoking cessation to be mandatory in Romanian medical curricula. Thus, students will earn theoretical, practical and behavioral skills to approach health effects of tobacco use, treatment and approach of smokers. Yet, considering real life situation in our country, for actual generations of practitioners we suggest intensive training in two modules: a basic one to cover lack of elementary knowledge during previous years and an advanced module for specialists. To future generations, a continuous, more coherent approach is to be settled, aiming to create brief advice expertise during medical university years of study. When graduating, future doctors willing to become smoking cessation experts will be provided postgraduate training to achieve this degree. Hopefully, within next two generations, many Romanian doctors will become capable to routinely deliver smoking cessation interventions, at European standards.

2.4. Development and implementation of guideline recommendations for tobacco use and dependence disease

A. Background

In 2008, the present status quo for approaching tobacco use and dependence in Romania consisted of already implemented national programs for assisting adult and adolescents tobacco users, and of a numerous team of smoking cessation specialists arising in almost 50 centers all over the country. In this context, it appeared like a strong necessity to provide standardized diagnosis and treatment criteria for all this new born infrastructure. Considering this finding, I have proposed to the Romanian Society of Pulmonology to create a working group within the specialty Tobaccology Section and to start working together for publishing the first Romanian national guideline aimed to offer recommendations for assistance and specialized treatment for patients suffering from tobacco use and dependence. This goal was achieved in 2008 by publication of the first guideline edition, updated afterwards in 2010, 2013 and 2016, by means of national and European educational grants „with collaboration of large editorial boards of national and European experts.

B. Personal contributions

Scientific achievements in this field: guideline publication and collaborative educational grants

One of the strong points of the guideline is that it was endorsed and revised by other health professionals societies (Internal Medicine, Family doctors, Alergology, Cardiology) and obtained approval from the National College of Doctors in Romania; in this manner treatment of tobacco use and dependence became legitimized among our colleagues and in the same time, smoking patients addressed to these specialities could receive specialized assistance also from the cardiology, internal medicine specialists, etc., not only in the pulmonology network, as before 2008.

The guide was accompanied by another useful material, aimed to respond basic knowledge needs of those professionals without any previous training in the field of tobacco use and dependence, described at item 2.


In the next 2 years, this guideline was promoted and implemented, through various scientific meetings and workshops developed under the umbrella of the Romanian Society of Pulmonologists in all aliend smoking cessation centers.

In respect to our national guideline regulations, the 2008 guide was updated and re-edited in a second edition, in 2010, with the same editors, an extended work group of revisors and also a patient’s group endorsement.


This second edition was also applied in current clinical practice of many clinicians in charge with smoking patients, for the next 2 years.

At the time of the next 2 years revision, due to promising collaboration I began since 2008 within the European Network for Smoking Prevention (ENSP) as associated member, I made them a proposal to enhance visibility of the Romanian GREFA Guideline and use it as background for an European guideline under the umbrella of this prestigious tobacco control European organization, based in Brussels. The proposal was welcomed and I started working in this project of updating the 2010 Romanian guide and turn it into an European 2012 (English language) version, providing most recent literature data and shared expertise from a group of European smoking cessation experts (France, Ireland, Greece, Sweden, Turkey, Russia, Romania).

The 2012 European Smoking Cessation Guideline was published in Brussels and launched within an event hosted by the European Parliament in October 2012, from behalf of the project’s leading organization, ENSP (www.ersnet.org). This ENSP guideline was co-funded by the Health Programme of the European Union.

Following this achievement, it seemed logical to make the Romanian audience of the GREFA guide benefit from the last, 2012, updated English edition of the document, so I have coordinated its translation into Romanian, which became available as the ENSP smoking cessation guideline – Romanian edition 2013 and it was launched in the 2013 national conference of the Tobaccology Section of the Romanian Society of Pulmonologists, in Oct. 2013, at Ramnicu Vilcea (www.srp.ro).


All this continuing process of updating and improving the content of the GREFA guideline every 2 years, has led to a sustained growing interest and human resources within the Romanian Society of Pulmonologists for gaining expertise in the domain of tobacco use and dependence management. In the same time, opening the European collaboration for guideline production, offered new opportunities to network and to provide our Romanian expertise in the field for those countries, ENSP members, that were less experienced and needed support for developing tools to provide treatment for smokers. This is how, I have joined an educational project, from behalf of the European Network for Smoking Prevention, and have applied, as Romanian partner, in the Global Bridges at Mayo Clinic and Pfizer Independent Grants for Learning and Change Request for Proposals, with the project: European Smoking Cessation Guidelines and Quality Standards project (ENSP-ESCG/QS).

6. **Director (responsible) in Romania for the educational grant:** **EPACTT Project** (*EuroPean Accreditation Curriculum on Tobacco Treatment project*), **run by** “Global Bridges – Healthcare Alliance for Tobacco Dependence Treatment – USA” **Project ID: 13106933 (2014-2016),** and having the goal to: “develop a European network of healthcare professionals and organizations dedicated to advancing evidence-based tobacco dependence treatment and advocating for effective tobacco control policy. This project was a logical follow up of the ENSP-ESCG Project started by ENSP in 2011 for producing the 2012 ENSP smoking cessation guideline. The project has increased the quality of the tobacco dependence treatment services in the selected countries (Armenia, Georgia, Ukraine, Russia, Moldova, Romania, Greece and Turkey).” Practically, it was a new update of the English guideline version from 2012, issued in 2015, with re-translation in national languages, but the novelty consisted in the fact that the project brought funds to provide also translation in national languages of few new countries (Armenia, Georgia, Moldova, Ukraine) that had no smoking cessation guideline available in their own countries, up to that time. The project had the acronym **EPACTT**, and was run for 2 years 2014-2016, with successful outcomes, finalized in the ENSP meeting, in April 2016, in Brussels. During this meeting, the EPACTT participants received a tobacco dependence training course with European accreditation training certificates. Project website: [http://elearning-ensp.eu/](http://elearning-ensp.eu/). Faculty: [http://elearning-ensp.eu/mod/page/view.php?id=19](http://elearning-ensp.eu/mod/page/view.php?id=19)
7. Director (responsible) in Romania for the educational grant: „EPACTT-PLUS: Expansion of the “EuroPean Accredited Course on Tobacco Treatment” project run by the European Network for Smoking and Tobacco Prevention (ENSP) as coordinating organization of the Healthcare Alliance for Tobacco Dependence Treatment and Pfizer Independent Grants for Learning and Change, identified by Grant ID: 25944945, under the Global Bridges at Mayo Clinic, call for European Region on 17 November 2015, duration 24 months (2016-2018).

The EPACTT PLUS/EPACTT 2 (http://ensp.org/epactt-2/) project is following successful implementation of the EPACTT project in 2015-2016 and aims to further develop accredit and deliver a user friendly and accredited online training programme in advanced tobacco treatment in 15 languages. EPACTT PLUS will adapt and translate the curriculum/training program on tobacco treatment we have developed as part of EPACTT-1, enhance it further- so that it can be deployed in English, Greek, Spanish, French, Polish, Armenia, Romanian, Georgian, Russian, Albanian, Italian, Serbian, Bulgarian, Slovenian and Ukrainian.

2.5. Research for development of personalized treatment and prevention programs for tobacco use and dependence

A. Background

Remaining in the same area of study, later in the research area, I was preoccupied in identification of those categories of smokers at high risk due to continuing tobacco exposure and in designing a more personalized approach to address them. Therefore, in the last decade I expanded the research area, related to the differential effects of tobacco use upon health response of the organism and to the efficacy of smoking cessation therapies for the case of several high risk tobacco users, such as COPD patients, smokers with cardiovascular or with psychiatric co-morbidities, etc. Majority of these studies exploring such elements were shared in international congresses and published in abstract in supplements of ISI Web of Science indexed journals (in ERJ, in Am. J. Crit. Care Med., or in European Psychiatry).

As I shared this piece of work in various international events, I was invited in 2014, by my colleagues members of the European Network for Smoking Prevention to apply, as Romanian research entity partner for a grant within the EU 3rd Health Programme (part of the H2020 EU call) which is the main instrument that the European Commission uses to implement the EU Health Strategy. This application was approved as Project “TOB-G: Tobacco Cessation Guidelines for High Risk Groups” (Grant Agreement number: 664292 - TOB-G - HP-PJ-2014).
B. Personal contributions

Scientific, professional and academic achievements in this field

a) Publications in the field

In order to develop more personalized treatment and prevention programs for tobacco use and dependence we have targeted in our smoking cessation center several categories of vulnerable smokers: respiratory disorders in patients, smokers with comorbidities, relapers, and special populations. The results were disseminated according to the following papers:


3. Antigona Trofor, Miron R, Ciobanu M, Barnea E, Esanu V. EFFICACY AND SAFETY OF VARENICLINE IN A SMOKERS POPULATION WITH HIGH PREVALENCE OF COMORBIDITIES. European Respiratory Journal. 2010. E2060. 36(suppl. 54):357s.


b) Research projects:


Project summary

TOB-G project aims to develop and implement an innovative and cost effective approach to prevent chronic diseases related to tobacco dependence. The specialized
guidelines for high risks groups will be developed according to ENSP’s evidence based and good practices in tobacco cessation and with ERS TCC scientific material on smoking health hazards. High risk populations are considered those who suffer from cardiovascular diseases, COPD, type 2 diabetes, adolescents & pregnant women. The developed guidelines will contain strategies and recommendations designed to assist health professionals in delivering and supporting effective treatment of dependence on tobacco. Recommendations will be made as a result of scientific reviews and evidence of good practices from scientific groups that will consist of health professionals of different expertise. To monitor the quality of the approach a pilot implementation of the tobacco cessation will be conducting for each group. The assessment of the effectiveness of the tobacco cessation guidelines will be the primary aim of the scientific groups and will be measured by the number of people quitting smoking after the pilot implementation. Since the tobacco cessation guidelines will be addressed to health professionals, the partnership will develop and implement an e-learning training for guidelines use. The project fits perfectly the objectives and priorities of the 3rd Health Programme, as it will assist health professionals to provide guidance and targeted prevention to high risk populations engaged to the unfavourable lifestyle of smoking. Training primary care physicians addresses the lack of specialist doctors in EU and increases access to tobacco cessation specialists. TOB-G project will enhance the overall European capacity in the treatment of tobacco dependence, thus, in the prevention of chronic diseases, through offering smoking cessation tools, appropriately assessed and fitted to the specific needs of high risk groups.

I have started to work in the TOB G project in June 2015, and the project is still ongoing, the first deliverables (TOB G guidelines for patients with Diabetes, COPD and Cardiovascular disease) are expected for in May-June 2017, while pilot’s results and e-learning based modules will be delivered by December 2017.

As Romanian partner- responsible for this project, I am in charge with coordinating two Work Packages (WP): WP4 and WP5, aiming to produce TOB G guidelines and 6 months evaluation pilot program for smoking cessation in smokers diagnosed with COPD, Diabetes and Cardiovascular disease (mainly arterial hypertension, arteritis and ischemic cardiopathy. As well, I am involved in dissemination, e-learning module and management activities in the other 4 WP of TOB G.

2.6. Development of evaluation tools for tobacco use and dependence integrated in a comprehensive respiratory health strategy

A. Background

This part of the thesis is complementary to the nowadays modern medicine, related to the health policy makers decisional mechanisms and tools. The actual European context of approaching tobacco use and dependence is closely linked to the actual tobacco control European legislation (The European Parliament and the European Union, 2014). Consequently, another research direction useful for my goal to provide tools for a comprehensive respiratory health strategy that will minimize harmful effects of tobacco
exposure at this level was to analyze attitudes and behaviors among smokers and the way they understand new European tobacco control measures. It was a long process, starting over the last decade by analysis of the situation in Romania before and after becoming an EU member. Some relevant results of these analysis are presented in the publications below.

B. Personal contributions

Scientific, professional and academic achievements in this field

a) Publications in the field (one publication in supplement of the European Respiratory Journal and one article published in Tobaccologia)

| Overview of last 20 years of tobacco control activities in Romania-achievements and future challenges |
| Antigona Trofor, Didilescu C., Radu-Loghin C. |

Abstract

Aim: To estimate efficiency of the past 20 years of tobacco control. To establish future objectives for a fully smoke-free society. Material and methods: Assessment of the existing tools needed to achieve a smoke-free Romania, in the major areas of tobacco control, was done. Weak points were identified. Future short-medium and long term objectives were defined. Results: Positive outcomes based on the past 20 years overview: -Law to restrict tobacco consumption and smoking in certain public places. – Governmental initiatives for smoking prevention, – Specialised centres for smoking cessation, – Intensive scientific activity inside Romanian Society of Pneumology (publications, surveys, participation to international congresses), smoking is included in the university’curricula, – National No-Tobacco Day, – Romanian Network for Smoking Prevention, – Tobacco Control (TC) National Resource Center, – Media campaigns to reduce tobacco use – Several EU projects for smoking prevention/cessation in young people Weakpoints – great smoking rates in general population and among doctors, – smoking in certain public places – tobacco products’advertising is still legal in Romania. – lack of financial support for TC activities, – absence of reimbursement for smoking cessation activity and therapy. Urgent objectives are: – Stronger law against tobacco use/advertising – Develop effective tobacco control policy – Free of charge/accessible smoking cessation services and therapy. Conclusions: Tobacco Control in Romania has a 20 years history and has proofed its efficiency. It is our duty to continue this tradition, bringing our society to a smoke-free standard, to the health benefit of our nation.
In the second article here below, I disseminated the first results of the reimbursed smoking cessation program run in Romania, after becoming EU member state.


b) Research projects: team member and Project Responsible

In line with these preoccupations, a new collaboration opportunity was recently added to my research efforts, through 2 European projects addressing this subject.

1. In the first project, entitled „European-study on Quantifying Utility of Investment in Protection from Tobacco (EQUIPT)” Funded through European Community’s Seventh Framework Programme Grant Agreement No. 602270, I acted as Research Advisory Group member. The project was part of the call HEALTH.2013.3.1-1, Comparative Effectiveness Research (CER) in health systems and health services interventions, Coordinator: Subhash Pokhrel, PhD (Brunel university, UK), project duration: 2013-2016, Total funding: 2 047 908, http://equipt.eu.

This project opened for me a window to better understand tobacco control mechanism’s of feedback on the individuals in the society and to co-work for transposition of these tools into real life instruments to improve dedicated care for smoking patients. It helped me conclude that local policy makers and public health procurers often lack the data and financial justification to make the case for tobacco control investments.

Brief summary

No doubt, there is a vast body of evidence around the cost-effectiveness of an individual intervention within the smoking cessation and tobacco control area but most of this is deemed inappropriate to decision-maker, because: (a) the evidence base, which is usually generated from wider contexts, do not necessarily resonate with the local population and their needs; and (b) there is a lack of user-friendly decision-support tools that synthesize costs, effectiveness and other relevant data for a large number of interventions into a single Return On Investment (ROI) metric. Addressing both gaps is timely in this current austere climate - perhaps for the first time in history, public health funding is exposed to such a highly competitive financial environment.

To fill in this important gap in evidence, ten institutions from seven European member states have worked together to develop a programme of research, coordinated by Health Economics Research Group (HERG) at Brunel University. Funded by the European Commission’s Seventh Framework Programme (FP7), EQUIPT is a comparative effectiveness research (CER) project that brings together expertise from many disciplines and aims to provide policy makers and wider stakeholders with bespoke information about the economic and wider returns that investing in evidence-based tobacco control including smoking cessation agendas, can generate.

The coordinator of this grant is European Network on Smoking and Tobacco Prevention from Brussels, Belgium and the responsible for the implementation of the project in Romania is the NGO AER PUR Romania (EU funding budget for Romania 60.000 €).

As Director of the Romanian partner of this research project, I am involved in all Work Packages (WP), more exactly in WP 1-7.

**Summary of the EUREST PLUS project**

This is an International Tobacco Control Policy Evaluation Survey carried out in Germany, Greece, Hungary, Poland, Romania, and Spain. This project is known as the ITC 6 European Country Project (6E) under the larger project called (EUREST-PLUS).

The International Tobacco Control (ITC) Project is a multi-country prospective cohort study designed to measure the psychosocial and behavioural impact of key policies of the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC).

Germany, Greece, Hungary, Poland, Romania, and Spain make up the six countries of the ITC 6 European Country Project (6E). In addition to the FCTC, each country is a part of the European Union, and as such must also comply with the European Commission’s Tobacco Products Directive (TPD), the latest of which was made law in 2014 with a compliance date of May 20, 2016. Previous to the TPD of 2014 was the TPD of 2001, under which all six European States had to meet minimum standards of tobacco labelling and packaging restrictions, as well as regulations regarding cross-border trading and product ingredients. The latest TPD (2014) sets regulations on the following areas:

- Ingredients and emissions, including maximum emission levels on tar, nicotine, and CO₂, as well as restrictions on additives such as flavours and stimulants;
- Labelling and packaging restrictions, setting minimum dimensions for packages of tobacco as minimum standards on graphic (combined) tobacco health warning labels;
- Traceability and security measures to combat illegal cigarette smuggling and counterfeit products.

**Cross-border purchase regulations**

E-cigarette product regulations including pan-European restrictions on the amount of nicotine allowed within e-cigarettes/e-liquid, product design elements such as reservoir sizes, and more.

To evaluate the effect of the FCTC and the TPD (2014), the ITC Project is conducting the ITC 6E Project as part of the European Regulatory Science on Tobacco: Policy Implementation to Reduce Lung Disease (EUREST PLUS) Project. The main objective of EUREST-PLUS Project is to monitor and evaluate the impact of the implementing acts of the TPD and assess these within the context of FCTC ratification at a European level.
The ITC 6E Project will run two parallel prospective cohort surveys with adult smokers in 22 other ITC countries—(Canada, United States, United Kingdom, Australia, Ireland, Thailand, Malaysia, China, South Korea, New Zealand, Mexico, Uruguay, France, The Netherlands, Brazil, Mauritius, Bangladesh, Bhutan, India, Kenya, Zambia, and Abu Dhabi – United Arab Emirates).

The ITC 6 European Country Wave 1 Survey was carried out from June to September 2016.

Main Objectives

To evaluate the psychosocial and behavioral impact of TPD implementation and FCTC implementation, through the creation of a longitudinal cohort of adult smokers in 6 EU MS (Germany, Greece, Hungary, Poland, Romania, and Spain; total n=6000) in a pre- vs. post-TPD study design (Work Package, or WP, 2 and 3). Moreover, these evaluation studies of the impact of the TPD and FCTC will be conducted with respect to vulnerable populations, including low-income/socio-economic status (SES) groups and those smokers with respiratory co-morbidities (and/or those with pre-morbid symptomatology). Another important topic that will be addressed in the scientific studies of the ITC 6E cohorts will be a focus on e-cigarettes, addressing basic issues of transition rates from cigarettes to e-cigarettes vs. dual use vs. reversion back to cigarettes vs. quitting all nicotine products.

To assess support for TPD implementation through secondary dataset analyses of the 2015 Special Eurobarometer on Tobacco Survey (SETS), a cross-sectional survey performed among 27,000 adults in all 28 EU MS, before the TPD is implemented, and to monitor progress in FCTC implementation in the EU over the past years through trend analyses on the merged datasets of the 2009, 2012 and 2015 SETS datasets (n=80,000), with a special focus on vulnerable populations (youth, minorities, unemployed, etc.) (WP5).

To document changes in e-cigarette product parameters (technical design, labelling/packaging and chemical composition) following TPD implementation of Article 20 of the TPD (WP6).

To enhance innovative joint research collaborations on chronic, non-communicable diseases (NCDs) in low- and middle-income countries (LMICs) and in vulnerable populations in high-income countries (HICs), a key priority of the Global Alliance for Chronic Disease (GACD) outlined in the call. We will specifically address these cross-country analyses through the pooling and comparisons across both other EU countries of the ITC Project (6E, UK, France, Netherlands), and other non-EU countries from LMICs and HICs from the global ITC Project (including key countries of comparison such as Australia, Canada, New Zealand, United States, China) (WP4).

The objectives of the ITC 6 European Country Survey are:

To examine the prevalence and patterns of tobacco use in all six European States.

The ITC 6 European Country Survey provides multidimensional estimates of prevalence and patterns of tobacco use among the populations of all six participating states. It describes the consumption patterns within each countries population, quitting behaviour, as
well as each population’s knowledge, beliefs, and attitudes about tobacco use. Specifically, the survey investigates each country’s growth or absence of with respect to electronic cigarettes (e-cigarettes).

**To examine the impact of the Tobacco Products Directive (2014) in all 6 countries throughout the course of the study period.**

The ITC 6E Survey evaluates the impact of the TPD in the following areas: Health warning labels and package descriptors, Tobacco ingredients and additives, Cross-border sales of tobacco products, E-cigarette use and behaviour.

**To compare smoking behaviour and the impact of policies between the 6 European countries and other ITC countries.**

The ITC Project aims to provide an evidence base to guide policies enacted under the FCTC, and to systematically evaluate the effectiveness of these legislative efforts. All ITC Surveys are developed using the same conceptual framework and methods, and the survey questions are designed to be identical or functionally equivalent in order to allow strong comparisons across countries.

This research design provides high levels of internal validity, allowing more confident judgments regarding the possible causal impact of the policy.

Recommendations to strengthen the current tobacco policies are made based on existing and derived survey information. The aim is to optimise the effects of tobacco control policies with regard to situational and individual difference moderators: (a) demographic variables; (b) personality variables (e.g. time perspective); (c) environmental context (e.g. number of peers/family members who smoke); and (d) the individual’s smoking history (e.g. past quit attempts, smoking intensity and quitting smoking).

**Survey Design**

The ITC 6E Survey is a longitudinal cohort study. In other words, the respondents who participate in this survey will be re-contacted in the future to participate in follow-up surveys. The respondents were recruited through a face-to-face multi-stage stratified random sample of the general population aged 18 or more.

**The Research Team**

The ITC 6 European Country Survey is conducted by researchers throughout Europe from both the six participating countries as well as other prestigious institution partners in Europe and abroad. The 13 partners are: European Network for Smoking Prevention-Brussels, Waterloo University-Canada, European Respiratory Society, Kings College London, UK, University of Maastricht, University of Athens, University of Crete, Catalan Institute of Oncology, Health Promotion Foundation- Poland, Smoking or Health Hungarian Foundation, German Cancer Research Center, Aer Pur Romania Association, and Kantar Public Brussels.

The EUREST PLUS project is still ongoing, we are expecting its preliminary results and ongoing publications to become available in 2018-2019.
SECTION II - CAREER PERSPECTIVES

CHAPTER 3. PLANS FOR THE DEVELOPMENT OF SCIENTIFIC AND PROFESSIONAL ACTIVITY

3.1. Design and implementation of new smoking cessation programs for adults from high risk groups

I intend to continue my research activity in the field of smoking cessation and include a new focus on smoking cessation for adults who have all categories of respiratory chronic diseases, representing high risk groups, by extending my interest to smokers with pulmonary tuberculosis, smokers with lung cancer, smokers with idiopathic pulmonary fibrosis or smokers with both respiratory and cardiovascular/diabetes co-morbidities.

I am in the present director in the international grant “Tobacco cessation guidelines for high risk groups - TOB-G” funded by European Commission through 3rd EU Health Programme. The project is implemented in the period 2015-2017.

The project aims to develop and implement an innovative and cost effective approach for smoking cessation for high risk population groups. High risk populations are considered those who suffer from cardiovascular diseases, chronic obstructive pulmonary disease (COPD), type 2 diabetes, adolescents & pregnant women. The project will allow the development of guidelines designed to assist health professionals in delivering and supporting effective treatment of dependence on tobacco for high risk groups. Recommendations will be made as a result of scientific reviews and evidence of good practices from scientific groups that will consist of health professionals of different expertise. To monitor the quality of the approach, a pilot implementation of the tobacco cessation will be conducted for each group. The assessment of the effectiveness of the tobacco cessation guidelines will be the primary aim of the scientific groups and will be measured by the number of people quitting smoking after the pilot implementation. Since the tobacco cessation guidelines will be addressed to health professionals, the partnership will develop and implement an e-learning training for guidelines use. The project will assist health professionals to provide guidance and targeted prevention to high risk populations engaged to the unfavorable lifestyle of smoking. Training primary care physicians addresses the lack of specialist doctors in EU and increases access to tobacco cessation specialists. Therefore, the TOB-G project will enhance the overall European capacity in the treatment of tobacco dependence.

As director of the Romanian team, I provide activities of: project management, scientific advisory board and executive board capacity building, and for dissemination of results. Also, I am involved in the Work package regarding literature review and collaboration for producing COPD high risk group guidelines for smoking cessation as well as in Work Package regarding development, implementation an evaluation of a pilot study encouraging smoking cessation in high risk groups (COPD, diabetes and cardiovascular diseases) and in Work package for e-learning modules development. I hope to have the opportunity to apply the experience achieved in the TOB G project in future similar projects addressed to other
chronic disease respiratory high risk smokers from the categories I mentioned above. Therefore, by continuing to approach other high risk respiratory smokers, we will envisage developing and extending the range of diagnostic tests and screening procedures as well as new and more targeted preventive and therapeutic approaches, in a continuous effort to preserve respiratory health.

3.2. Exploring particular patterns of tobacco use and dependence among smokers with respiratory diseases

As the pattern of tobacco smoking in COPD patients represented a constant concern throughout my past decade research activity, one of the last directions of development regarded the personalized approach of this high risk category of patients. This research is ongoing within the pilot Work Package in the „Tobacco cessation guidelines for high risk groups- TOB G“ project I am coordinating in 2015-2017. During this pilot cessation real life phase I observed some relevant aspects about the way how these smokers can overcome their craving for nicotine, inbalance with their lung function and respiratory symptoms severity. It seems the classical tools we are using to assess and score the dependence to nicotine are not anymore so reliable as in the case of the non-COPD patients who have a normal lung function.

I am enthusiastic in continuing to develop the result of the observations concerning such findings, in a future research project in the same area. Based on my academic and research experience, I trust gathering in the future a research team that could produce high-level scientific production, competitive in applying for national and European funding, in this direction.

A major challenge in this research field is to acknowledge of individual and specific disease factors that cause or modify pattern of smoking behaviour and thus impact the cessation process, when triggered. As I mentioned before, at a certain point in my scientific activity, I have studied also smoking behaviour among pulmonary tuberculosis patients and among lung cancer patients. Is to be mentioned that these two categories of respiratory disorders are also of high risk in continuing smokers sub-populations. Also, consistent with my earlier results, they have a particular tobacco dependence pattern and response to cessation therapy. That’s why this will be an interesting future research direction to investigate.

3.3. Design of new protocols for smoking cessation and prevention in adolescents

I am interested to fructify my past experience in the pilot and national programs for smoking cessation in youngsters by refreshing the programs’ design in 2008, as those initiatives were very much welcomed by both young smokers on a side and their parents and teachers on the other side, in the high schools where I implemented the Adolescents Smoking Cessation project. Since 2009, there was a gap in such healthy smoke-free approaches among this category of high risk smokers. In Romania, it is not allowed yet to indicate
pharmacological treatment for tobacco dependence - under 18, so the major approach must be based on educational and counseling sessions, adapted to the adolescent age group needs and beliefs.

The most successful programs alike are using peers and young facilitators, of closed age to the target group. Based on my previous expertise in the field and on my keeping in touch with the Adolescent Smoking Cessation researcher’s network up to now, I plan to apply for a research grant addressed to school children. I have in view three research domains:

1. An internet/mobile application for preventing smoking initiation.
2. Design of a personalized approach, based on my authorship of the previous interactive and incentives based counseling sessions in the Adolescents Smoking Cessation project – to provide effective support for quitting in already young smokers.
3. Design of a specific smoking prevention program by targeting new tobacco products nowadays that might attract young smokers, such as e-cigarette devices or new alternatives in trend.

3.4. Investigation of biomarkers of tobacco exposure in active and passive smokers

In my past research trajectory dedicated to study of tobacco use and its impact on human body, in particular at the respiratory system level, I have often monitored tobacco intake or cessation progress by determining biomarkers of tobacco exposure in the organism, in principal carbon monoxide in exhaled air and urinary cotinine. These two represent the cheapest and simple tools, useful for routine clinical practice in a smoking cessation centre.

My scientific activity contains numerous articles and studies on this subject. Recently, our group has co-authored, in collaboration with a Ph.D. student in the Discipline of Pneumology an article, accepted for publication in a journal indexed in ISI Web of Knowledge (Biochemistry in assessing tobacco exposure - Smokers versus Non-smokers - Correlations with Clinical Practice (Antigona Trofor, Ovidiu Petris, Letitia Trofor, Milena Adina Man, Dumitru Filipceanu, Ramona Miron).

This piece of work has raised my interest on various other biomarkers possible to use for demonstration of nicotine passage through the body, such as: anatabine, anabasine, thiocyanate, uric acid and nitric oxide. Moreover, cotinine, the metabolite of nicotine can be determined also in hair, saliva or serum, yet, I could not explore these methods up to now. Hence, if I will have the chance to conduct Ph.D. students, this will be a high research priority for me: the study of biomarkers of tobacco use, others than cotinine in urine and exhaled CO. The most feasible among these ones, could be plasmatic uric acid, being well known, that plasmatic uric acid acts against oxidative stress induced by tobacco smoking.

Another research sub-direction, in this respect will be the study of biomarkers of tobacco exposure in non smokers, passively exposed to tobacco smoke, in homes or in those environments where smoking is still allowed by actual legislation.

Finally, it’s worth prospecting the usefulness of biomarkers resulting from those tobacco products other than standard cigarettes, that gain more and more field nowadays (e-cigarettes, vaping devices, “heat not burn” tobacco or “roll your own (RYO)” tobacco.
3.5. Build up and evaluation of monitoring tools for tobacco control measures in Romania by targeting respiratory health strategies

Smoking and other forms of tobacco consumption are considered the single most important cause of preventable morbidity and premature mortality worldwide. Efforts to reduce the devastation of tobacco-related deaths and illness in the EU consist of the Tobacco Products Directive (TPD), and the ongoing implementation of the WHO Framework Convention on Tobacco Control (FCTC). I will continue developing research activities to promote respiratory health through tobacco use prevention and treatment, in respect to this legislative framework.

I am responsible in the international research project - European Regulatory Science on Tobacco: Policy implementation to reduce lung diseases (EUREST-PLUS) funded by European Commission through its program Horizon 2020 (2016-2019). The main objective is to monitor and evaluate the impact of the implementing acts of the TPD and assess these within the context of FCTC ratification at an EU level. The 4 specific objectives hence are: 1) To evaluate the psychosocial and behavioral impact of TPD implementation and FCTC implementation, through the creation of a longitudinal cohort of adult smokers in 6 EU member states (Germany, Greece, Hungary, Poland, Romania, Spain) in a pre- vs. post-TPD study design. Moreover, these evaluation studies of the impact of the TPD and FCTC will be conducted with respect to vulnerable populations. 2) To assess support for TPD implementation through secondary dataset analyses of the 2015 Special Eurobarometer on Tobacco Survey (SETS), a cross-sectional survey performed among 27,000 adults in all 28 EU member states, before the TPD is implemented and to monitor progress in FCTC implementation in the EU over the past years through trend analyses on the merged datasets of the 2009, 2012 and 2015 SETS datasets (n=80,000). 3) To document changes in e-cigarette product parameters (technical design, labeling/packaging and chemical composition) following TPD implementation of Article 20 of the TPD. 4) To enhance innovative joint research collaborations, through the pooling and comparisons across both other EU countries of the ITC Project, and other non-EU countries from low and middle income countries and high income countries.

For this project, I am involved in all Work Packages, by providing scientific management activities and I will lead, from behalf of Romanian team, a key paper disseminating project’s results: „Differences in knowledge of the health effects of smoking and effectiveness of health warnings”; also I will collaborate with researchers from the other international teams in another two key papers about: „Differences across countries in respiratory co-morbidities among smokers” and “Dual users of e-cigarettes and cigarettes”.

The expected results of this important H2020 international research project should serve as basis for starting new and promising research projects on this subject. Some examples about new possible linked research directions are: post effect study on the longitudinal cohort included in EUREST PLUS regarding changes in attitudes and beliefs on various items inquired initially-in relation with progresses made in TPD implementation across Europe, or developing those research lines that have incited debates among EUREST PLUS researchers such as: impact of mentholated cigarettes on respiratory system or unknown health effects of the new in trend e-cigarettes and “roll your own” tobacco products.
CHAPTER 4. FUTURE PLANS FOR THE ACADEMIC ACTIVITY PROGRESS

a. Teaching materials for students

The plans include development together with the colleagues from the Discipline of Pneumology of several teaching materials for Respiratory Diseases courses and practical workshops manuals for students from the “Grigore T. Popa” University of Medicine and Pharmacy Iasi. One example is the writing of a course guide for English and French series, which are deficitary in such resources, my contribution being a part dedicated to treatment of tobacco use and dependence and to respiratory diseases induced by tobacco exposure.

b. Involvement of undergraduate and PhD students in research and health promotion activities about respiratory diseases

I will continue my activities of coordinating graduating thesis and research projects of undergraduate students and I hope I will have the possibility to involve also PhD students in research and health promotion activities about respiratory disorders, with focus on tobacco induced respiratory disorders.

The project “European Regulatory Science on Tobacco: Policy Implementation to Reduce Lung Disease (EUREST PLUS), Type of Project: H2020 programme, H2020-HCO-2015 call (running 2016-2019) is supporting and funding two part-time positions for PhD students.

c. Development of post-graduate courses for health care professionals

I intend to develop together with my colleagues from the Discipline of Pneumology several postgraduate courses in the field of respiratory health promotion through prevention and treatment of tobacco use and dependence, for all categories of health professionals. This process will be eased by the e-learning modules developed in the Project “TOB-G: Tobacco Cessation Guidelines for High Risk Groups” (Type of Project: H2020 programme, 3-rd EU Health Programme Projects Grants (HP-PJ) call), (2015-2018) and also by means of the EPACTT (2014-2016) and EPACTT PLUS (2016-ongoing) educational grants for developing a smoking cessation curricula at European level. These last two projects are run by “Global Bridges – Healthcare Alliance for Tobacco Dependence Treatment – USA.

d. Activities of national and international cooperation and networking

I will focus on enhancing the activities of national and international cooperation and networking with the aim to increase the academic, professional and research level of the activities performed in Romania in the field of pneumology and respiratory health promotion.
SECTION III - REFERENCES


California Environmental Protection Agency Air Resource Board, California Air Toxics Program 2015. California Environmental Protection Agency Air Resource Board, Reducing toxic air pollutants in California’s Communities. Retrieved from https://www.arb.ca.gov/toxics/toxics.htm


Canadian Lung Association, NATIONAL LUNG HEALTH FRAMEWORK 2010.


Dahlén I, Janson C. Anxiety and depression are related to the outcome of emergency treatment in patients with obstructive pulmonary disease. *Chest* 2002, **122**: 1633-37.


Durmowicz EL. The impact of electronic cigarettes on the paediatric population. *Tob Control* 2014, **23**: 41–6.


Smoking and public health in Romania. Knowledge, attitudes and practices regarding tobacco use among general population in Romania Bucharest: Center for Health Policies and Services in Romania, 2004, p. 25-45.


Tramontini R, Barreto M. Nitric oxide as a marker of smoking abstinence. University of Toronto 2010, 11-96


Trofor A, Mihaescu T, Cojocaru LE, Mardare D. Adolescents welcome the first Romanian pilot program to provide them smoking cessation - impact on recruitment, XV -th annual congres of ERS- Copenhagen, Danemarca. The European Respiratory Journal 2005, 26(suppl. 49): 154s.


Trofor A, Mihaescu T, Esanu V, Grigoras C. Smoking cessation with bupropion-is it succesful enough? ERS Annual Congress Copenhagen, 2005, poster 247s.


Trofor A, Mihaltan F, Mihaicuta S. et.al., Ghidul Societăii Romane de Pneumologie: Ghid de renuntare la fumat si asistenta de specialitate a fumatorului (GREFA), Tehnopress, Iasi; 2010.

Trofor A, Miron R, Ciobanu M, Barnea E, Esanu V. Efficacy and safety of Varenicline in a smokers population with high prevalence of co-morbidities. ERS Congress in Barcelona 2010, E-communication session-E2060.


