

**PROCEEDINGS AND ON-SITE PROGRAMME**

# 9<sup>th</sup> Annual Conference of the SRNT Europe

**3rd-6th October, 2007  
Madrid (Spain)**

*Helping smokers to quit*

**[www.srnt2007madrid.com](http://www.srnt2007madrid.com)**





# 9<sup>th</sup> Annual Conference of the SRNT Europe

<b>Presentation.....</b>	<b>3</b>
<b>Committees.....</b>	<b>4</b>
<b>Scientific Programme.....</b>	<b>5</b>
<b>Speakers Proceedings.....</b>	<b>16</b>
<b>Abstracts: Oral Communications.....</b>	<b>48</b>
<b>Posters.....</b>	<b>65</b>
<b>Paper Presentations.....</b>	<b>74</b>
<b>Registration.....</b>	<b>74</b>
<b>Accommodation.....</b>	<b>75</b>
<b>Methods of Payment.....</b>	<b>75</b>
<b>General Information.....</b>	<b>76</b>
<b>About Madrid.....</b>	<b>77</b>

# PRESENTATION

Dear Colleagues,

It is with great pleasure that we invite you to participate in the **9th Annual SRNT Europe Conference** that will be held 3rd - 6th October 2007 at the NH Hotel Eurobuilding in Madrid (Spain).

Madrid is a beautiful city, with a strong cultural and historical heritage, located in the heart of Spain. It is cosmopolitan and colourful but preserves a strong national identity. Madrid offers visitors wonderful architecture, traditional neighbourhoods (barrios), vibrant nightlife, access to some of the world's finest art, outstanding museums, delicious food, great shopping, and an excellent climate!

The scientific programme will span basic, clinical and public health sciences and will include invited addresses by leaders in these fields. A vital component of the programme will be the poster sessions and oral presentations showing the most recent research findings in the field of nicotine and tobacco.

SRNT Europe Board warmly welcomes you all to Madrid.

Carlos A. Jiménez-Ruiz  
*Conference Chair*

Karl O. Fagerström  
*Conference co-Chair*

Eva Kralikova  
*President SRNT Europe*

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**Juan Antonio Riesco Miranda**

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**Barbara Steen**

# SCIENTIFIC PROGRAMME

3<sup>rd</sup> October 2007

09:30-12:30  
[Salon Edimburgo]

**Pre-Conference Symposium 1.**

14:30-17:30  
[Salon Edimburgo]

**Pre-Conference Symposium 2.**

16:30-19:00

**Registration.**

18:00-18:30  
[Salon Madrid]

**Welcome and opening address.**

18:30-20:00  
[Salon Madrid]  
(S.T.)

**Opening lectures.**

**Title: "Past, present and future of smoking cessation".**

*Introduced by:* Juan A. Riesco Miranda.

*Speakers:*

"The pre-clinical point of view. Nicotine and nicotinic receptors: from molecular biology to cognition".  
Jean Pierre Changeux.

"Smoking cessation in the past and in the future".  
Karl O. Fagerström.

20:00-22:00  
[Hall Plaza Mayor]

**Welcome reception.**

4<sup>th</sup> October 2007

08:30-09:30  
[Salon Madrid]  
(S.T.)

**Clinical lecture.**

**Title: "Exposure reduction, harm reduction and tobacco control".**

*Introduced by:* Paul Van Spiegel.

*Speaker:* Thomas E. Eissenberg.

09:30-11:15  
[Salon Madrid]  
(S.T.)

**Simultaneous sessions.**

**Round table discussion.**

**Title: "Reimbursement of pharmacological treatments for smoking cessation".**

*Chair:* Christina Gratiou and Carlos A. Jiménez-Ruiz.

*Speakers:*

"Do we have to find a new way of reimbursement for smoking cessation?".  
Michael Fiore.

"Reimbursement for pharmacological treatments for smoking cessation. The experience of smoking cessation services in UK".  
Gay Sutherland.

"Proposal of reimbursement for smoking cessation products. The experience in the Autonomous Region of Madrid".  
Angel Guirao García.

[Salon Edimburgo]

**Session 1: oral communications on basic research.**

*Chair:* David Balfour and Jacques Le Houezec.

**1**

**"Subtype-specific regulation of rat brain nachrs during nicotine and cocaine self-administration".**

Manolo Mugnaini.

Chiara Mutinelli, Paolo Repeto, Maria Pilla.

GlaxoSmithKline Medicines Research Centre. Verona. Italy.

(S.T.) Simultaneous translation English-Spanish.

**2** \_\_\_\_\_  
**“A differential role for dopamine in nicotine self-administration that is dependent on infusion speed”.**

Robert E. Sorge.

Paul B.S. Clarke.

*McGill University, Dept. of Pharmacology and Therapeutics*

*Rm. 1320 McIntyre Medical Building, 3655 Sir William Osler, Montreal, QC, Canada.*

**3** \_\_\_\_\_  
**“The effects of non-contingent nicotine on responding for a compound light stimulus”.**

Nicholas Montgomery.

Claire S Birch & David JK Balfour.

*University of Dundee. Scotland. UK.*

**4** \_\_\_\_\_  
**“Analysis Of Nicotine Preference In Male And Female Rats With Free Access To Oral Nicotine During Adolescence and Adulthood”.**

Tanseli Nesil.

Gonca Dalkurt Mola, Lutfiye Kanit, Sakire Pogun.

*PhD student.*

*Ege University School of Medicine Physiology Dept. 35100 Izmir /Turkey.*

**5** \_\_\_\_\_  
**“The Effects of Chronic Nicotine on Fear Conditioning and Anxiety in Rats”.**

Evrin Gulbetekin 1.

Tanseli Nesil 2,3, Aysegul Keser 3,4, Sakire Pogun 3,4.

*Ege University, Faculty of Sciences, Psychology Dept. 1; Institute of Sciences, Biotechnology Dept. 2; Center for Brain Research 3; School of Medicine, Physiology Dept. 4; Izmir, Turkey.*

**6** \_\_\_\_\_  
**“Environmental tobacco smoke exposure and hair nicotine concentration in non-smoking pregnant women in Korea”.**

Yu-Jin Paek.

Hye-Mi Chang, Cheol-min Lee\*.

*Dept of Family Medicine, Hallym University Sacred Heart Hospital, \*Health Care Center, SNUH.*

*896, Pyungchon-dong, Dongan-ku, Anyang-si, Gyeonggi-do, 431-070, South Korea.*

**7** \_\_\_\_\_  
**“The impact of smoking on health-related and subjective quality of life: a general population survey”.**

Hanne Heikkinen.

Piia Jallinoja, Samuli I. Saarni, Kristiina Patja.

*National Public Health Institute -KTL, Department of Health Promotion and Chronic Disease Prevention Mannerheimintie 166, 00300 Helsinki, Finland.*

11:15-11:45

Coffee break.

11:45-13:30  
 [Salon Madrid]  
 (S.T.)

**Simultaneous sessions.**

**Basic research panel.**

**Title: “Neurological pathways implicated in addiction”.**

**Chairs:** Cristiano Chiamulera.

**Speakers:**

“The endocannabinoid system”.

Rafael Maldonado.

“The nor-adrenergic pathway”.

Cristiano Chiamulera.

“The dopaminergic pathway”.

Marco Diana.

[Salon Edimburgo]

"The GABAergic pathway: Focus on GABAB".  
John F. Cryan.

**Session 2: oral communications on clinical research.**

Chair: Jean François Etter and Guy Sutherland.

**1** —————  
**"The effect of baseline dependence on treatment outcomes of varenicline for smoking cessation".**

Karl Fagerström.  
Cristina Russ, Carmen Arteaga.  
*\*Fagerström Consulting Smokers Information Centre  
Kavelleristen 9, Berga Alle 1, Helsingborg, Sweden S- 25452.*

**2** —————  
**"Pre-cessation treatment with NRT: a randomized trial".**

Jean-Francois Etter.  
Jacques Cornuz, Philippe Huguelet, Thomas pernegger.  
*University of Geneva. 1, rue Michel-Servet. Switzerland.*

**3** —————  
**"Cognitive and motivational predictors of relapse to smoking: A prospective study".**

Jane Powell.  
Alan Pickering, Lynne Dawkins, Robert West, John Powell.  
*Goldsmiths, University of London. Lewisham Way, New Cross, London SE14 6NW. UK.*

**4** —————  
**"Does cue induced brain activation predict outcome in smoking cessation treatment".**

Christian G. Schütz.  
*University of Bonn, Department of Psychiatry and Department of Radiology. Sigmund-Freud-tr. 25,  
53105 Bonn, Germany.*

**5** —————  
**"Patterns of change in reward motivation, response inhibition, mood and craving over 3 months of smoking abstinence".**

Lynne Dawkins.  
Jane Powell, Alan Pickering, John Powell, Robert West.  
*University of East London.  
School of Psychology, Romford Road, Stratford, University of East London, London. UK.*

**6** —————  
**"Long-term Abstinence is Enhanced by Immediate and Delayed Quitting with Varenicline vs Bupropion".**

David Gonzales.  
Douglas E Jorenby, Carmen Arteaga, Theodore C. Lee.  
*OHSU Smoking Cessation Center (Gonzales)  
Health & Sciences University, Portland, OR 97239. USA.*

**7** —————  
**"Efficacy, safety, and effect on weight of adding a nicotine patch to rimonabant for smoking cessation: a randomized controlled trial".**

Nancy Rigotti, MD.  
Yuchiao Chang, PhD; David Gonzales\*, PhD; Lowell Dale\*\*, MD; Daniel Lawrence\*\*\*, PhD.  
*Harvard Medical School; \*Oregon Health & Science University; \*\*Mayo Medical Center; \*\*\*University of Wisconsin, for the CIRRU Study Group. Tobacco Research & Treatment Center, Mass. General Hospital, 50 Staniford St., Boston, MA 02114, USA.*

8

**“Effect of Jarsin® or Cr3+ on morning saliva cortisol in quitting smokers, a stress treatment effect?”.**

Mike Franklin (1).

Paul N Aveyard (2), Isabel Bermudez (1), Jackie Ingram (2)

1. School of Life Sciences, Oxford Brookes University (2) University of Birmingham. (1) Oxford OX3 0BP, UK; (2) Birmingham B15 2TT, UK.

9

**“Predictors of Change in Smoking following Emergency Hospitalization for Chest Pain”.**

Beth Bock, PhD.

Raymond Niaura, PhD; Joseph Fava, PhD.

Brown Medical School.

Miriam Hospital, Coro Building 5th floor, One Hoppin St., Providence RI 02903, USA.

13:30-15:00

Lunch.

15:00-16:00

**Poster Display 1** (Poster Boards 1 to 38).

[Salon Roma]

Chairs: Cristiano Chiamulera.

16:00-17:30

**Clinical research symposium.**

[Salon Madrid]

Title: **“Smokeless tobacco”.**

(S.T.)

Chairs : Yves Martinet.

Speakers:

“Mortality and morbidity attributable to smokeless tobacco”.

Birgitta Stegmayr.

“Smokeless tobacco products”.

Inger Wahlberg.

“The role of smokeless tobacco in a general harm reduction strategy”.

John Britton.

“Can smokeless tobacco aid smoking cessation: what is the evidence?”

Jonathan Foulds.

17:30-18:00

Coffee Break.

18:00-19:30

**Satellite Symposium 1.**

[Salon Edimburgo]

(S.T.)

5<sup>th</sup> October 2007

08:30-09:30

[Salon Madrid]

(S.T.)

**Basic research lecture.**Title: **“Tobacco dependence: abnormal learning in cortico-striatal loops”.**

Introduced by: David Balfour.

Speaker: Gaetano Di Chiara.

09:30-11:15

[Salon Madrid]

(S.T.)

**Simultaneous sessions.  
Clinical research panel.**Title: **“New treatments for smoking cessation”.**

Chairs: Karl O. Fagerström.

Speakers:

“Varenicline”.

Carlos A. Jiménez-Ruiz.

"Nicotine vaccine".  
Jacques Cornuz.

"Can smoking reduction promote smoking cessation?".  
José Ignacio de Granda Orive.

"What else is on the smoking cessation horizon".  
Peter Hajek.

[Salon Edimburgo]

**Session 3: oral communications on epidemiology/health care/other research.**

*Chair:* Ivan Berlin and Robert West.

**1**

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**"Early onset of smoking as a predictor of cannabis use: Modifying role of behavioral symptoms".**

Tellervo Korhonen.

Anja C. Huizink, Danielle M. Dick, Lea Pulkkinen, Richard J. Rose, Jaakko Kaprio.

*University of Helsinki, Department of Public Health.*

*PO Box 41, 00014 Helsinki, Finland.*

**2**

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**"Onset of tobacco use and transition to other drug use among college undergraduates in north of Iran".**

Zahra Mohtasham Amiri.

Abbas Jafari shakib.

*Department of Community Medicine, School of Medicine, Guilan University of Medical sciences, Rasht.*

*P.O Box 41635/3381 Rasht, Iran.*

**3**

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**"Exploring personal meanings around smoking and smoking cessation strategies among health workers".**

Lumira Lagapa.

Alvin Concha, Maria Elinore Alba-Concha, Lillian Lao.

*Davao Medical Center.*

*Dept of Family and Community Medicine, Davao Medical Center, Bajada, Davao City 8000, Philippines.*

**4**

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**"A qualitative evaluation of a smoke-free policy in the workplace".**

Molinar Roberta\*.

Giordano\*, L., Senore\*, C. Dotti\*\*, A., Bosco\*\*, G.

*\*CPO Piemonte, \*\*Spresal ASL7. Via San Francesco da Paola 31, 10123 Torino. Italy.*

**5**

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**"Cost-effectiveness of Varenicline for Smoking Cessation in Five European Countries".**

Maureen Rutten-van Mölken,1\*.

Martine Hoogendoorn 1, Andrej Rasch 2, Kristian Bolin 3.

*\*Presenting author.*

*1 Institute for Medical Technology Assessment (iMTA), Erasmus MC, Rotterdam, The Netherlands; 2 Health Economics and Health Management (AG 5), Faculty of Health Sciences, University of Bielefeld, Bielefeld, Germany; 3 Lund University Centre for Health Economics, Lund, Sweden.*

*M Rutten-van Mölken, Ph.D. Erasmus MC. Institute for Medical Technology Assessment -P.O. Box 1738. 3000 DR Rotterdam. The Netherlands.*

**6**

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**"Normalizing and Resocializing:TTC's efforts to introduce lights and prevent smoking bans in Spain".**

Richard D. Hurt.

Monique E. Muggli, Jon O. Ebbert, Carlos A. Jimenez-Ruiz, Juan A. Riesco Miranda.

*Mayo Clinic.*

*NDC 200 1st Street SW Rochester, MN 55905, USA.*

**7****“Tobacco use in Finland and in Sweden 1988-2005”.**

Kristiina Patja.  
 Samu Hakala, Paul Nordgren, Margaretha Haglund.  
*National Public Health Institute, KTL.*  
*Mannerheimintie 166, 00300 Helsinki. Finland.*

**8****“Preventing Smoking And Smoking Related Diseases In Russia: What Do The Doctors Need?”.**

Marine Gambaryan.  
 Anna Kalinina.  
*National Research Centre for Preventive Medicine.*  
*10, Petroverigsky per, 101990, Moscow, Russian Federation.*

11:15-11:45

Coffee break.

11:45-13:30

[Salon Madrid]  
(S.T.)**Simultaneous sessions.****Basic science research symposium.**Title: **“Molecular characterization of the nicotinic AchR”.**

Chairs: Sakire Pogun.

**Speakers:**

“Acetylcholine binding proteins: structural models of the extracellular domain of the nicotinic receptors”.  
 August B. Smit.

“Cell lines as in vitro factories for nicotinic receptor characterization”.  
 Ronald J. Lukas.

“In vivo studies with nicotinic ligands”.  
 M. Imad Damaj.

“Neuronal nicotinic acetylcholine receptors as molecular targets for drugs discovery”.  
 Murali Gopalakrishnan.

[Salon Edimburgo]

**Session 4: oral communications on clinical research.**

Chair: Jaakko Kaprio and Serena Tonstad.

**1****“External Validation Of A COPD Diagnostic Questionnaire In Smokers”.**

D. Kotz.  
 P. Nelemans, C.P. van Schayck, G.J. Wesseling.  
*Department of General Practice, Care and Public Health Research Institute, Maastricht University.*  
*P.O. Box 616, 6200 MD Maastricht, The Netherlands.*

**2****“Piloting physical activity as an aid to smoking cessation during pregnancy”.**

Dr. Michael Ussher.  
 Dr. Paul Aveyard, Dr. Tim Coleman, Professor Robert West, Lianne Straus, Professor Bess Marcus, Dr.  
*St. George's, University of London.*  
*Cranmer Terrace, London SW17 0RE, UK.*

**3****“Attrition in an Ongoing Trial with Low Income Postpartum Smokers: Practice and Policy Implications”.**

Bradley N. Collins, Ph.D.  
 J. Ibrahim, K. Jaffe, N.M. Tolley, D. Nehemia, P. Wileyto, M. Hovell, J. Audrain-McGovern.  
*Health Behavior Research Center, Temple University Department of Public Health. 1701 N. 13th St,*  
*Weiss 160 (265-61), Philadelphia, PA, USA.*

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**4** —————  
**“Smoking behaviour and nicotine metabolism in Caucasians, Orientals and Mixed Ethnicity”.**

Dr. NoorZurani Md Haris Robson, MBBS, M.Med, PhD.

Dr. Kim Wolff, PhD, Dr Alyson Bond, PhD.

*Institute of Psychiatry, Kings College London and University Malaya, Kuala Lumpur.*

*Dept Primary Care Medicine, Faculty of Medicine, University Malaya, 50603 Kuala Lumpur, Malaysia.*

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**5** —————  
**“Tobacco prevalence’s evolution in three classes from Third-year Medicine Students”.**

Adriana Jiménez-Muro Franco.

Adriana Marqueta Baile, Isabel Nerín de la Puerta.

*Unidad de Tabaquismo, Facultad de Medicina, Universidad de Zaragoza. C/ Domingo Miral s/n, Edif.*

*A, 1 planta. Zaragoza. Spain.*

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**6** —————  
**“Motivational Interviewing to Help Hispanic Parents of Children with Asthma to Quit Smoking”.**

Belinda Borrelli, PhD.

McQuaid, E., Novak, S., Hammond, K., Becker, B., Amador, J., Jusino, L, & Lee, C.

*Brown Medical School, Centers for Behavioral and Preventive Medicine. Coro-Building-West, 5th Floor, Providence, RI, 02903, USA.*

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**7** —————  
**“Understanding Demand for Smoking Cessation Treatment Among Young Adults in the U.S.”.**

Susan J. Curry, Ph.D.

Amy K. Sporer, MS, Dianne C. Barker, MHS, Sherry L. Emery, PhD, George Balch, PhD.

*University of Illinois at Chicago, Institute for Health Research and Policy. 1747 W. Roosevelt Rd., Suite 558, Chicago, IL 60608, USA.*

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**8** —————  
**“Reducing the number of cigarettes smoked as a harm reduction approach: Evidence from mortality data”.**

Jaakko Kaprio.

Tellervo Korhonen, Ulla Broms, Markku Koskenvuo.

*University of Helsinki, Dept of Public Health.*

*PO Box 41, 00014 Helsinki, Finland.*

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**9** —————  
**“Efficacy Of Smoking Cessation Interventions For Hospitalized Smokers: A Meta-Analysis”.**

Rigotti NA, Marcus Munafo\*, Lindsay Otead\*\*.

*Harvard Medical School, USA; \*University of Bristol, UK; \*\*University of Oxford, UK.*

*Harvard Medical School.*

*Tobacco Research & Treatment Center, Mass. General Hospital, Boston, MA 02114 USA.*

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**10** —————  
**“Adherence: The Achilles Heel of OTC Nicotine Replacement”.**

Scott J. Leischow, Ph.D.

James W. Shaw, Ph.D., Pharm.D., M.P.H.; Myra L. Muramoto, M.D., M.P.H.

*The University of Arizona (Leischow and Muramoto), The University of Illinois (Shaw). Arizona Cancer Center, University of Arizona, 1515 N. Campbell Avenue, Tucson, Arizona, USA, 85719.*

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**11** —————  
**“Use Of Over The Counter Available Nicotine Replacement Products On Tobacco Cessation”.**

Prof.Rama Kant 1\*

Dr.Madhu Pathak 2,Dr.Pooja Ramakant 3,Bobby Ramakant 4.

*TCC,King George Medical University and Satellite centers, Lucknow*

*Address: C-2211, C-Block crossing, Indira Nagar, Lucknow. 226 016. India.*

13:30-15:00

Lunch.

15:00-16:00

[Salon Roma]  
(S.T.)**Poster display 2** (Poster Boards 39 to 81).*Chair:* Eva Kralikova and Sakire Pogun.

16:00-17:30

[Salon Madrid]  
(S.T.)**Round table discussion.****Translating Research into Advocacy: Evidence-Based Arguments for Smoking Prevention.***Chairs:* Eva Kralikova.*Speakers:*"Evidence-based strategies for smoking prevention".  
Elif Dagli."Educating advocates: health professionals training".  
Patrick Sandström."Prevention of smoking uptake among adolescence".  
Laurence Moore."Community-based smoking prevention programmes. The experience of the Spanish Respiratory Society."  
Carlos A. Jiménez Ruiz.

[Salon Edimburgo]

**Basic research debate.***Title: "Alfa 7 nicotinic receptors: a silent voice or a siren song?"**Chairs:* Rafael Maldonado.*Speakers:*"A siren song".  
M. Imad Damaj."A silent voice".  
Daniel Bertrand.

17:30-18:00

Coffee break.

18:00-19:30

[Salon Edimburgo]  
(S.T.)**Satellite Symposium 2.**

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**6<sup>th</sup> October 2007**

08:30-10:15

[Salon Madrid]  
(S.T.)**Clinical Panel.***Title: "Consensus to measure craving and withdrawal syndrome in a clinical setting".**Chairs:* Philip Tonnesen.*Speakers:*"Alterations in reward processing during nicotine abstinence: mechanisms and motivational significance".  
Paul Kenny."How to measure craving and withdrawal in Clinical Trials".  
Saul Shiffman."Proposal for a questionnaire to measure craving in a clinical setting".  
Robert West.

[Salon Edimburgo]

**Basic research conference.**

Title: **“Neuroimaging in tobacco and nicotine dependence: current status and future developments”.**

Introduced by: Ivan Berlin.

Speaker: Edythe London.

10:15-10:40

Coffee break.

10:40-12:30

[Salon Madrid]  
(S.T.)

**Symposium.**

Title: **“Smoking cessation for special populations. Do we need different objectives, treatment and regimes?”.**

Chairs: Dorota Goreka.

Speakers:

“Smoking cessation in psychiatric patients”.  
Hubertus Friederich.

“Smoking cessation in pregnant women”.  
Cheryl Oncken.

“Smoking cessation in pulmonary patients”.  
Philip Tonnesen.

“Smoking cessation in cardiovascular patients”.  
Serena Tonstad.

12:30-13:00

[Salon Madrid]

Members meeting.

13:00

[Salon Madrid]

**Closing Ceremony.**

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## Speakers Proceedings

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■ Speakers Index	
■ Proceedings .....	16

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## Abstracts

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### ■ Oral Communications:

• Session 1 .....	48
• Session 2 .....	51
• Session 3 .....	55
• Session 4 .....	59

### ■ Posters:

• Posters Display 1 .....	65
• Posters Display 2 .....	69

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## SPEAKERS INDEX

---

• Bertrand, Daniel .....	16	• Hajek, Peter .....	30
• Britton, John .....	16	• Jiménez-Ruiz, Carlos A. (2) .....	31
• Changeux, Jean Pierre .....	17	• Kenny, Paul .....	32
• Chiamulera, Cristiano .....	17	• London, Edythe .....	33
• Cornuz, Jacques .....	18	• Lukas, Ronald J. ....	35
• Cryan, John F. ....	19	• Moore, Laurence .....	35
• Damaj, M. Imad .....	21	• Oncken, Cheryl .....	36
• de Granda Orive, José Ignacio .....	21	• Sandström, Patrick .....	37
• Di Chiara, Gaetano .....	22	• Shiffman, Saul .....	39
• Diana, Marco .....	22	• Smit, August B. ....	39
• Eissenberg, Thomas E. ....	24	• Stegmayr, Birgitta .....	40
• Fagerström, Karl .....	24	• Sutherland, Gay .....	41
• Fiore, Michael .....	25	• Tonnesen, Philip .....	42
• Foulds, Jonathan .....	26	• Tonstad, Serena .....	43
• Friederich, Hubertus .....	28	• Walhberg, Inger .....	45
• Gopalakrishnan, Murali .....	28	• West, Robert .....	46
• Guirao García, Ángel .....	29		

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## The $\alpha 7$ nicotinic acetylcholine receptor: a silent voice

**Daniel Bertrand.**

Department of Neuroscience. Medical Faculty, Geneva Switzerland.

The identification of a gene encoding for a homomeric nicotinic acetylcholine receptor (nAChR) that is activated by acetylcholine but inhibited by the snake toxin  $\alpha$ -bungarotoxin opened a new door in our understanding of this family of ligand gated channels in the mammalian brain. Importantly, this observation reconciled previous observations that  $\alpha$ -bungarotoxin strongly labeled different areas of rat brain. Since then numerous studies have addressed the properties of the  $\alpha 7$  nAChR in mammalian brain, but many of them remained elusive as very few synapses in which determinant contributions of such homomeric receptor subtype could be revealed. Most studies revealed, however, that the  $\alpha 7$  nAChR plays a major modulatory role by regulating neuronal activity by its presynaptic influence on neurotransmitter release.

While initial studies pointed out a remarkable property of the  $\alpha 7$  nAChR which displays a higher sensitivity to nicotine than acetylcholine it must be recalled that half activation of the receptor is observed for concentration of nicotine as high as 10 mM which is far above a plausible concentration of this alkaloid in the brain. In view of the high threshold of the  $\alpha 7$  receptor activation by nicotine, it was thought that while these receptors may play a role in cognitive functions, they were probably not involved in the addictive properties of nicotine.

However, to further understand if the  $\alpha 7$  receptor contributes to nicotine addiction, it is necessary to recall how nicotine concentration is thought to evolve in the brain of a smoker as a function of time and how such a concentration of alkaloid can affect receptor activity. In the case of cigarette smoking, a peak of nicotine concentration is quickly reached after a few puffs and once established the nicotine concentration progressively decays during the following tens of minutes. Measurements of nicotine in the brain indicate that it reaches, in the cerebrospinal fluid, a concentration in the low micromolar range. An important feature of neuronal nicotinic receptors is their capacity to desensitize upon sustained exposure to agonist concentrations that are insufficient to activate the receptors. Experiments carried out at the major brain  $\alpha 4\beta 2$  nicotinic acetylcholine receptor revealed that exposure to a sustained concentration of nicotine such as that occurring in the smokers brain profoundly desensitize this receptor subtype. Subsequent activation of the receptor by acetylcholine is therefore practically abolished and nicotine is often proposed to act by antagonizing this subtype of heteromeric nicotinic acetylcholine receptors through its desensitizing effects. In contrast, a different picture is observed when considering the  $\alpha 7$  receptor where it was found that this homomeric receptor is not desensitized by low nicotine concentrations. The  $\alpha 7$  receptor therefore remains functional whereas the  $\alpha 4\beta 2$  receptor is desensitized. These *in vitro* results suggest that sustained nicotine exposure displaces the equilibrium of activity of the nicotinic cholinergic system in favor of the  $\alpha 7$  receptor.

Importantly, blockade of the  $\alpha 7$  nicotinic receptor by specific antagonists such as methyllycaconitine have been shown to attenuate the addictive properties of nicotine. These results suggest that counter intuitively to the *in vitro* data the  $\alpha 7$  receptor might also participate in the effects of nicotine on the central nervous system and that properties and distribution the multiple subtypes of neuronal nicotinic acetylcholine receptors must be taken into account when attempting to understand a complex phenomenon such as nicotine addiction.

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## The role of smokeless tobacco in a general harm reduction strategy

**John Britton.**

Center for Respiratory Research. Medical and Surgical Sciences. Clinical Sciences Building, City Hospital. Nottingham. UK

Smokeless tobacco products are a topic of great controversy in public health and tobacco control. On one side of this controversy is the argument that all tobacco products are harmful and have no place in a healthy society. On the other is the argument that addiction to tobacco smoking is a fact of life, and for those who are unable to quit tobacco use altogether, switching to a less hazardous form of tobacco, such as a smokeless product, would reduce the harm they sustain as a result of tobacco use.

Harm reduction strategies are commonplace elsewhere in medicine and in many other aspects of life, but have not been widely applied to tobacco use. There are many uncertainties over the likely outcome of pursuing harm reduction in general, and of whether smokeless products can offer any benefit in that context. If smokeless tobacco products can provide a less hazardous source of nicotine that is acceptable to smokers who will not otherwise quit, then that use is easily justified. If, on the other hand, the availability of smokeless products results in uptake, and possible progression to smoking, by people who would not otherwise have used tobacco, that would result in an adverse impact on public health. The balance of these opposing effects will depend on just how effective smokeless can be as a substitute for smoking, how harmful it is relative to smoking, how widely used it would be by people who would not otherwise have smoked, and how much harm these people would sustain.

In this presentation I will review the evidence behind these concerns and questions. I will explore the evidence on the effectiveness of conventional tobacco control strategies, and thus assess the likely trend in tobacco smoking in countries with an established smoking population. I will review the harm arising from smokeless tobacco use in relation to smoking as well as no tobacco use. I will also review the trends in smokeless use and of smoking in selected countries that have both smokeless and smoked tobacco products available on the market, and draw some conclusions on the likely and potential effects on public health if smokeless products were to be made more widely available. I will to assess the potential role of smokeless tobacco in a wider harm reduction framework.

Funding source: The University of Nottingham

## The preclinical point of view: Nicotine and nicotinic receptors: from molecular biology to cognition

**Jean-Pierre Changeux.**  
Institut Pasteur, Paris, France.

In the brain, nicotinic receptors (nAChR) are important targets of the neuromodulator acetylcholine. At least ten neuronal nAChR subunits ( $\alpha 2$ - $\alpha 10$ ,  $\beta 2$ - $\beta 4$ ) have been identified in the vertebrate brain which assemble to form a variety of pentameric oligomers possessing different physiological and pharmacological properties and distribution in the central nervous system. All of them behave as allosteric proteins that mediate the fast (msec) opening of the ion channel (activation) together with its short-term (100 msec to hrs) modulation (desensitization, potentiation, up-regulation).

To understand the role of a particular subunit, or combinations of subunits, mice lacking the  $\beta 2$ ,  $\alpha 4$  and  $\alpha 6$  subunits were generated by homologous recombination. For instance, adult  $\beta 2^{-/-}$  mice lack high affinity nicotine binding sites as well as nicotine effects on both dopamine release and electrical responses of mesencephalic dopaminergic neurons. Moreover,  $\beta 2^{-/-}$  mice show deficits in nicotine self-administration. An automated method to quantify mouse behavior further reveals in the  $\beta 2^{-/-}$  mice deficits in executive functions. Yet, these studies have demonstrated individual subunits to be necessary for a given function, but have failed, especially for ubiquitously expressed genes, to demonstrate that they are sufficient to account for this function.

To obviate this difficulty, we have developed a new strategy based upon the observation that a key nAChR subunit,  $\beta 2$ , can be efficiently re-expressed stereo-selectively on a  $\beta 2$  knock-out background using a lentiviral vector. Specific regeneration of fully functional high-affinity nAChRs in the Ventral Tegmental Area (VTA) has allowed us to prove that these receptors are sufficient to restore nicotine induced dopamine release in the Nucleus Accumbens and nicotine self-administration in mice, a model for nicotine rewarding action in smokers. Moreover, slow exploratory behaviour of VTA expressing mice was completely restored in a sequential locomotor task testing executive function. These data highlight the important role of endogenous cholinergic regulation of the dopaminergic system in higher cognitive function and the method offers the versatility required to differentially analyse the contribution of defined neuronal circuits in nicotine addiction.

## Neurological pathways implicated in addiction: the noradrenergic pathway

**Cristiano Chiamulera.**

Neuropsychopharmacology Lab., Section of Pharmacology,  
Department of Medicine & Public Health, University of Verona,  
Verona, Italy.

Tobacco addiction is a complex disorder characterized by stages of acquisition, maintenance, cessation and relapse. The latter is widely considered as the major target for therapeutic intervention for smoking cessation. Relapse may occur after few hours/days after the smoking quit attempt, as well as after months/years, due to different determinant factors such as withdrawal, cue reactivity, smoking lapse.

Basic research has shown that different brain processes are involved in relapse, such as affective, motivational and cognitive. Nicotine, the addictive substance contained in tobacco, exerts multiple pharmacological effects - at different neuroanatomical levels - on these processes. Moreover, prolonged exposure to nicotine in smokers may eventually induces neuroadaptive changes that have been shown to underlie vulnerability to factors of relapse.

The affective response of smokers is one of these processes involved in tobacco addiction: emotional state and/or trait, emotional responses to cues and/or context, interoceptive affective stimuli, etc., have been shown to be responsible of relapse to cigarette. As it was also shown for other types of addiction, the neuroanatomical pathway that uses noradrenaline as neurotransmitter (the noradrenergic system) is strongly implicated in the affective response by smokers.

Nicotine per se increases the levels of cortical noradrenaline, as well as it was shown that hypothalamic levels correlate with nicotine self-administration in laboratory animals. It is well-known from the addiction literature that locus coeruleus noradrenergic neurons show changes in firing pattern (that is an altered noradrenaline release at nerve terminals) during withdrawal. In smokers, locus coeruleus noradrenergic auto-receptors (which exerts a negative feed-back on the system) are down-regulated, suggesting that during smoking the noradrenergic system undergoes a neuroadaptation to a downward allostasis, which on the other hand may be evident as an upward tonic hyperactivity or an affective stimuli sensitization after cessation.

Noradrenaline re-uptake blocker nortryptiline has been demonstrated to have beneficial effects in smokers on withdrawal and relapse prevention. Bupropion and reboxetine, which under different mechanisms and selectivity block the re-uptake of noradrenaline, have been shown to reduce nicotine self-administration. Bupropion has been also shown to reduce locus coeruleus noradrenergic neurons firing, suggesting that the blockade of noradrenaline re-uptake and the increase of noradrenaline levels, may primarily be effective at inhibitory auto-receptors rather than at excitatory post-synaptic receptors.

From a different perspective, an important role it has been recently proposed for the noradrenergic system in the recall of drug-related emotional memories. Clinical evidence on propranolol effect for the treatment of post-traumatic stress disorders, have suggested its potential efficacy as a specific inhibitor of those conditioned memories known as determinant factors for relapse to drug abuse, and therefore suggesting a novel mode of action for intervention on ex-addicts at high-risk of relapse. Human studies have demonstrated the efficacy of propranolol to reduce withdrawal symptoms in treatment-resistant cocaine addicts. A recent double-blind, placebo-controlled clinical trial showed a positive effect of propranolol in patients with severe cocaine withdrawal symptoms. Propranolol has been also shown to decrease the general motivational activation observed during the early phase of psychostimulants withdrawal, but also to reduce environmental cues-induced relapse in the long-term.

Laboratory animal studies have initially shown that propranolol inhibited stress and cocaine-associated cues-induced cocaine self-administration behaviour. Noradrenergic beta-receptors have been shown to be over-activated during drug withdrawal and correlates with locus coeruleus noradrenergic neurons hyper-activation.

In our laboratory, we are testing the effects of propranolol on a rat model of cue-induced relapse to nicotine-seeking behaviour. The experimental approach is based on operant conditioning to i.v. nicotine self-administration. Sprague Dawley rats have been trained to lever press for 1-sec i.v. nicotine (0.03 mg/kg) infusions (FR = 1, 3-hr session duration, 1 session/day; then on FR = 2). Each nicotine infusion is contingent to 1-sec tone + green lamp + yellow lamp component (Cues). After 4-6 weeks on nicotine self-administration, saline is substituted for nicotine - without Cues - in order to induce extinction of responding. When responding is extinguished (after approx. 10-23 extinction sessions), rats are re-exposed to Cues contingently upon responding for saline, in order to induce reinstatement (Relapse).

Propranolol (1 or 10 mg/kg i.p.) or vehicle were given immediately prior to Relapse session to each rat. Treatments with propranolol decreased Cues-induced reinstatement compared to vehicle, where during the latter condition responding was 2.5-fold compared to previous extinction session, whereas propranolol 1 or 10 mg/kg treatments further reduces responding, even in presence of Cues. These preliminary data suggest a potent propranolol effect to inhibit Cues-induced reinstatement of nicotine-seeking behaviour in rats.

Further studies are in progress in order to assess propranolol activity after longer periods of abstinence with another experimental approach, that is the reconsolidation of drug-related memories. Re-exposure of laboratory animals to drug-related cues and context induces a reactivation of drug-related memories, a process which lead to reconsolidation of such as motivational engrams. This effect may be experimentally tested one day after reactivation sessions by measuring lever pressing for a previously nicotine-associated manipulanda as expression of drug-seeking behaviour. By

using this protocol, propranolol has been shown to block cocaine-associated memories reconsolidation.

This experimental approach may suggest novel therapeutic strategies, that is the selective inactivation of those 'bad' nicotine-related memories that may trigger cue reactivity and relapse. Of course, different beta-blockers molecules should be tested in order to propose potential new drugs with an optimal efficacy/tolerability profile for relapse prevention.

In conclusion, evidence are growing on the role of the noradrenergic system in nicotine dependence and tobacco addiction, in particular as far as concerns the potential therapeutic effects for new and old drugs acting with this mechanism. However, it is important to remind the multiple effects of nicotine on brain, as well as the bio-behavioural complexity of the smokers. We recommend further studies on the interactions between noradrenaline transmission and other neurochemical systems in order to develop potential new medications and combinations in adjunct to integrate the existing therapeutic agents for smoking cessation.

Study funded by Fondazione Cariverona, Verona, Italy.

No other conflict of interest to be declared for this contribution.

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## Nicotine vaccine

### Jacques Cornuz, MD

Department of ambulatory care and community medicine  
Lausanne University Hospital,  
Switzerland

Despite the known health risks, people continue to smoke and use tobacco primarily as a result of their addiction to nicotine. The therapies prescribed in smoking cessation interventions, such as nicotine replacement, bupropion and varenicline, have modest efficacy. Consequently, there is a need for alternative and improved treatments.

One novel approach is provided by immunization against nicotine. The rationale is to induce antibodies which bind nicotine in the blood, thereby preventing it from crossing the blood-brain barrier. Thus, the reinforcing action of nicotine in the brain, which is the driving force in nicotine addiction and tobacco smoking, can be diminished or even abolished. Nicotine is a small non-immunogenic molecule and can be conjugated to a carrier protein to induce antibodies. Such nicotine conjugates have been shown to induce enough antibodies in animals to sequester the drug in the blood, abolish nicotine addiction and prevent reinstatement of nicotine seeking behavior in vaccinated animals.

Several candidate vaccine against nicotine has been developed. One of them is based on a virus-like particle (VLP)-nicotine conjugate. The presentation of an antigen in a highly ordered, repetitive array, such as protein shells or coats of

certain viruses, provokes strong antibody responses, whereas the same antigen presented as a monomer is non- or poorly immunogenic. The coat protein of the bacteriophage Q<sub>β</sub> forms non-infectious VLP when expressed recombinantly in *Escherichia coli*. Using chemical cross-linkers, any antigen can be placed directionally onto the VLP surface, rendering it highly immunogenic. Antigens coupled to such VLPs induce potent and long-lived antibody responses in mice as well as humans. Specific antibodies of the IgG but not IgE isotype can be detected, demonstrating that potent antibody responses may be induced in the absence of isotypes causing allergic problems.

In pre-clinical animal studies, this candidate vaccine induced strong and specific IgG antibody responses. In a phase I study, 32 healthy non-smokers were immunized with the NicQ<sub>β</sub> vaccine at doses of 50 µg and 100 µg in presence or absence of Alum, one of the adjuvants approved for use in humans. A single injection induced an anti-nicotine response in 100% of subjects, antibody levels were boosted by either a second injection or by the addition of Alum, and the vaccine was well tolerated. Based on these encouraging results, a phase IIb multi-center trial in smokers ready to quit has been performed. The results of the 6-month randomized double blind trial and the subsequent 6-month open follow-up period of this trial assessing safety and tolerability as well as immunogenicity and efficacy, of the vaccine against nicotine will be presented.

Funding: Cytos AG

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## Neurological pathways implicated in addiction.

### The GABAergic pathway: Focus on GABAB

#### John F. Cryan

School of Pharmacy; Department of Pharmacology & Therapeutics, University College Cork, Cork, Ireland

Smoking-related illness is a major public health problem in today's society being the second-leading cause of death in the world. Therefore, there is great impetus to develop effective therapies that will aid in facilitating smoking cessation. It is largely accepted that nicotine is the active ingredient in tobacco smoke that leads to and maintains tobacco addiction. Therefore, most preclinical research efforts are directed at developing interventions that alter the rewarding components of nicotine.

A growing body of evidence suggests that repeated administration of drugs of abuse induce long-term molecular changes in brain plasticity that contribute to the manifestation of dependence (Kelz and Nestler, 2000). Members of the AP-1 family of transcription factors are specifically thought to be involved in the ontogeny of addiction. Indeed, repeated administration of a variety of drugs of abuse, including nicotine induces an accumulation of *c-FosB*, a highly stable truncated

form of *FosB*, in the striatal complex (Kelz and Nestler, 2000). Thus, one can hypothesize that any potential successful therapy for nicotine dependence should attenuate both the rewarding and the molecular changes induced by nicotine.

A number of preclinical and clinical studies suggest that activation of GABAB receptor may be a useful strategy for cocaine, opiate and alcohol dependence (Brebner et al., 2002). Recently, polymorphisms within the GABAB(2) subunit gene have also been shown to be associated with nicotine dependence in humans (Beuten et al., 2005). Furthermore, GABAB receptor agonists such as baclofen reduce nicotine self-administration in rats (Corrigall, 1999). However, baclofen has many side-effects including sedation, muscle relaxation and hypothermia that could limit its widespread use. Positive modulation of metabotropic receptors is a novel principle for enhancing neurotransmission in a use-dependent fashion. Recently, a novel GABAB receptor allosteric positive modulator, GS39783 was characterized. GS39783 increases both the potency and efficacy of endogenous GABA at GABAB receptors without having intrinsic activity (Cryan et al., 2004). Hence, GS39783 lacks many of the behavioural and physiological side-effects of full GABAB receptor agonists (Cryan et al., 2004). Of particular interest, GS39783 reduces the behavioral effects of cocaine (Smith et al., 2004; Slattery et al., 2005; Lhuillier et al., 2006).

Animals, like humans, learn to seek environmental stimuli which have been previously associated with rewarding events, a process known as conditioned place preference (CPP). Consequently most drugs of abuse including nicotine are effective in supporting CPP, making it a prime test of nicotine reinforcement. In the present studies, we investigated the effects of GS39783 on the behavioural (establishment of CPP), and molecular (accumulation of *c-FosB* in the nucleus accumbens) consequences of nicotine exposure.

We demonstrated that GS39783 blocked the acquisition of nicotine-induced place preference. GABAergic mechanisms have long been implicated in drug dependence largely due to known direct interactions of the GABA and the dopamine transmitter systems (Kalivas et al., 1990). It is probable that GS39783 attenuates the increase of dopamine release, via its action on dopaminergic neurons of the VTA, resulting in a reduction of the salience of rewarding stimulus. Thus, this reduction might limit the establishment of the association between nicotine and paired cues. Interestingly, we also observed that a single administration of GS39783 prior to the test failed to significantly affect the expression of nicotine-induced place preference. These present results are consistent with previous data showing that GABAB receptor positive modulator blocked the establishment but not the expression of behavioural sensitization to cocaine (Lhuillier et al., 2007).

We next assessed whether the behavioral changes observed translated into alterations at the molecular level. Although molecular adaptations to chronic nicotine have been hypothesized to play a major role in the manifestation of nicotine dependence (Walters et al., 2005), very few studies to date have investigated the ability of potential therapeutic

agents to modulate such responses. Repeated nicotine self-administration induces a strong accumulation of  $\_FosB$  in the NAc, but not in dorsal striatum (Pich et al., 1997). We confirmed these results in our model of nicotine reinforcement. Further, GS39783 was effective in inhibiting this accumulation when injected chronically during the acquisition phase of place preference. In contrast to this result, a single administration of GS39783 before the final test failed to block nicotine-induced  $\_FosB$  accumulation. This result is in agreement with the observation that  $\_FosB$  is an extremely stable variant of FosB which slowly accumulates during chronic drug exposure (Kelz and Nestler, 2000). Taken together, these results show that chronic GABAB positive modulation is sufficient to counteract the effects of chronic nicotine administration.

We took advantage of the fact that both behavioral and biochemical tests in this study were performed on the same group of animals to compare both data. We found a strong positive correlation between  $\_FosB$  expression and preference for nicotine. Genetic overexpression of  $\_FosB$  in striatal tissues enhances cocaine place preference at low doses (Kelz et al., 1999) while, mice carrying an inactivating mutation of FosB show reduced preference for cocaine (Hiroi et al., 1997). Our data therefore strengthen this existing body of literature suggesting strong associations between the accumulation of  $\_FosB$  and the manifestation of rewarding properties of drugs of abuse.

There is an increasing demand for a non-nicotinic, non-dopaminergic therapeutic approach to addiction (Cryan et al., 2003). In line with this, several clinical studies demonstrated the efficacy of GABAB receptor agonists for the treatment of alcoholism, cocaine or heroin dependence (Brebner et al., 2002). However, the long-term side effects of baclofen may affect its compliance in the smoking population. Together, our data demonstrate that GABAB receptor positive modulation during the conditioning phase of place preference counteracts the rewarding and the long-lasting molecular adaptation induced by repeated administration of nicotine. However, the fact that we only obtain a significant blockade of the acquisition of CPP and not on its expression may limit the therapeutic potential, given that most smokers are already dependent when they attempt smoking cessation therapies. However, future studies must examine the effects of GS39783 in other models of nicotine dependence such as in the acquisition, maintenance and reinstatement of nicotine self-administration. Further, it is clear that there are many more aspects of the addiction process that need to be countered in order to develop successful therapeutic strategies for smoking (Cryan et al., 2003). Among those, counteracting the impact of drug-induced withdrawal and craving are essential. Therefore, interventions should not be limited to only inhibiting the rewarding effects of a drug per se, but should also be aimed at reducing the manifestation of withdrawal and craving and reducing withdrawal-induced deficits in mood and anxiety (Volkow, 2005). It should be noted that GABAB receptor positive modulators reduce anxiety in preclinical paradigms (Cryan et al., 2004) suggests that they may have additional benefits as smoking cessation aids. Nonetheless, the examination of the behavioral effects of GS39783 in animal models of drug withdrawal and relapse is

now warranted. Furthermore, given that the molecular effects of GS39783 in the current study parallels its behavioural effect, studies investigating the molecular mechanisms underlying how GABAB receptor positive modulators can modify NAc  $\_FosB$  may provide novel therapeutic targets for nicotine dependence.

## References.

- Beuten J, Ma JZ, Payne TJ, Dupont RT, Crews KM, Somes G, Williams NJ, Elston RC and Li MD (2005). *Am J Hum Genet* 76:859-864.
- Brebner K, Childress AR and Roberts DC (2002) *Alcohol Alcohol* 37:478-484.
- Brunzell DH, Russell DS and Picciotto MR (2003). *J Neurochem* 84:1431-1441.
- Corrigall WA, Coen KM, Adamson KL, Chow BL and Zhang J (2000) *Psychopharmacology (Berl)* 149:107-114.
- Cryan JF, Gasparini F, van Heeke G and Markou A (2003). *Drug Discov Today* 8:1025-1034.
- Cryan JF, Kelly PH, Chaperon F, Gentsch C, Mombereau C, Lingenhoehl K, Froestl W, Bettler B, Kaupmann K and Spooren WP (2004) *J Pharmacol Exp Ther* 310:952-963.
- Donny EC, Caggiula AR, Mielke MM, Jacobs KS, Rose C, Sved AF. (1998) *Psychopharmacology* 136:83-90.
- Erhardt S, Mathe JM, Chergui K, Engberg G and Svensson TH (2002) *Naunyn Schmiedeberg's Arch Pharmacol* 365:173-180.
- Hiroi N, Brown JR, Haile CN, Ye H, Greenberg ME and Nestler EJ (1997) *Proc Natl Acad Sci U S A* 94:10397-10402.
- Kalivas PW, Duffy P and Eberhardt H (1990) *J Pharmacol Exp Ther* 253:858-866.
- Kelz MB, Chen J, Carlezon WA, Jr., Whisler K, Gilden L, Beckmann AM, Steffen C, Zhang YJ, Marotti L, Self DW, Tkatch T, Baranaukas G, Surmeier DJ, Neve RL, Duman RS, Picciotto MR and Nestler EJ (1999). *Nature* 401:272-276.
- Kelz MB and Nestler EJ (2000) *Curr Opin Neurol* 13:715-720.
- Lhuillier L, Mombereau C, Cryan JF and Kaupmann K (2007) *Neuropsychopharmacology*. 32:388-98, 2007
- Pich EM, Pagliusi SR, Tessari M, Talabot-Ayer D, Hooft van Huijsduijnen R and Chiamulera C (1997) *Science* 275:83-86.
- Slattery DA, Markou A, Froestl W and Cryan JF (2005) *Neuropsychopharmacology* 30:2065-2072.
- Smith MA, Yancey DL, Morgan D, Liu Y, Froestl W and Roberts DC (2004) *Psychopharmacology (Berl)* 173:105-111.
- Volkow ND (2005) *Am J Psychiatry* 162:1401-1402.
- Walters CL, Cleck JN, Kuo YC and Blendy JA (2005) *Neuron* 46:933-943.

Supported by Novartis Institutes for BioMedical Research Basel and NIDA/NIMH grant U01MH60962.

## In vivo studies with nicotinic ligands

### M. Imad Damaj

Associate professor of Pharmacology  
Virginia Commonwealth University  
Department of Pharmacology  
Richmond, VA - USA

After initial in vitro evaluation of nicotinic ligands on the main nicotinic receptors, analogs will be evaluated in various mouse models of nicotine dependence. We first study the potential agonistic/antagonistic properties of these analogs on nicotinic acute effects using a battery of tests such as analgesia, hypothermia and locomotor activity. These nicotine-like pharmacological responses in the mouse were chosen because they are centrally mediated and they involve to a large extent  $\alpha 4\beta 2^*$  nAChR subtypes. In addition, these mouse models are ideal for initial screening; because a large number of compounds can be readily evaluated, they have been used to evaluate nicotine action for many years, and they represent a simple and reliable means of determining potency.

Compounds with a desired potency will be tested for their ability to block nicotine-induced conditioned place preference, a measure of nicotine reward. We will also study their potential to engender nicotine-like responding in drug discrimination. Finally, these analogs will be tested for their efficacy in a nicotine withdrawal model that measure both affective and physical signs. Full characterization of these compounds will allow us to design an effective evaluation strategy for newly synthesized compounds with distinctive in vitro and in vivo profiles. Results from these studies, coupled with findings from the in vitro characterization work, will also help identify molecular targets that are related to their effects on nicotine dependence.

## Can smoking reduction promote smoking cessation?

### José Ignacio de Granda Orive

Respiratory Department (Smoking Clinic Unit)  
Defense Central Hospital Gómez Ulla  
Madrid Spain

At every given time, the large majority of smokers are not motivated or willing to try and give up. Some smokers are entirely happy with their smoking, a larger group would like to smoke less and a third group wants to quit. With the abrupt quitting message we are only addressing those wanting to quit. Maybe not even all, since some of them may have tried many times already and learned that they cannot quit abruptly. They may have given up on giving up. Some interesting results are given in recent studies that have recruited smokers not motivated to quit but interested in reducing their smoking<sup>1,2</sup>. Over the last 5–15 years, it has been understood that many smokers who are not interested in quitting can be interested in reducing their smoking. The data from these studies suggest that quitting occurs in insufficiently motivated smokers, and

quitting is stimulated by two things: the reduction regime that the smoker participates in and the use of pharmacological treatment. Altogether, this shows that exposing smokers not interested in quitting to an reduction smoking treatment does not, at the time, endanger a weak or non-existing interest in quitting. With the results from the presented studies on reduction smoking, it seems possible to increase motivation among unmotivated smokers to finally give up<sup>1</sup>.

The most interesting observation made from this studies was that some quitting occurred across these samples of smokers not interested in quitting, smokers in the active groups had higher quitting rates than those reported from the placebo groups, although statistically significant in only half of the studies<sup>3-6</sup>. Falba et al<sup>7</sup> in a interesting study, conclude that those smokers that quit smoke after a reduce program are less likely to relapse. Pisinger et al<sup>8</sup> found, in a group of smokers unmotivated for quit or that they couldn't quit, that reduction of > 50% in number of cigarettes was a good predictor of cessation. Batra et al<sup>9</sup> in a study that examined the efficacy of nicotine chewing gum in reduce or promote cessation in smokers, found that nicotine chewing gum for unmotivated quit smokers was a good alternative for reduce harm and promote cessation.

Reduction smoking could be added to the clinician's weapons for those who are not interested in giving up smoking because we have learned that reduce smoking could promote cessation.

### Bibliography:

- 1) Fagerström KO. Can reduce smoking be a way for smokers not interested in quitting to actually quit? *Respiration*. 2005; 72: 216 – 20.
- 2) Hughes JR, Carpenter MJ. The feasibility of smoking reduction: an update. *Addiction*. 2005; 1074 – 89.
- 3) Wennike P, Danielsson T, Landfeldt B, Westin A, Tønnesen P. Smoking reduction promotes smoking cessation: Results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. *Addiction*. 2003; 98: 1395–402.
- 4) Kralikova E, Kozak J, Rasmussen T. The clinical benefits of NRT-supported smoking reduction. *Nicotine Tob Res*. 2002; 4: 243.
- 5) Rennard S, Glover ED, Leischow S, Daughton DM, Glover P, et al. Efficacy of the nicotine inhaler in smoking reduction. *Nicotine Tob Res* 2002; 3: 380.
- 6) Hatsukami D, Rennard S, Manoj KP, Kotylar M, Malcolm R, et al. Effects of sustained-release bupropion among persons interested in reducing but not quitting smoking. *Am J Med*. 2004; 116: 151–7.
- 7) Falba T, Jofre Bonet M, Bush S, Duchovny N, Sindelar J. Reduction of quantity smoked predicts future cessation among older smokers. *Addiction* 2004; 99: 93 – 102.
- 8) Pisinger C, Vestbo J, Borch Johnsen K, Jorgensen T. Smoking reduction intervention in a large population based – study. *The Inter 99 study*. *Prev Med*. 2005; 40: 112 – 8.
- 9) Batra A, Klinger K, Langfeldt B, Friederich M, Westin A, Danielsson T. Smoking reduction treatment with 4 mg nicotine gum: A double – blind, randomized, placebo – controlled study. *Clin Pharmacol Ther*. 2005; 78: 689- 96.

## **Tobacco dependence: abnormal learning in cortico-striatal loops**

**Gaetano Di Chiara**

Department of Toxicology, University of Cagliari, Cagliari, Italy

It has been proposed (Di Chiara, 2000) that, in the early stages of nicotine dependence, smoking is controlled by incentive learning processes facilitated by dopamine release. However, after extensive experience of smoking, responding would switch from an incentive mode to an habit-based, outcome-unrelated mode. Thus, in highly-dependent smokers, smoking behaviour would become a 'habit' initiated automatically by drug-related stimuli in the absence of incentive motivational processes. As habit becomes a more influential determinant of drug seeking behaviour, the strength of incentive motivational processes may actually diminish. Combined behavioural/brain microdialysis studies in animals and neuropsychological/brain imaging studies in humans suggest that the behavioural disturbances of tobacco dependence are the result of abnormal learning induced by the action of dopamine released by nicotine in different domains of the corticostriatal system. Funded by NIDE project, European Commission.

ORIGINAL INVESTIGATION

## **The dopaminergic pathway**

**Marco Diana**

"G. Minardi" Laboratory of Cognitive Neuroscience, Department of Drug Sciences  
University of Sassari, Italy

In spite of the fact that actions of dopamine, as a neurotransmitter in its own right, were foreseen as early as the 1930s (Blaschko 1939) and explicitly postulated in the 1950s (Carlson et al. 1958), it took over a decade more to begin to explore the electrophysiological features, characteristics, and responsiveness to drugs of central dopaminergic neurons (Bunney et al. 1973b; Groves et al. 1975). In the 1960s much effort was employed attempting to map the location of catecholamine neurons in the mammalian central nervous system. The use of the histofluorescence technique (Falck et al. 1962) coupled with lesion experiments enabled anatomists to locate dopaminergic cell bodies in the mesencephalon (Anden et al. 1964; Bertler et al. 1964). Subsequent work (Dahlstrom and Fuxe 1964; Anden et al. 1965; Ungerstedt 1971) refined and extended those initial and pioneering findings and formed the basis for modern anatomical, biochemical, and electrophysiological investigation of central dopaminergic neurons.

Drug addiction is a brain disorder caused by the repetitive use of various chemicals which alter normal functioning of the central nervous system with consequent behavioral abnormalities. In the search to understand which neurotransmitter systems play upon this behavioral pathology, dopamine has long been thought to play a fundamental role. However, its primary role is commonly and erroneously attributed to the increase in activity after acute administration of addicting drugs. On the

contrary, the mesolimbic dopamine transmission appears to be drastically reduced in its tonic activity when measured in animal models, which mimic the human condition of drug addiction, and in the available human studies conducted in addicted subjects. This paper is a brief review of the pertinent literature which strongly supports this concept. Various experimental approaches such as electrophysiological, biochemical, behavioral, biomolecular and even anatomical, show that dopamine neurons work insufficiently in the crucial phases of the entire drug addiction cycle such as withdrawal from chronic treatment. This hypodopaminergic state is viewed as one of the main causes that triggers drug-seeking and taking, even after prolonged drug-free periods, perpetuating the vicious cycle. In addition, albeit reduced in its activity, the system remains hyperresponsive to abused drugs conferring long-lasting vulnerability to the system. We propose that decreased dopamine function in addicted subjects results in a decreased interest to non drug-related stimuli and increased sensitivity to the drug of choice.

At the behavioral level self-administration and Intracranial self-stimulation studies convincingly support these contentions. Self-administration has a prominent significance because it reflects an operant (active) behavior phenomenologically identical to the human condition. Basically, the experimental animal presses a lever and receives a bolus of the drug. An intravenous catheter is connected to a pump, which delivers the intravenous fluid injections. The experimental preparation is, therefore, a chronically intravenous catheterized animal, which may be semi-restrained in a chair (e.g., primates) or allowed to freely move within the experimental chamber (e.g., rodents) during the self-administration session. A drug is considered to be self-administered when either the rate of drug responding is greater than the rate of response on a control lever (which results in saline injections), or when the response rate is greater in the subject whose response produces drug injections compared to its yoked control (Davis and Nichols, 1963; Pickens and Thompson, 1975). Drugs abused by humans have been demonstrated to be readily self-administered by laboratory animals and, more pertinently in the present context, accumulating evidence suggests that the withdrawal phase leads to an increased consummatory behavior of diverse drugs of abuse such as ethanol, opiates, cocaine, and nicotine (Grasing et al., 2003; Hutcheson et al., 2001; Khantzian, 1985; Koob, 1996; Mucha et al., 1986; Valdez et al., 2004; Weiss et al., 1996, 2001).

Another behavioral model used to investigate the rewarding/addicting properties of a drug in laboratory animals is the intracranial self-stimulation (ICSS) method (Kornetsky et al., 1979). This procedure is based on the observation that rats will press a lever to pass a small current through electrodes located in various brain areas (Olds and Milner, 1954), including those that give course to the ascending DA-containing axons projecting to the forebrain. This method consists of placing a stimulating electrode in the medial forebrain bundle or other brain areas (such as lateral hypothalamus, VTA, prefrontal cortex, NAcc, etc.) and allowing animals to self-stimulate so neuronal reward circuits are activated. As a result, laboratory animals can directly activate (self-stimulate) those brain

circuits that natural and conditioned reinforcers stimulate (Bozarth and Wise, 1981; Goeders and Smith, 1983; Hoebel et al., 1983; Phillips and LePiane, 1980; Phillips et al., 1981). Drugs of abuse such as cocaine (Markou and Koob, 1991), amphetamine (Harrison et al., 2001; Kokkinidis and Zacharko, 1980; Paterson et al., 2000), ethanol (Schulteis et al., 1995), morphine (Schulteis et al., 1994), and nicotine (Epping-Jordan et al., 1998; Harrison et al., 2001) enhance the reinforcing impact of such electrical stimulation. Conversely, acute withdrawal from diverse drugs of abuse precipitates a

deficit in brain reward function, which can be indexed by elevated ICSS reward thresholds. These increases in brain stimulation threshold, to maintain ICSS, have been observed for the major drugs of abuse, such as opiates (Schaefer and Michael, 1986; Schulteis et al., 1994), cocaine (Markou and Koob, 1992), amphetamine (Cryan et al., 2003a; Lin et al., 1999; Wise and Munn, 1995), ethanol (Schulteis et al., 1995), and nicotine (Cryan et al., 2003b; Epping-Jordan et al., 1998; Kenny et al., 2003). In addition, Kenny et al. (2003) provided further evidence for the role of the VTA in ICSS during acute nicotine withdrawal. Indeed, either activation or blockade of group II mGluRs within the VTA elevated or decreased, respectively, ICSS thresholds in nicotine-dependent rats (Kenny et al., 2003). Therefore, increased ICSS thresholds constitute a good behavioral animal model of the aversive motivational state associated with the negative reinforcement of drug withdrawal in dependent animals and add further evidence to the notion that VTA DA cells and their projections play a key role in perpetuating the addiction cycle (Diana, 1996, 1998; Shippenberg and Koob, 2002).

The DA cells located within the VTA project to the limbic subcortical areas (i.e., NAcc, amygdala, and olfactory tubercle) and to the limbic cortices (i.e., medial prefrontal, cingulate, and entorhinal), thereby constituting the mesolimbocortical system (Anden et al., 1966; Bjorklund and Lindvall, 1975; Lindvall and Bjorklund, 1974; Loughlin and

Fallon, 1983; Ungerstedt, 1971). Investigations examining the acute effects of drugs of abuse provide comprehension of their cellular sites of action but do not give relevant information about the neural changes related to the phenomenon of continuous drug exposure needed to provide realistic experimental models of drug addiction. The path to drug addiction begins with the act of taking drugs, which then becomes chronic, with relapses possible even after long periods of abstinence. Therefore, studying the effects of chronic exposure to drugs of abuse on the mesolimbic DA system is more relevant in the context of drug addiction than studying their acute effects.

Ethanol withdrawal decreases spontaneous activity of rat VTA DA neurons *in vivo* (Diana et al., 1992b, 1993b) and mice *in vitro* (Bailey et al., 1998) with no difference in the number of spontaneously active cells (Diana et al., 1995b; Shen and Chiodo, 1993). This hypoactivity of DA cells correlates well with a reduction of extracellular DA levels in the NAcc (Diana et al., 1993b; Fadda and Rossetti, 1998; Rossetti et al., 1992a) and might represent the neural basis of the dysphoric state observed upon abrupt interruption of chronic ethanol.

Similarly, morphine withdrawal causes a profound decline of firing rate and bursting activity of VTA DA cells (Diana et al., 1995a), which persists long after the behavioral signs of withdrawal have ceased (Diana et al., 1999). The adaptive changes occurring at the synaptic level and underlying the reduction in spontaneous activity of VTA DA cells *in vivo* have been intensively investigated (Bonci and Williams, 1996, 1997; Manzoni and Williams, 1999). In fact, during acute withdrawal from prolonged morphine administration, an upregulation of the cAMP-dependent cascade produces a long-lasting increased probability of GABA release in the VTA (Bonci and Williams, 1996, 1997). Additionally, an increased sensitivity to presynaptic inhibition by both group 2 mGluRs and GABAB receptors results in a reduced release of glutamate (Manzoni and Williams, 1999). Thus, withdrawal from chronic morphine modifies both inhibitory and excitatory inputs to VTA DA cells, though in opposite ways. Interestingly, while VTA-DA neurons appear to be back to normal within 2 weeks after acute withdrawal, acute morphine administration produced greater responses in rats with a history of morphine dependence than in controls (Diana et al., 1999). This latter finding suggests an increased sensitivity of VTA DA cells to morphine itself, which may be relevant to the phenomenon of drug craving and relapse (Diana et al., 1999; Pulvirenti and Diana, 2001). Cannabinoid withdrawal effects on VTA DA neuronal activity (Diana et al., 1998b) are reminiscent of those reported for ethanol and morphine. More interestingly, a reduction in VTA DA neuronal function is also observed when somatic signs of withdrawal are not detectable (Diana et al., 1998b). Furthermore, when a pharmacologically precipitated withdrawal is induced with

the specific cannabinoid antagonist SR 141716A, the somatic signs of withdrawal accompany the dampened VTA DA neuronal activity (Diana et al., 1998b). Similarly, nicotine withdrawal produces a decline of firing rate of VTA DA neurons that rapidly (within 2 days) returned to control levels (Liu and Jin, 2004; Rasmussen and Czachura, 1995). Like the effects of withdrawal from other drugs of abuse (Diana et al., 1993b, 1995, 1998b), the number of spontaneously active DA cells was not altered at any time after nicotine withdrawal. Thus, this study, together with other investigations (Bailey et al., 1998, 2001; Diana et al., 1992, 1993b, 1995a, 1998b), suggests that the hypodopaminergic state accompanying the acute phases of withdrawal is not mediated by depolarization inactivation of DA neurons but most likely reflects alterations of intrinsic properties and extrinsic afferent regulatory mechanisms (Bonci and Williams, 1996, 1997; Diana and Tepper, 2002; Manzoni and Williams, 1999; Pulvirenti and Diana, 2001) modified by a chronic drug regimen and disclosed by withdrawal.

These studies strengthen the notion that VTA DA neurons are involved in the mechanisms accounting for the subjective aversive components of withdrawal (dysphoria), rather than the somatic facets of it, and provide an important neural basis for motivational components of self-administration and ICSS studies.

#### **Acknowledgments**

This work was supported, in part, by grants from M.I.U.R. (PRIN 2004; 2006) and R.A.S to the author.

## Exposure reduction, harm reduction, and tobacco control

### Thomas Eissenberg

Associate Professor of Psychology and  
Institute for Drug and Alcohol Studies  
Virginia Commonwealth University, USA

Within the public health community, prevention and cessation have been the twin pillars of tobacco control. Nonetheless, in the past several years, there has been a growing public health interest in harm reduction. That is, there may be ways to decrease the risk of death and disease for those people for whom prevention and cessation have failed. This goal of decreased risk of tobacco-caused death and disease should be highly valued for anyone interested in public health. Recently marketed products indicate that harm reduction may also be a tobacco industry goal. However, because of the industry's profit motive and history of deception and scientific misconduct, the public health community is right to be skeptical of industry goals and harm reduction products. This skepticism is heightened when these products are based on the untested assumption that reducing user exposure to specific tobacco toxicants will reduce risk of death and disease. This talk will focus on potential reduced exposure products for tobacco users, results from studies evaluating them, and on-going efforts to relate exposure reduction to harm reduction. Regulatory models and financing of product evaluation will also be discussed. With careful evaluation and strict regulation, harm reduction can be a third pillar with which to control tobacco-caused death and disease. Dr. Eissenberg's research is supported by the United States' National Institutes of Health (National Cancer Institute, National Institute on Drug Abuse, and Fogarty International Center).

## Smoking cessation in the past and in the future

### Karl Fagerstrom

Smoker's Information Centre  
Helsingborg, Sweden

Smoking cessation is gradually entering main stream medicine in some countries. It has been found very cost effective in comparison to most other medical treatment and prevention practices.

Some 30 years ago when I started to work with smokers, they were fairly representative of the general population in most respects. Today, when the prevalence has been halved in some countries –for example Sweden– the smokers seeking treatment are different from the general population.

Some have given up with help of the information provided, the social pressure, price increases and smoking bans. The remaining smokers might have had 'good reasons' to ignore this pressure. Therefore they often present with co-morbidity sometimes to the extent warranting a full diagnosis, and at other times of a more sub-clinical nature. Offering encouragement in

the form of advice to eat carrots and drink water when the "pain" of withdrawal sets in is no longer working, if it ever has. Today, counsellors need professional and state-of-the-art training in order to correctly assess and address the problem of tobacco dependence. Such knowledge may involve insights into common co-morbidity conditions and use of more intensive behavioural and pharmacological treatments. There is also some evidence that success rates are declining over time in countries where prevalence has fallen significantly. Also there are indications that today's smokers may be more dependent, as measured by the FTND. However, it is possible that smokers can be more difficult to help even though their FTND score is not higher. Things like more co-morbidity and lower social class in future smokers may be as determining factors for outcome.

There is an agreement that tobacco smoking can be very addictive. Sometimes we say it is actually as, or even more, addictive than alcohol, heroin and cocaine. Seldom are the consequences drawn. Few clinicians treating alcoholics or heroin addicts would ask their patients to set a quit date when they quit abruptly and for life. When the correct consequences are realised, treating tobacco dependence will most likely be very different in the future. The treatment objectives and procedures used in the management of tobacco dependence will be more similar to those used with other addictions. Currently there is in principle only one objective — complete abstinence — reached by abrupt quitting. Even without purposefully changing this objective we are starting to see a gradual sliding into reduced smoking before quitting. With bupropion and varenicline smokers start active treatment a week before quitting and often the smokers cut down on their smoking. The nicotine vaccines, if they reach the market, will take several weeks, if not months, before they are effective. No doubt reduction before quitting will be more common. New indications for the treatment of tobacco dependence are to come. The first is already here since some regulatory authorities have approved Reduction to Quit for NR products, as it seems to be a method that is of interest to smokers not interested in quitting abruptly. Another might be relapse prevention which might be particularly well suited for immunotherapy. It is, however, likely that we may have to offer other objectives too, if we want to help more smokers from suffering the harmful effects of tobacco smoking. To be realistic, there are smokers living such poor and miserable lives that they do not want to subject themselves to additional, at least short-term, misery for an investment to bear full fruit in health status toward their retirement age. Such smokers can still be well-adjusted in our society, but more often they are found among prisoners, addicts, homeless and mentally ill people. Smoking cessation may have to change its name to 'treatment of tobacco dependence' as cessation will not be the only objective. It could be complemented with reduced risk, harm and dependence by reducing intake of smoke, using less harmful tobacco products such as smoke-free tobacco, or partial or full replacement with NR products. It could also be positive to transfer daily smokers into occasional smokers with the help of any of the above-mentioned methods.

Funding: None.

## Insurance Coverage for Tobacco Dependence Treatments

**Michael C. Fiore**

Center for Tobacco Research and Intervention. University of Wisconsin Medical School. USA

During this presentation, I will summarize new research and thinking on an innovative strategy to increase the use and effectiveness of evidence-based tobacco dependence treatments. That strategy is third-party payment for evidence-based treatments.

The potential of evidence-based tobacco dependence treatments to drive down tobacco use rates has not been fully realized for a number of reasons. First, while a number of clinically effective smoking cessation treatments exist<sup>1</sup>, the use of these treatments remains low. In the United States for example, approximately 20 million of the current 45 million smokers try to quit each year<sup>2</sup>. Yet, only 22 to 25% of these smokers report that they used any of the evidence-based counseling and medication treatments that have been identified as effective<sup>1,3,4,5</sup>. Importantly, cost has been identified as a barrier to the use of evidence-based treatments, particularly, evidence-based medications<sup>6</sup>. Regarding this point, insurance coverage that partially or fully offsets the cost of evidence-based cessation treatments may remove this barrier to use. This presentation will focus on the potential of insurance coverage and other cost offsets to increase the rates at which smokers use evidence-based treatments and successfully quit.

An expanding array of research over the past two decades highlights the finding that providing insurance coverage for treatment of tobacco dependence results in higher rates of evidence-based treatment use and higher overall cessation rates among covered populations. In a study published in by Hughes and colleagues in 1991<sup>7</sup>, the authors randomly assigned 106 smokers seen in a family practice clinic who received brief physician advice to quit were randomly assigned to pay \$20, \$6, or \$0/box for prescription nicotine gum. Following up on these patients six months later, the authors reported that decreasing the cost of treatment increased the incidence of obtaining gum, the amount of gum used, and the incidence of long-term use ( $p < .05$ ). They also found that decreased cost of medication resulted in increased cessation attempts and increased 1-week cessation ( $p < 0.05$ ) and appeared to increase abstinence at 6-months follow-up (19% vs. 6% vs. 8%,  $p < 0.10$ ). Finally, the authors concluded that cost-benefit estimates suggest that an insurance plan or health maintenance organization would recoup any costs in subsidizing nicotine gum and perhaps incur a net financial gain.

In a highly influential article from 1998, Curry and colleagues<sup>8</sup> investigated whether insurance coverage influences demand for and use of smoking cessation services. In a longitudinal, natural experiment, they compared the use and cost effectiveness of three forms of insurance coverage with a standard form of coverage that included a behavioral program and NRT. The study involved seven employers and more than 90,000 enrollees in a health maintenance organization. The

four conditions contrasted ranged from the plans that offered 50% coverage of both a behavioral program and NRT to full coverage of both the behavioral program and NRT. Estimated annual rates of use of smoking cessation services ranged from 2.4% (among smokers with reduced coverage) to 10% (among those with full coverage). Smoking cessation rates ranged from 28% among those with full coverage to 38% among those with one of the more reduced coverage plans. The estimated percentage of all smokers who would quit smoking per year as a result of using the services ranged from 0.7% (with reduced coverage) to 2.8% (with full coverage). The authors concluded that the use of smoking cessation services varies according to the extent of coverage, with the highest rates of use among smokers with full coverage. Although the rate of smoking cessation among benefit users with full coverage was lower than the rates among users with plans requiring co-payments, more enrollees quit with full coverage because more enrollees tried to quit with full coverage.

Schauffler and colleagues in 2001<sup>9</sup> assessed the impact and costs of coverage of an Health Maintenance Organization (HMO) tobacco dependence treatment benefit that included no patient cost sharing. In this study, 1,204 smokers were randomly assigned to receive either self help materials (control condition) or self help treatments plus group counseling plus over the counter nicotine replacement gum and patch (intervention condition). Patients did not share any of the costs of the two conditions. One year quit rates were 18% in the intervention condition and 13% in the control condition. Moreover, rates of quit attempts and use of nicotine gum or patch were also higher in the treatment group. Finally, the annual cost of the benefit per user who quit ranged from \$965 to \$1,495 to \$965 or from \$0.47 to \$0.73 per HMO member per month. The authors concluded that full coverage of a tobacco dependence treatment benefit by health maintenance organizations is an effective and low cost strategy for significantly increasing quit rates, quit attempts, and use of nicotine gum and patch in adult smokers.

Kaper and colleagues in 2005<sup>10</sup> investigated whether financial reimbursement for smoking cessation treatment (SCT) would encourage the use of SCT and would increase abstinence rates. They randomly assigned more than 1,200 smokers to an intervention group that included an offer of reimbursement for nicotine replacement therapy, bupropion and behavioral counseling or no reimbursement. The authors found that significantly more smokers in the intervention group than the control group used SCT (10.8% vs. 4.1%) and that significantly more smokers in the intervention group were abstinent at six months (5.5%) than in the control group (2.3%). They concluded that reimbursement for SCT seems efficacious in increasing the use of SCT and may double the number of successful quitters. These same authors followed the participants of this study two years later and reported that sustained abstinence was 4.3% in the intervention group compared to 1.6% in the control group<sup>11</sup>. The authors concluded that reimbursement for cessation treatment may positively affect sustained abstinence.

The economic case for coverage of tobacco dependence treatment is compelling. A growing body of research indicates

that modifiable health risks are significantly correlated with increased healthcare utilization and expenditures 12-14 and smoking is particularly associated with substantial excess medical costs 15-18. For example, Pronk, et al. (1999) investigated health plan charges in a population aged 40 or older and determined that, over 18 months, current smokers incurred 18% higher medical charges than never smokers. In a report titled, *The Business Case for Coverage of Tobacco Cessation*, the actuarial consulting firm of Leif Associates, Inc. reported that more than 17% of a typical insured commercial population are smokers who can generate as much as 30% in higher health care costs than nonsmokers 19.

Insurance coverage for tobacco dependence treatments can play an important role in increasing the rate of such evidence-based treatments<sup>20</sup>. This finding has changed substantially the perspective of insurers regarding tobacco dependence treatment coverage. For example, in the U.S. evidence-based cessation counseling and medications are now mandated as covered benefits for all Medicare enrollees. Moreover, many States are offering such benefits to their Medicaid enrollees and state employees. Finally, more private insurers are expanding their coverage of cessation treatments, although such coverage is far from universal. The end result of expanded insurance coverage for tobacco dependence treatment is clear – a greater rate of cessation success among enrollees. Clinicians, health care administrators, and tobacco control advocates each can play a role in encouraging health plans to support this outcome.

#### References:

1. Fiore MC, Bailey WC, Cohen SJ: *Treating tobacco use and dependence: Clinical Practice Guideline*. Rockville, MD, U.S. Department of Health and Human Services, U.S. Public Health Service, 2000
2. Centers for Disease Control and Prevention: *Tobacco use among adults - United States, 2005*. MMWR 2006, 55:1145-1148
3. Cokkinides VE, Ward E, Jemal A, Thun MJ: Under-use of smoking-cessation treatments: results from the National Health Interview Survey, 2000. *Am J Prev Med* 2005, 28:119-122
4. Cummings KM, Hyland A: Impact of nicotine replacement therapy on smoking behavior. *Annu Rev Public Health* 2005, 26:583-599
5. Piasecki TM, Fiore MC, Baker TB: Profiles in discouragement: Two studies of variability in the time course of smoking withdrawal symptoms. *Journal of Abnormal Psychology* 1998, 107:238-251
6. Roddy E, Antoniak M, Britton J, Molyneux A, Lewis S: Barriers and motivators to gaining access to smoking cessation services amongst deprived smokers—a qualitative study. *BMC Health Serv Res* 2006, 6:147
7. Hughes JR, Wadland WC, Fenwick JW, Lewis J, Bickel WK: Effect of cost on the self-administration and efficacy of nicotine gum: a preliminary study. *Prev Med* 1991, 20:486-496
8. Curry SJ, Grothaus LC, McAfee T, Pabiniak C: Use and cost effectiveness of smoking-cessation services under four insurance plans in a health maintenance organization. *N Engl J Med* 1998, 339:673-679
9. Schaffler HH, McMenemy S, Olson K, Boyce-Smith G, Rideout JA, Kamil J: Variations in treatment benefits influence smoking cessation: Results of a randomised controlled trial. *Tobacco Control* 2001, 10:175-180
10. Kaper J, Wagena EJ, Willemsen MC, van Schayck CP: Reimbursement for smoking cessation treatment may double the abstinence rate: results of a randomized trial. *Addiction* 2005, 100:1012-1020
11. Kaper J, Wagena EJ, Willemsen MC, van Schayck CP: A randomized controlled trial to assess the effects of reimbursing the costs of smoking cessation therapy on sustained abstinence. *Addiction* 2006, 101:1656-1661
12. Anderson LH, Martinson BC, Crain AL, Pronk NP, Whitebird RR, O'Connor PJ, Fine LJ: Health care charges associated with physical inactivity, overweight, and obesity. *Prev Chronic Dis* 2005, 2:A09
13. Martinson BC, O'Connor PJ, Pronk NP, Rolnick SJ: Smoking cessation attempts in relation to prior health care charges: The effect of antecedent smoking-related symptoms? *American Journal of Health Promotion* 2003, 18:125-132
14. Ohinmaa A, Schopflocher D, Jacobs P, Demeter S, Chuck A, Golmohammadi K, Klarenbach SW: A population-based analysis of health behaviours, chronic diseases and associated costs. *Chronic Dis Can* 2006, 27:17-24
15. Bolin K, Lindgren B: Smoking, healthcare cost, and loss of productivity in Sweden 2001. *Scand J Public Health* 2007, 35:187-196
16. Centers for Disease Control: Annual smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 1997-2001. *MMWR Morb Mortal Wkly Rep* 2005, 54:625-628
17. Leigh JP, Hubert HB, Romano PS: Lifestyle risk factors predict healthcare costs in an aging cohort. *Am J Prev Med* 2005, 29:379-387
18. Pronk NP, Goodman MJ, O'Connor PJ, Martinson BC: Relationship between modifiable health risks and short-term health care charges. *JAMA* 1999, 282:2235-2239
19. Leif Associates: *The business case for coverage of tobacco cessation*, Colorado Clinical Guidelines Collaborative, 2003
20. Manley MW, Griffin T, Foldes SS, Link CC, Sechrist RA: The role of health plans in tobacco control. *Annu Rev Public Health* 2003, 24:247-266

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## Can Smokeless Tobacco Aid Smoking Cessation: What is The Evidence?

### Jonathan Foulds

Professor, UMDNJ-School of Public Health  
 Director, Tobacco Dependence Program at UMDNJ-School of Public Health, USA

There is a diverse range of smokeless tobacco products in use in different parts of the world. A useful summary guide, with photographs, is available from the U.S. National Cancer Institute and Centers for Disease Control, and online at:

[www.cancercontrol.cancer.gov/tcrb/stfact\\_sheet\\_combined10-23-02.pdf](http://www.cancercontrol.cancer.gov/tcrb/stfact_sheet_combined10-23-02.pdf).

All of these commonly used varieties deliver pharmacologically active doses of nicotine by direct absorption through the lining of the oral or nasal mucosa. These different products vary as much as 130-fold in their content and delivery of

tobacco toxins<sup>1</sup>. Some have very high concentrations of tobacco-specific nitrosamines (TSNAs) and are a significant cause of oral cancer whereas others, including the snus used in Sweden, have relatively low concentrations of TSNAs and appear to either not cause cancer, or to present a lower level of risk<sup>2,3,4</sup>. Smokeless tobacco used in Asia is commonly mixed with a number of other products, including areca nut, which is itself both psychoactive and carcinogenic. So in most contexts it does not make sense to talk about “smokeless tobacco” as if it is a single product with homogeneous characteristics.

### **Characteristics of some smokeless tobacco products that may aid smoking cessation.**

One major characteristic of smokeless tobaccos (in general) that make them worth considering for smoking cessation is the simple fact that they do not deliver toxins directly into the lungs of users. Given that a very large part of the harm to health caused by smoking is a direct result of smoke delivery to the lungs (e.g. causing lung cancer and COPD), a product that avoids this mode of delivery has obvious potential for harm reduction.

However, oral cancer is clearly a major concern and is a proven consequence of some forms of smokeless tobacco. Given that some forms of smokeless tobacco contain much lower quantities of TSNAs than others, this paper will focus on the potential use of smokeless products known to be relatively low in these cancer-causing substances – namely snus products originally developed in Sweden, and other oral tobacco products (including new low TSNA products) marketed in North America and a few other places.

There is already excellent evidence showing that pharmaceutical nicotine replacement products are effective aids to smoking cessation. The efficacy of these products is undoubtedly related to their ability to deliver nicotine and so reduce nicotine withdrawal symptoms and cravings. There is also solid evidence that within the nicotine replacement products, efficacy is related to the dose of nicotine delivered (e.g. for heavy smokers 4mg gum is more effective than 2mg). So one basic pre-requisite for smokeless tobacco products to help smokers to quit is the ability to provide the user with blood nicotine levels at least as high or higher than those provided by NRT products.

There is clear evidence that some popular smokeless tobacco products provide users with blood nicotine concentrations that are significantly higher than those typically achieved by NRT. For example, one study found that General Snus delivered blood nicotine levels more than twice those provided by 2mg nicotine gum<sup>5</sup>. Another recent study found that Copenhagen moist snuff provided a peak blood nicotine level (16ng/ml) that was more than twice that delivered by the 4mg Commit NRT lozenge (7 ng/ml)<sup>6</sup>. It should be noted, however, that not all smokeless products deliver adequate blood nicotine levels. In the same study, other brands of smokeless tobacco (Stonewall, Ariva and Revel) produced peak blood nicotine levels in the 2-4 ng/ml range. Given that a single cigarette typically provides peak blood

nicotine levels in the range 10-20 ng/ml, it appears likely that many NRT and smokeless tobacco products underdose and so are likely suboptimal smoking cessation aids. However, some smokeless tobacco products deliver nicotine levels significantly higher than NRTs and may therefore have advantages in this respect.

One other characteristic of smokeless tobacco is that it is intended for long term use. This differs from NRTs, which are intended for short term (6-12 weeks) of use. To the extent that there may be advantages in terms of preventing relapse to smoking, resulting from long term use, this is another potential smoking cessation advantage of smokeless tobacco products.

### **Evidence of Smokeless Tobacco Aiding Smoking Cessation**

At the time of writing there are no placebo-controlled randomized trials published that evaluate the safety and efficacy of smokeless tobacco for smoking cessation. One might question whether this is really the correct model for evaluating these products, given that clinicians will be very unlikely to ever prescribe a tobacco product when they could prescribe a safe and effective medication instead (even assuming similar efficacy).

It could be argued that there is already sufficient evidence for certain smokeless products aiding smoking cessation as to make the traditional randomized placebo-controlled trial unnecessary. This evidence can be summarized as follows:

1. Some smokeless tobacco products deliver blood nicotine levels equivalent to or greater than the blood nicotine levels provided by efficacious NRT products<sup>5,6</sup>.
2. Those smokeless tobacco products delivering high nicotine levels have been shown to relieve nicotine cravings and withdrawal symptoms at least as effectively as NRT products (and better than some lower-delivery smokeless tobacco products)<sup>6</sup>.
3. Population-based studies from Sweden have demonstrated that a large proportion of ex-smokers used snus to quit smoking, and that among those using an aid to try to quit, a higher proportion of snus-users than NRT-users succeeded in quitting<sup>7,8</sup>.
4. A few small clinical studies of smokers using smokeless products as an aid to cessation have reported good quit rates<sup>9,10</sup>.

Despite the strength and consistency of the evidence that some types of smokeless tobacco can aid smoking cessation, and the inappropriateness of health professionals prescribing such products, it appears that the only way to convince skeptics is to conduct a traditional clinical trial to demonstrate that smokeless tobacco aids smoking cessation. Providing such a trial is adequately powered and designed, there will

be no doubt about the result, just as there would be no doubt about the efficacy of any new NRT product that can deliver an adequate dose of nicotine.

1. McNeill A, Bedi R, Islam S, Alkhatib MN, West R. Levels of toxins in oral tobacco products in the UK. *Tob Control*. 2006 Feb;15(1):64-7.
2. Luo J, Ye W, Zendejdel K, Adami J, Adami HO, Boffetta P, Nyren O. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet*. 2007 Jun 16;369(9578):2015-20.
3. Levy DT, Mumford EA, Cummings KM, et al. The relative risks of a low-nitrosamine smokeless tobacco product compared with smoking cigarettes: estimates of a panel of experts. *Cancer Epidemiol Biomarkers Prev* 2004;13:2035-42.
4. Foulds J, Ramstrom L, Burke M, Fagerstrom K. The effect of smokeless tobacco (snus) on public health in Sweden. *Tobacco Control* 2003; 12:349-59.
5. Lunell E, Lunell M. Steady-state nicotine plasma levels following use of four different types of Swedish snus compared with 2-mg Nicorette chewing gum: a crossover study. *Nicotine Tob Res*. 2005 Jun;7(3):397-403.
6. Kotlyar M, Mendoza-Baumgart MI, Li ZZ, Pentel PR, Barnett BC, Feuer RM, Smith EA, Hatsukami DK. Nicotine pharmacokinetics and subjective effects of three potential reduced exposure products, moist snuff and nicotine lozenge. *Tob Control*. 2007 Apr;16(2):138-42.
7. Ramström LM, Foulds J. The role of snus (smokeless tobacco) in initiation and cessation of tobacco smoking in Sweden. *Tobacco Control* 2006 Jun;15(3):210-4.
8. Furberg Furberg H, Bulik C, Lerman C, et al. Is Swedish snus associated with smoking initiation or smoking cessation? *Tob Control*. 2005; 14:422-424.
9. Sharp L, et al. Smoking cessation among patients with head and neck cancer: cancer as a "teachable moment". *European Journal of Cancer care* 2007, (in press).
10. Tilashalski K, Rodu B, Cole P. Seven year follow-up of smoking cessation with smokeless tobacco. *J Psychoactive Drugs*. 2005 Mar;37(1):105-8.

#### **Acknowledgement of funding:**

Jonathan Foulds is primarily funded by New Jersey Department of Health and Senior Services. His other current research funding (also as P.I.) is from the Cancer Institute of New Jersey, and the Robert Wood Johnson Foundation. He is also a co-investigator on grants from the National Institutes of Health. He has worked as a consultant and received honoraria from pharmaceutical companies involved in production of tobacco dependence treatment medications, as well as a variety of agencies involved in promoting health (e.g. W.H.O., N.I.H., etc). A number of these agencies have provided sponsorship funds for educational events conducted by the program he directs. The program he directs (Tobacco Dependence Program at UMDNJ-School of Public Health) conducts trainings and charges health professionals and their organizations for providing these. He has also worked as an expert witness in litigation, including for plaintiffs in law suits against tobacco companies. He has not received any funding from the tobacco

industry other than deposition fees from defendants attorneys in litigation against the tobacco industry (i.e. while acting as a witness for the plaintiffs). He is paid for writing a regular column on a health website: [http://www.healthline.com/blogs/smoking\\_cessation/](http://www.healthline.com/blogs/smoking_cessation/).

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## **Smoking cessation in psychiatric patients**

### **Hubertus M. Friederich**

Smoking Cessation Center  
University Hospital, Dpt. of Psychiatry and Psychotherapy  
Osianderstraße 24, D-72076 Tübingen, Germany

Treating tobacco dependence alone is a challenge. Even if one follows the evidence based european recommendations on tobacco treatment the chances of being a nonsmoker after one year are (only) about 30%. And then it is clear that these prospects are a result of studies exclusively performed with smokers not reporting other psychiatric diseases or psychopharmacological treatment. But how does the usual smoker in the street looks like? Do smokers apart from their tobacco dependence have other psychiatric diseases, and if yes which diseases and with which prevalence? Within the psychiatric and psychotherapeutic clinic and practice the association between a higher smoking prevalence and certain psychiatric diseases is obvious. Smoking and other dependencies especially seem to be strongly linked together. While and since the psychiatric hospital in Tübingen became smokefree we gained own experiences about this linkage. The lecture will demonstrate the associations between smoking and psychiatric diseases, their biological and psycho-social causes as well as the ideas and treatment approaches with psychiatrically co-morbid smokers. Because there exists almost no scientific evidence for smoking cessation strategies in psychiatric patients all possible methods including harm reduction should be considered and discussed.

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## **Neuronal Nicotinic Acetylcholine Receptors as Molecular Targets for Drug Discovery**

### **Murali Gopalakrishnan**

Project Leader and Associate Volwiler Research Fellow  
Neuroscience Research  
Global Pharmaceutical Research & Development  
Abbott Laboratories, USA.

Neuronal nicotinic receptors are pentameric ligand-gated ion channels expressed in mammalian central nervous system including in regions associated with cognitive processing. Emerging physiological and pharmacological evidence have suggested nAChR subtypes such as  $\alpha 4\beta 2$  and  $\alpha 7$  as potential targets for the treatment of disorders involving cognitive and attention deficits associated with conditions such as Alzheimer's disease, schizophrenia and others. Accordingly, ligands selectively targeting both subtypes have emerged over

the years.  $\alpha 7$  b2 NNR selective ligands, previously shown to be efficacious in preclinical models of cognition, have begun to show signals of efficacy in initial proof-of-concept clinical studies (Wilens and Decker, 2007). With  $\alpha 7$  nAChRs, the property of relatively high  $\text{Ca}^{2+}$  permeation enables its participation in electrical signaling as well as  $\text{Ca}^{2+}$ -dependent processes that modulate intracellular events including second messenger cascades and neuroprotection. Structurally diverse  $\alpha 7$  nAChR agonists with improved subtype selectivity and superior CNS access have recently emerged. For example, agonists such as A-582941 that exhibit high affinity to rat and human  $\alpha 7$  nAChRs have been shown to enhance cognitive performance across behavioral assays including the delayed matching to sample, social recognition, inhibitory avoidance and sensory gating deficit - models that capture domains of working memory, short-term recognition memory, long-term memory consolidation and pre-attention respectively. At behaviorally efficacious plasma concentrations, agonists such as A-582941 can also increase the phosphorylation of ERK1/2 and CREB in brain regions associated with cognitive processing such as the cingulate cortex and hippocampus (Gopalakrishnan et al., 2006). More recently, positive allosteric modulators of  $\alpha 7$  nAChRs belonging to diverse chemotypes have also been described (Faghieh et al., 2007). Positive allosteric modulators that differentially affect ACh profiles have been characterized including those molecules that (i) predominantly affect peak current responses (Type I profile), and (ii) affect both peak current responses and time course of agonist-evoked response (Type II profile; Gronlien et al., 2007; Bertrand and Gopalakrishnan, 2007). Both types of compounds have been shown to exhibit *vivo* efficacy in animal models. This presentation will overview recent advances and challenges in the identification and characterization of subtype selective nAChR ligands with therapeutic potential in disease states, as for example, those associated with cognitive dysfunction.

#### References:

- Wilens, T.E. and Decker, M.W., Neuronal nicotinic receptor agonists for the Treatment of Attention-Deficit/Hyperactivity Disorder: Focus on cognition, *Biochemical Pharmacology*, in press.
- Faghieh R, et al., Advances in the discovery of novel positive allosteric modulators of the  $\alpha 7$  nicotinic acetylcholine receptor. *Recent Patents CNS Drug Discovery* 2007; 2:99-106.
- Gronlien JH et al., Distinct profiles of  $\alpha 7$  nAChR positive allosteric modulation revealed by structurally diverse chemotypes. *Mol Pharmacol*, in press. 2007.
- Gopalakrishnan, M et al., Broad-spectrum efficacy in cognition models revealed by  $\alpha 7$  neuronal nicotinic receptor agonism via activation of the MAP kinase pathway. *Soc. Neurosci. Abstr.* 2006, 32, # 325.8.
- Bertrand, D. and Gopalakrishnan, M. Allosteric Modulation of  $\alpha 7$  and  $\alpha 4_2$  nicotinic acetylcholine receptors. *Biochemical Pharmacology*, in press, 2007.
- Murali Gopalakrishnan, Ph.D., Project Leader & Associate Volwiler Research Fellow, Abbott Laboratories, Illinois-60064
- Dr. Gopalakrishnan received his undergraduate degree in pharmacy from Banaras Hindu University, India; his graduate training from SUNY at Buffalo (Ph.D.) where he studied regulation of calcium and potassium channels under the mentorship of David J. Triggle, Ph.D.; his post-doctoral training at the Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston with Arthur M.

Brown, M.D., Ph.D., where he investigated the structure-function of voltage-gated calcium channels. Dr. Gopalakrishnan joined Abbott Laboratories in 1993, and since then, has contributed to and/or led research programs on diverse receptor and ion channel targets in the areas of neuroscience, pain and urology. He is currently Project Leader of the neuronal nicotinic receptor program focusing on the discovery and development of subtype-selective neuronal nicotinic receptor ligands for CNS disorders. He is an author of over 100 peer-reviewed articles, 30 book chapters and reviews, as well as a co-inventor on various patents.

#### Angel Guirao García.

Coordinador General del Plan Regional de Prevención y Control del Tabaquismo.

Dirección General de Salud Pública y Alimentación  
Comunidad de Madrid.

Smoking is recognized as a chronic and recurrent addictive disease. It is the leading avoidable cause of death in the world. As a standard of appropriate healthcare delivery, all health care professionals should correctly diagnose and treat those who smoke in order to help them quit smoking.

Smoking cessation pharmacotherapy has been extensively developed in the last decade. New drugs have appeared to help the smoker to quit. Existing medications and their doses have been adjusted to improve efficacy. The availability of pharmacological treatments to alleviate nicotine withdrawal syndrome and promote cessation, has led to an important debate on the need for financing these agents by the public health care system. Different guidelines from various countries have stated that there are effective and safety pharmacological treatment for smoking cessation. Evidence A. Furthermore, they indicate that the cost/effectiveness ratio of this type of treatment is significantly greater than that of other treatments of other chronic diseases such as arterial hypertension or hypercholesterolemia. Evidence A. They not only refer to this but also refer to the fact that treatment to stop smoking is the "gold standard" intervention of all the preventive ones.

All of this data should make sanitary administrators think of financing pharmacological treatment for smoking cessation.

On the one hand, scientific evidence shows the result of private or public funding of smoking cessation drug treatments is that a larger number of smokers make a serious attempt to quit. This increases the number of ex-smokers and also mildly increases the prolonged abstinence rates without too great of an increase in costs.

On the other hand, it must also be considered that smoking is not only a chronic disease but also an addiction. Curing this disease requires the smoker to take responsibility for his/her state of health and to show a willingness to make a serious effort to stop smoking. The best drug treatment for smoking cessation will not be effective if the smoker has no motivation to quit. It could be thought that funding smoking cessation drug treatments would help an undetermined number of smokers

with scarce motivation to quit smoking to use the treatment, thus incurring in an unnecessary and useless expense . Even more, the financial coverage of the treatments to quit smoking could give rise to making prescriptions without sufficient consideration. That is, adequate motivation and commitment by the smokers would not be required and the indication of the different types of treatment might even not be the best. It is worth establishing prescription criteria .

Recently, the Madrid Community has created a functional network of smoking cessation consultations distributed throughout all their hospitals. The treatment carried out in this community is funded on the basis of the conditions established in a consensus document. According to this document, drug treatment would be funded under the following conditions:

- The treatment should only be prescribed when the smoker expresses his/her agreement to stop smoking and establishes a date to do so.

- In order to optimize the available resources, some priority groups could be identified among the smoking population. Standing out among these are:

- Patients with smoking induced disease, whose natural history can be reverted or stopped, such as COPD, cardiovascular disease with different types of manifestation or cancer with perspectives of remission.

- Patients with the disease that has not been induced by smoking but which is worsened by it, such as that which occurs with bronchial asthma, diabetes, bronchiectasis, chronic respiratory failure of any etiology, sleep apnea syndrome, etc.

- Smokers who, even though they have no disease, indicate serious desires to quit smoking, have made previous attempts and are not capable of controlling their consumption, whether due to intensity of dependence or because of having psychiatric comorbidity.

- Professionals considered as models due to the influence that their profession has on the behaviors of the population, such as health care or teaching professionals.

- Only the drug treatments that have been shown to be effective and safe and are recommended by the different national and international guidelines of smoking cessation treatment would be used. Prescription and form of use would be done in accordance with the indications of these guidelines.

- In order to optimize the use of drug treatment, this should be given to the smoker slowly according to his/her follow-up visits. All of the medication should never be given at the beginning of the treatment.

- If the attempt fails, free treatment should not be offered again until 6 months after the failure date.

- The following situations would be considered as failure and require treatment to be withdrawn:

- Daily smoker of 1 or more cigarettes in spite of having been in treatment for 4 weeks.

- Occasional smoker of 3 or more time a week in spite of having been in treatment for 4 weeks.

- According to the criterion of the responsible physician.

Taking into account these considerations, the Smokers Clinic of the Public Health Institute of Community of Madrid has had the following expenditure in financing pharmacological treatments for smoking cessation. A total of 760 smokers were seen in this Clinic during 2006. 68% of them received any form of nicotine replacement therapy and 27% received bupropion. At 6 month follow up, 395 (52%) smokers had ceased. The expenditure in pharmacological treatments all along that year was 95.425 Euros. That means 125 euros per attended smoker and 241 euros per attended ex-smoker. This expenditure can be assumed by public health systems and it seems to be competitive with expenditure due to other chronic disorders.

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## What else is on the smoking cessation horizon

**Peter Hajek.**

Queen Mary's School of Medicine and Dentistry, University of London

The presentation will look at some of the behavioural and pharmacological interventions which may hold a promise for the future. The UK National Institute for Health and Clinical Excellence has commissioned a review of some of the interventions which are not currently approved by the UK National Health Service but are either popular or hold a promise for future. The review was completed in 2006 and it covered, in alphabetical order, acupuncture, Allen Carr's Easyway, Cytisine, Glucose, Hypnosis, NicoBloc, Rapid smoking, and St. Johns Wort. We shall review the findings and recommendations of this analysis. The review pointed to gaps in evidence for some potentially promising approaches, which await further work. It also emphasized, together with a recent review of cytisine literature by JF Etter, the considerable promise of cytisine. Old studies suggest this is effective and if this is confirmed by trials using current stringent methodology, the cytisine could become by far the most economical pharmacotherapy for smoking cessation. The presentation will also look at some developments in nicotine replacement treatments, particularly the moves to a more liberal licensing, use on NRT prior to quitting, long-term use, and developments in alternative nicotine replacement products, both from pharmaceutical and from tobacco industries. We may also consider some new data on group treatments, and briefly review several compounds for which some encouraging data have been reported.

## Varenicline

**Carlos A. Jiménez-Ruiz**

Smokers' Clinic.

Public Health Institute. Comunidad de Madrid. Spain.

Varenicline has recently been approved as a treatment for smoking cessation in the USA and Europe. Varenicline acts as a selective partial agonist at nicotinic receptors in the neurons of the ventral tegmental area of the brain. As a partial agonist, it has characteristics common to agonists and antagonists. As an agonist, varenicline is capable of stimulating nicotinic receptors, thus controlling craving and withdrawal. However, as an antagonist, varenicline can block the effect of nicotine on the receptor. Another defining characteristic is that varenicline is almost completely excreted via the urine, without hepatic metabolism.

The most recent Cochrane meta-analysis indicated that varenicline increased the odds of successful long-term smoking cessation approximately threefold compared with pharmacologically unassisted quit attempts (odds ratio 3.22; 95% CI 2.43-4.27) Varenicline also helped more smokers to quit than bupropion (odds ratio 1.66; 95% CI 1.28-2.16). Nausea was the most common adverse effect, although this was usually mild and with a self-limiting tendency over time.

To date, two studies have investigated long-term treatment with varenicline. One showed that prolonging the use of varenicline to 24 weeks of treatment could significantly increase continuous abstinence rates, in comparison to placebo, at both 6- 12-month follow-up: the results were 70.6% versus 49.6% (odds ratio 2.48; 95% CI 1.95-3.16.) at six months, and 43.6% versus 36.9% (odds ratio 1.34; 95% CI 1.06-1.69) at 12 months. Importantly, the increased duration of treatment does not increase adverse effects. These preliminary results support prolonging treatment with varenicline for 24 weeks in smokers who are abstinent at the end of the first 12 weeks of treatment, but more studies are needed to confirm this.

Another study analyzed the efficacy of varenicline at the usual doses versus placebo, but using the drug continuously for 12 months. The study enrolled 251 smokers in the active group versus 126 in the placebo group, and the results were striking. The point prevalence abstinence rate was never less than 35.1%, and reached 49% after 8 weeks of treatment. The differences between varenicline and placebo were significant at all times. At one-year follow up 7-day point prevalence abstinence rates were 36.7% in the active group and 7.9% in the placebo group. The incidence of adverse effects with varenicline was no greater during use for one year, and no new events were detected.

Fundings: None.

## Community-based smoking cessation programmes.

### The experience of the spanish respiratory society. Separ

**Carlos A. Jiménez-Ruiz**

Smoking Prevention Section. SEPAR.

Spanish Respiratory Society, SEPAR is a national based Scientific Society that meets together all the Spanish Pulmonologists and Lung Surgeons. One of its main objectives is to prevent Spanish General Population from the different risk factors of pulmonary disorders.

Smoking is a chronic relapsing disorder that causes 56.000 annual deaths in Spain. Lung cancer, COPD and the worsening of many other pulmonary disorders are directly related with the use of tobacco. For many years SEPAR has contributed to the development of campaigns against smoking in the Spanish General Population. Recently, the board of directors of SEPAR decided to organise a Smoking Control Campaign targeted to Spanish General Population to be developed during year 2007.

#### The main objectives of this campaign have been as follows:

- a) To increase the sensibilization of the Spanish General Population on Smoking Prevention.
- b) To increase the sensibilization of Spanish General Population on treatment for smoking cessation.
- c) To spread out the important role of Spanish Pulmonologist on Smoking Control.

The Princess of Spain has accepted to be the Honour President of the Campaign. This campaign has had the support of the Spanish Health Ministry and the Councillors of Health from the different Spanish Communities.

#### The main activities of this campaign have been as follows:

a) Edition of a Calendar. At the beginig of the Year 2007 a Special Calendar was edited. Each month of the year was associated with the image of a wellknown Spanish artist or journalist or singer. These people inveted a phrase for each month of the calendar. The phrase sent a message in favor of smoking control. The calendar was spread out among Spanisg population using the main Spanish Radio and TV programmes.

b) Collaboration with Patients Associations. A booklet has been edited. This booklet contains information about different aspects of smoking: smoking related disorders, mortality and morbidity causes by smoking, factors related with initiation on smoking, nicotine addiction, second hand smoke, and smoking cessation treatments. The booklet is written

in an informal style and its easy reading and understanding. 10,000 booklets were edited and distributed among the members of these patients associations. The booklet was presented to the media and had a strong impact in press, radio and TV.

c) Guidelines on Smoking Cessation. The Smoking Section of the SEPAR produced guidelines for smoking cessation. These guidelines not only included some recommendations for using pharmacological treatment for smoking cessation, but also, it included a proposal for public financing of smoking cessation treatments. These guidelines was revised and authored by international experts on smoking cessation.

d) Travelling Campaign. A big trailer was prepared. The trailer carried a big lounge with 25 people capacity for showing a 3D film with information about prevention and treatment for smokers. The trailer carried digipanel with information on benefits to quit and counselling for quitting. The trailer was attended by 2 nurses. These nurses gave anti-smoking advice and measured CO in expired air and performed spirometries to people who went to the trailer. The trailer crossed the entire country. It visited 36 cities and more than 12.000 smokers received direct information about how to quit. The indirect messages reached more than 10 million people.

Spanish Respiratory Society has complied with the objective to spread out information on smoking cessation and prevention among Spanish General Population,

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## **Alterations in reward processing during nicotine abstinence: Mechanisms and motivational significance**

**Paul J. Kenny**

Assistant Professor  
Department of Molecular Therapeutics  
The Scripps Research Institute – Florida, USA

Addiction to tobacco smoking may depend not only on the positive reinforcing and hedonic actions of nicotine, but also on escape from the aversive consequences of nicotine withdrawal. Indeed, the duration and severity of nicotine withdrawal may predict relapse in abstinent human smokers. Further, the efficacy of nicotine replacement therapy, at least in certain individuals, is related to its ability to prevent the onset and reduce the duration of nicotine withdrawal.

Accumulating evidence suggests that affective components of withdrawal may play a more important role than somatic aspects in the maintenance of dependence to drugs of abuse, including nicotine. Importantly, withdrawal from nicotine and other major drugs of abuse can decrease brain reward function, reflected in elevated intracranial self-stimulation (ICSS) thresholds in rats. Avoidance and alleviation of such withdrawal-induced reward deficits are hypothesized to play an important role in maintaining drug-taking behavior. Thus,

an understanding of the mechanisms of nicotine withdrawal-associated reward deficits, as measured by elevated ICSS thresholds, may provide important insights into the persistence of the tobacco habit in human smokers.

Considerable evidence suggests that glutamate-mediated transmission in the ventral tegmental area (VTA) regulates aspects of nicotine's rewarding effects. It has been suggested that neuroadaptations that occur during prolonged nicotine exposure, which give rise to altered reward processing during withdrawal, may reside in the same neural elements that mediate the acute rewarding actions of these drugs. Hence, we hypothesized that adaptations in glutamate-mediated transmission in the VTA may contribute to the reward deficits associated with nicotine withdrawal. Consistent with this hypothesis, we found that the group II metabotropic glutamate (mGluII) receptor agonist LY314582 precipitated withdrawal-like elevations of ICSS thresholds in rats rendered nicotine dependent through nicotine infused chronically via osmotic minipumps, but not in nicotine-naïve control rats. At higher doses, LY314582 also elevated reward thresholds in non-dependent control rats. Microinfusion of LY314582 into the VTA likewise precipitated ICSS threshold elevations in nicotine-dependent rats at doses that did not alter reward thresholds in control rats. Conversely, a single injection of the mGluII receptor antagonist LY341495 attenuated the elevated ICSS thresholds usually observed in rats undergoing spontaneous nicotine withdrawal. Taken together, these observations suggest that mGluII receptors, which act as presynaptic autoreceptors that decrease glutamate-mediated transmission upon activation, negatively regulate the basal activity of brain reward circuitries. Further, the development of nicotine dependence is associated with increased activity of mGluII autoreceptors in the VTA, perhaps to counter prolonged activation of excitatory glutamate transmission in this reward-related brain region during chronic nicotine exposure. Most importantly, the increased activity of inhibitory mGluII receptors in nicotine-dependent rats contributes to the decreased function of brain reward systems associated with nicotine withdrawal.

The ability to assess components of the nicotine withdrawal syndrome in genetically modified mice with altered expression of targeted genes offers a promising approach to identify and understand neurobiological substrates contributing to the persistence of the tobacco habit in smokers. Hence, our recent work has focused on adapting the ICSS procedure for use in mice. Using this procedure, we are characterizing the effects of nicotine abstinence on brain reward function in mice. We have demonstrated that spontaneous withdrawal or withdrawal precipitated with the nicotinic acetylcholine receptor (nAChR) antagonist mecamylamine elevated ICSS thresholds in C57BL/6 mice rendered nicotine dependent via osmotic minipump, similar to previous observations in rats. These data demonstrate that the reward deficits associated with nicotine withdrawal can be assessed in mice using the ICSS procedure, and highlight the potential utility of this approach for the testing of genetically modified mice to identify novel substrates of nicotine dependence and withdrawal processes.

The studies outlined above assessed the effects of withdrawal from non-volitional nicotine exposure delivered via osmotic minipumps on the activity of brain reward systems in rats and mice. In recent studies we have assessed the effects of cessation of volitional nicotine intake in rats that had daily access to intravenously (IV) self-administered nicotine infusions. Specifically, we assessed reward thresholds immediately before and after rats were permitted to self-administer IV nicotine infusions during 1 or 12 h daily sessions. We found that nicotine self-administration transiently increased the sensitivity of brain reward systems, detected by post-nicotine lowering of reward thresholds in 1 and 12 h rats. This observation is consistent with the well-established stimulatory effects of acutely administered nicotine on brain reward systems. This nicotine-enhanced reward sensitivity was reversed by the high-affinity nAChR antagonist dihydro- $\beta$ -erythroidine (DH $\beta$ E). Surprisingly, in contrast to the elevated reward thresholds observed in rats during withdrawal from nicotine delivered via osmotic minipump, cessation of self-administered nicotine infusions resulted in a gradual lowering of reward thresholds in 1-h and 12-h rats, an effect that persisted for at least 36 days after nicotine intake had ceased. Hence, a history of nicotine self-administration was associated with hypersensitivity in brain reward systems during nicotine abstinence. These data demonstrate that rats can voluntarily consume quantities of nicotine sufficient to increase the sensitivity of brain reward systems, an action likely crucial in establishing and maintaining the nicotine habit. Moreover, self-administered nicotine may reset the sensitivity of reward systems to a new increased level. This action so far appears unique to nicotine amongst drugs of abuse, and may serve as a novel source of motivation that contributes to the persistence of the tobacco habit in human smokers.

This work was supported by the National Institute on Drug Abuse (DA020686 to P.J.K.), and the James and Esther King Biomedical Research Program from the Florida Department of Health (P.J.K.).

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## Neuroimaging in Tobacco and Nicotine Dependence

### Current Status and Future Developments

#### Edythe D. London

Professor of Psychiatry and Biobehavioral Sciences  
 Professor of Molecular and Medical Pharmacology  
 David Geffen School of Medicine, University of California Los Angeles, USA

The worldwide prevalence of nicotine dependence and the health problems caused by cigarette smoking render the prevention of cigarette smoking and the development of new treatments to facilitate smoking cessation as goals whose attainment could have worldwide impact. Many who experiment with smoking progress to dependence and others who would like to quit continue to smoke despite well-publicized information of the risks of smoking. Both the progress to dependence and the difficulty of smoking cessation must, to some extent, reflect interactions

of nicotine and perhaps other components of cigarette smoke with brain function. For this reason, an understanding of how tobacco smoking and nicotine per se affect brain function can be fundamental to the development of new, more effective therapies and prevention strategies based on knowledge of the neurobiological vulnerability factors for nicotine dependence. In this regard, the development of tools and technology for noninvasive imaging has paralleled and accelerated our understanding of the biology of nicotine dependence over the past several decades.

In the mid-1980's, *in vivo* and *ex vivo* receptor imaging of nicotinic acetylcholine receptors (nAChRs) in rodent models demonstrated the distributions of high affinity binding sites for nicotine. Shortly thereafter, metabolic mapping revealed a close association between nAChR localization and response to nicotine, demonstrating the functional importance of the sites that had been characterized *in vitro*. Imaging of the cerebral response to nicotine has been extended in human studies using positron emission tomography (PET), demonstrating global reductions in glucose metabolism. Studies of regional cerebral blood flow, performed using various nuclear medicine methods (single photon emission computed tomography, X3-133 inhalation) supported this finding. However, regional assessments demonstrated relative activation of the prefrontal cortex, thalamus and visual system in response to nicotine administration or cigarette smoking (in general agreement with rodent studies).

In addition to these studies of regional brain function, substantial progress in the areas of medicinal chemistry and radiotracer development has facilitated the study of the acute and chronic effects of nicotine on specific neurochemical systems. Such developments have, for example, allowed the noninvasive assay of nAChRs with radiolabeled analogues of A-853808, selective for  $\alpha$ 2-containing nAChRs, demonstrating surprisingly high levels of saturation of these receptors with acute smoking in human subjects and upregulation of these sites following chronic nicotine administration in nonhuman primates. Other findings have shown a reduction in binding potential for a D2/D3 dopamine receptor radioligand ([C-11]raclopride) due to acute smoking (consistent with an effect of smoking to increase intrasynaptic dopamine), and a dependence of this effect on genotype. Furthermore, a reduction in the activities of both monoamine oxidase A and B in human smokers compared with nonsmokers, assayed using radiolabeled substrates for the enzymes, suggested a reduction in the enzymatic degradation of dopamine.

The aforementioned findings, obtained with nuclear medicine procedures paralleled advances that utilized magnetic resonance imaging to probe alterations in brain structure and function, as related to cigarette smoking. Among the evidence for smoking-related brain changes are structural differences consistent either with agenesis of gray matter of the prefrontal lobe or with detrimental effects of smoking. Functional MRI (fMRI) has been used to show the effects of acute nicotine administration and to delineate functional differences in relation to cognitive deficits (primarily in working memory and attention).

This presentation will cover a historic development of our current view of nicotine action, as determined by brain imaging, and it will address the potential of future developments that will derive from the combination of brain imaging with other assessments. The field is ripe for advances with the availability of improved radiotracers and equipment, such as high-resolution and high-field animal scanners, and the accessibility of genetic assessments.

#### Partial Reference List:

PB Clarke, RD Schwartz, SM Paul, CB Pert, A Pert (1985): Nicotinic binding in rat brain: autoradiographic comparison of [3H]acetylcholine, [3H]nicotine, and [125I]-alpha-bungarotoxin. *J Neurosci.* 5:1307-1315.

ED London, SB Waller, JK Wamsley (1985): Autoradiographic localization of [3H]-nicotine binding sites in the rat brain. *Neurosci. Lett.* 53:179-184.

ED London, RJ Connolly, M Szikszay, JK Wamsley, M Dam (1988): Effects of nicotine on local cerebral glucose utilization in the rat. *J. Neurosci.* 8:3920-3928.

EP Broussolle, DF Wong, RJ Fanelli, ED London (1989): In vivo specific binding of [3H]-nicotine in the mouse brain. *Life Sci.* 44:1123-1132.

ED London, RJ Fanelli, AS Kimes, RL Moses (1990): Effects of chronic nicotine on cerebral glucose utilization in the rat. *Brain Res.* 520:208-214.

JE Flesher, U Scheffel, ED London, JJ Frost (1994): In vivo labeling of nicotinic cholinergic receptors in brain with [3H]cytisine. *Life Sci.* 54:1883-1890.

ED London, U Scheffel, AS Kimes, KJ Kellar (1995): In vivo labeling of nicotinic acetylcholine receptors in brain with [3H]epibatidine. *Eur. J. Pharmacol.* 278:R1-R2.

JS Fowler, J Logan, GJ Wang, ND Volkow, F Telang, W Zhu, D Franceschi, N Pappas, R Ferrieri, C Shea, V Garza, Y Xu, D Schlyer, SJ Gatley, YS Ding, D Alexoff, D Warner, N Netusil, P Carter, M Jayne, P King, P Vaska (1996): Brain monoamine oxidase A inhibition in cigarette smokers. *Proc Natl Acad Sci USA* 93:14065-14069.

JS Fowler, ND Volkow, GJ Wang, N Pappas, J Logan, R MacGregor, D Alexoff, C Shea, D Schlyer, AP Wolf, D Warner, I Zezulkova, R Cilento (1996): Inhibition of monoamine oxidase B in the brains of smokers. *Nature* 379:733-736.

AG Horti, AO Koren, HT Ravert, JL Musachio, WB Mathews, ED London, RF Dannals (1998): Synthesis of a radiotracer for studying nicotinic acetylcholine receptors: 2-[18F]fluoro-3-(2(S)-azetidylmethoxy)pyridine (2-[18F]A-85380). *J. Labelled Compd. Radiopharm.* XLI: 309-318.

M Ernst, JA Matochik, SJ Heishman, JD Van Horn, PH Jons, JE Henningfield, ED London (2001): Effect of nicotine on brain activation during performance of a working memory task. *Proc. Nat. Acad. Sci. USA.* 98:4728-4733.

M Fujita, JP Seibyl, DB Vaupel, G Tamagnan, M Early, SS Zoghbi, RM Baldwin, AG Horti, AO Koren, AG Mukhin, S Khan, A Bozkurt, AS Kimes, ED London, RB Innis (2002): Whole-body biodistribution, radiation absorbed dose, and brain SPET imaging with [123I]5-A-85380 in healthy human subjects. *Eur. J. Nucl. Med.* 29:183-190.

JE Rose, FM Behm, EC Westman, RJ Mathew, ED London, TC Hawk, TG Turkington, RE Coleman (2003): PET studies of the influences of nicotine on neural systems in cigarette smokers. *Am. J. Psychiatry* 160:323-33

JM Stapleton, SF Gilson, DF Wong, VL Villemagne, RF Dannals, RF Grayson, JE Henningfield, ED London (2003): Intravenous nicotine reduces cerebral glucose metabolism: a preliminary study. *Neuropsychopharmacology* 28:765-772.

AS Kimes, AG Horti, ED London, SI Chefer, C Contoreggi, M Ernst, P Friello, AO Koren, V Kurian, J Matochik, O Pavlova, D Vaupel, AG Mukhin (2003): 2-[18F]F-A85380: PET imaging brain nicotinic acetylcholine receptors and whole body distribution in humans.

*FASEB J* 10:1331-1333.

M Fujita, M Ichise, CH van Dyck, SS Zoghbi, G Tamagnan, AG Mukhin, A Bozkurt, N Seneca, D Tipre, CC DeNucci, H Iida, DB Vaupel, AG Horti, AO Koren, AS Kimes, ED London, JP Seibyl, RM Baldwin, RB Innis (2003): Quantification of nicotinic acetylcholine receptors in human brain using [123I]5-A-85380 SPET. *Eur. J. Nucl. Med. Mol. Imaging* 30:1620-1629.

AL Brody, RE Olmstead, ED London, J Farahi, JH Meyer, P Grossman, GS Lee, J Huang, E Hahn, MA Mandelkern (2004): Smoking-induced ventral striatal dopamine release. *Am. J. Psychiatry* 161:1211-1218.

AL Brody, MA Mandelkern, ME Jarvik, GS Lee, EC Smith, JC Huang, RG Bota, G Bartzokis, ED London (2004): Differences between smokers and non-smokers in regional gray matter volumes and densities. *Biol. Psychiatry* 55:77-84.

J Xu, A Mendrek, MS Cohen, J Monterosso, P Rodriguez, SL Simon, A Brody, M Jarvik, CP Domier, R Olmstead, M Ernst, ED London (2005): Brain activity in cigarette smokers performing a working memory task: Effects of smoking. *Biol. Psychiatry* 58:143-150.

AL Brody, MA Mandelkern, ED London, RE Olmstead, J Farahi, D Scheibal, J Jou, V Allen, E Tiongson, SI Chefer, AO Koren, AG Mukhin (2006): Cigarette smoking saturates brain 4\_2 nicotinic acetylcholine receptors. *Arch. Gen. Psychiatry* 63: 907-915.

AL Brody, MA Mandelkern, RE Olmstead, D Scheibal, E Hahn, S Shiraga, E Zamora-Paja, J Farahi, S Saxena, ED London, JT McCracken (2006): Gene variants of the brain dopamine reward pathway determine smoking-induced dopamine release in the ventral caudate/nucleus accumbens. *Arch. Gen. Psychiatry* 63: 808-816.

JK Staley, S Krishnan-Sarin, KP Cosgrove, E Krantzler, E Frohlich, E Perry, J Dubin, E Brenner, RM Baldwin, GD Tamagnan, JP Seibyl, ED London, S O'Malley and CH van Dyck (2006): Human tobacco smokers have higher 2\* nicotinic acetylcholine receptors during early abstinence. *J. Neurosci.* 26: 8707-8714.

J Xu, A Mendrek, MS Cohen, J Monterosso, S Simon, A Brody, M Jarvik, P Rodriguez, M Ernst, and ED London (2006): Effects of acute smoking on brain activity vary with abstinence in smokers performing the n-back task: a preliminary study. *Psychiatry Res. Neuroimaging* 148: 103-109.

J Xu, A Mendrek, MS Cohen, J Monterosso, S Simon, M Jarvik, R Olmstead, AL Brody, M Ernst, ED London (2007): Effect of cigarette smoking on prefrontal cortical function on nondeprived smokers performing the Stroop task. *Neuropsychopharmacology* 32:1421-1428. Epub 2006 Dec 13.

AL Brody, MA Mandelkern, RE Olmstead, J Jou, E Tiongson, V Allen, D Scheibal, ED London, JR Monterosso, ST Tiffany, A Korb, JJ Gan, MS Cohen (2007): Neural substrates of resisting craving during cigarette cue exposure. *Biol. Psychiatry.* E-published ahead of print, Jan. 8.

Supported by NIH grants P20DA022539 and Philip Morris USA.

## Cell lines as in vitro factories for nicotinic receptor characterization

**Ronald J. Lukas**

Division of Neurobiology, Barrow Neurological Institute,  
Phoenix, AZ, USA.

Basic studies of nicotinic acetylcholine receptors (nAChR) rely on use of a variety of experimental approaches and model systems, all with weaknesses and strengths, but often complementing each other. Translational or clinical studies of nAChR and nicotinic ligand effects on the human brain and body are often founded on basic work, and the development of novel nicotinic drugs for treatment of neurological or psychiatric conditions or as aids to smoking cessation is facilitated by studies using in vitro systems and animal work. In particular, it is important to understand mechanisms involved in effects of nicotinic ligands on nAChR and the cells that express them, mechanisms involved in nicotine dependence, and nAChR subtype interaction profiles of nicotinic drugs considered for use clinically. On all these counts, cell lines stably and naturally or heterologously expressing specific nAChR subtypes have value.

The most fundamental studies have involved heterologous expression work to define which nAChR subunits can combine to form functional nAChR subtypes. Human cell lines can be used as models as are *Xenopus* oocytes for this work as well as for studies of chimeric or mutant subunits. We have succeeded in stably expressing human  $\alpha 4b2$ -,  $\alpha 4b4$ -,  $\alpha 4b2a5$ - and  $\alpha 7$ -nAChR in SHEP1 epithelial cell hosts to complement our studies of naturally expressed  $\alpha 3b4$ \*- ganglionic nAChR (SH-SY5Y cells) and muscle-type nAChR ( $\alpha 1b1gd$ -nAChR; TE671/RD cells). Progress also is being made in expressing  $\alpha 6$ \*-nAChR. Studies encompass work with fluorescent reporters fused to nAChR subunits, other investigations show neuronal cytotoxicity of  $\alpha 7$ -nAChR gain-of-function mutants, and surprising results indicate unexpected functional roles of subunit cytoplasmic domains thought to be quite far from ligand binding sites and the receptor pore.

Expression of nAChR subtypes allows us to screen for and describe actions of known and new nicotinic ligands. For example, we are able to screen against new drugs that might act at muscle-type or ganglionic nAChR subtypes, thereby selecting against drugs that might have adverse, autonomic or muscular side effects. These studies also allow us to provide in vitro pharmacological fingerprints of drug action that can be used to identify attributes of drugs that have specific and desired effects in vivo. This knowledge then can be used to inform drug discovery as well as indicate which nAChR subtypes are involved in specific behaviors.

Perhaps more of interest to attendees of this conference, human cell lines are useful in deciphering mechanisms involved and targets engaged upon interaction with drugs that are known or potential aids to smoking cessation. For example, cell line work has allowed us to suggest that chronic exposure to nicotine as would occur in nicotine-dependent tobacco product users leads to long-lasting, functional inactivation of every nAChR subtype tested to date. However, at concentrations

of nicotine achieved in plasma of human smokers, only  $\alpha 4$ \*-nAChR undergo persistent functional loss, and the decrement in function is about 50%. Thus, we suggested that nicotine dependence involves self-medication with nicotine to achieve a neurochemical endpoint of diminished  $\alpha 4$ \*-nAChR function. Selective inhibition of  $\alpha 4b2$ -nAChR function also occurs with mecamylamine, another aid to smoking cessation. We have found that an active, human metabolite of bupropion also selectively induces inhibition of human  $\alpha 4b2$ -nAChR function. Moreover, we have found that cytosine (Tabex) and varenicline (Chantix) are indeed partial agonists at  $\alpha 4b2$ -nAChR. However, at concentrations lower than those required to produce partial agonism, both of these agents act as antagonists of human  $\alpha 4b2$ -nAChR function. These latter data stimulate ideas about mechanisms involved in partial agonism and suggest the existence of microheterogeneity in ligand binding sites on nAChR. For example, low concentration antagonism by cytosine or varenicline of responses to carbamylcholine or epibatidine is surmountable by increasing full agonist concentrations, suggesting a competitive mechanism of cytosine or varenicline action. However, once cytosine or varenicline exert their partial agonist effects at higher concentrations, nAChR function is limited to levels achieved in the presence of cytosine or varenicline whether or not a full agonist is present. This suggests a non-competitive mechanism in which cytosine or varenicline bind to a site different from that occupied by full agonists. Of clinical and smoking cessation relevance, our studies with mecamylamine, chronic nicotine, varenicline and cytosine, and bupropion metabolites all suggest that inhibition of  $\alpha 4b2$ -nAChR function is a common neurochemical endpoint for all current smoking cessation aids. More work is needed to determine whether these effects revealed when using cell lines that serve as factories for nAChR studies accurately predict effects of aids to smoking cessation on nAChR subtypes expressed by real neurons.

Supported by US National Institutes of Health (NIH) U19-DA019377, NIH R01-DA015389, the Barrow Neurological Foundation, and Targacept, Inc.

## Prevention of smoking uptake among adolescents

**Laurence Moore**

Cardiff Institute of Society, Health and Ethics, Cardiff  
University, United Kingdom

Tobacco use by adolescents is a worldwide public health problem. The Global Youth Tobacco Survey found that 17.3% of 13 to 15-year olds reported using tobacco products and 8.9% were current smokers, with highest rates of current smoking in the Americas (17.5%) and the European region (17.9%). While tobacco use in adolescence takes time to translate into tobacco-related morbidity and mortality in middle-to old age, evidence shows that 82% of adult smokers took up the habit in adolescence, with addiction to nicotine usually starting early. Additionally, early smoking uptake is related to the daily number of cigarettes smoked in adulthood and may also be

associated with lower quit rates in later life. Tackling smoking uptake is of relevance for developed and developing countries, and the need to develop comprehensive and effective tobacco prevention and control programmes is well established.

Schools are potentially valuable settings for smoking prevention because of the consistent access to students over a number of years. Systematic reviews have, however, found mixed evidence of effectiveness of school-based smoking prevention programmes. One concluded that there was 'little to no evidence of long-term effectiveness' because only one of the eight RCTs included showed significantly decreased smoking prevalence in the intervention group five years post-intervention. As considerable time and resources continue to be invested in ineffective school-based interventions, more innovative and rigorously evaluated smoking prevention programmes are required.

This presentation will focus on two complementary approaches to schools-based smoking prevention. The first approach is a development of peer-led education, in which influential students were identified and given training to disseminate anti-smoking messages and norms amongst their peer group. The intervention was based on diffusion of innovation theory and adapted from approaches found to have been successful in interventions to improve sexual health behaviour. The intervention was carefully developed, piloted and tested for feasibility, and then tested for effectiveness in a large scale Medical Research Council cluster randomised trial conducted among 10,000 students in 59 senior schools in the United Kingdom. Overall smoking prevalence amongst the whole year group increased from 5.7% at baseline when the students were aged 11 or 12 to 13.8% at one-year follow-up and 20.3% at two-year follow-up when the students were aged 14 or 15. Adjusting for the baseline differences, smoking prevalence (both self-report and cotinine validated) was lower in intervention than in control schools at all three follow-up time points. At one-year follow-up, the odds ratio of being a smoker in intervention compared with control group was 0.77 (95% CI 0.59, 0.99). Over the two-year follow-up period there was a significant reduction in the odds of being a regular smoker in an intervention compared with a control school with the 95% confidence intervals not including a null effect.

The second approach is the implementation and enforcement of school policies to ban smoking among students, staff and school visitors. Previous research by the author has identified a significant association between the presence and strength of school smoking policies and student smoking prevalence. However, there is variation across schools in policy content, enforcement and student awareness. This presentation will discuss recent findings from further research on school smoking policies, which highlights the need for careful design, implementation and enforcement of school smoking policies, and in particular the need to integrate such policies into the ethos of the school. These findings will be discussed in the context of evidence from systematic reviews of the potential effectiveness of multi-component smoking prevention programmes in schools, consistent with the principles of the settings approach adopted by the health promoting schools movement.

The presentation will discuss the implications of these two strands of research for future schools based smoking prevention programmes, for future research, and for the integration of adolescent smoking prevention and smoking cessation interventions.

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## Smoking Cessation in Pregnant Women

**Cheryl Oncken**

University of Connecticut Health Center. University of Connecticut School of Medicine.  
USA.

Maternal smoking during pregnancy one of the leading causes of adverse fetal and infant outcomes in many countries. Consequently, maternal smoking is a significant public health concern. Smoking by pregnant mothers increases the risk of spontaneous abortion, low birth weight (<2500 grams), premature delivery, sudden infant death syndrome, and learning and behavioral problems in the offspring (i.e., attention deficit disorder). Prenatal tobacco exposure may also increase the risk of smoking in the offspring. Because of the serious health risks to the mother, infant, and child, effective interventions are needed to help pregnant women quit smoking.

Although the prevalence of smoking during pregnancy appears to be declining, the majority of women who smoke prior to pregnancy do not quit smoking during pregnancy. Younger women, and women who are of a lower socioeconomic status, have particularly high rates of smoking during pregnancy. Recent U.S. data suggest that pregnant smokers have a higher incidence of mental disorders (major depression as well as other mood disorders) compared to nonsmokers. Moreover, among women who are able to quit smoking during pregnancy, the majority (>70%) relapse postpartum.

Patient education studies aimed primarily at low-income pregnant smokers have shown that augmented behavioral interventions have a consistent impact on increasing smoking cessation rates. A meta-analysis including eight studies that utilized A Pregnant Women's Guide to Quit Smoking adapted to their language, patient population and maternity setting showed that the combined cessation rates for the experimental groups were approximately 17.5 % versus 4.8 % for usual care. This same report estimates that women who smoke less than 10 cigarettes per day have a 20% success rate with an augmented behavioral counseling intervention; women who smoke 10-19 cigarettes per day have a 15% rate of cessation; women who smoke more than 20 cigarettes per day have a 5% chance of cessation. Thus, the chances of quitting smoking during pregnancy are less for heavier versus lighter smokers. Even among light smokers, many do not quit smoking during pregnancy, even with augmented behavioral interventions.

Similarly, another meta-analysis (consisting of seven studies) compared various augmented behavioral interventions to usual

care. Studies in the analysis had a diverse representation of pregnant smokers (including studies with participants with private health plans as well as those from public clinics). Examples of augmented interventions included counseling with a health educator plus pregnancy-specific materials and follow-up letters, or health education discussions combined with pregnancy-specific materials followed by mailings for 7 weeks, or social support with buddy letters. Studies with minimal interventions (< 3 minutes) or interventions labeled as "usual care" were used for comparison. Augmented interventions yielded quit rates of 16.8% versus 6.6% in the control groups. In addition, the Cochrane Database of Systemic Reviews of interventions for promoting smoking cessation during pregnancy (48 trials) showed that there was a significant reduction in smoking in the intervention groups (interventions varied by intensity) versus the control groups (relative risk 0.94, 95% CI .93 to .95) or approximately a 6% difference in quit rates. Together, these reports indicate there is a consistent, but limited, benefit of augmented behavioral interventions on quit rates during pregnancy. Moreover, there is considerable room to enhance quit rates. Although not included in the above meta-analyses, it is noteworthy that a few recent behavioral studies using vouchers or contingency management have shown promising results to increase abstinence rates in pregnancy. However, more studies are needed in this area.

Pharmacotherapy may improve smoking cessation rates in pregnancy; however, very few studies have examined the safety and efficacy of medications to treat pregnant smokers. Short-term studies suggest that nicotine gum produces lower overall nicotine and exposure compared to usual smoking in subjects who smoke at least 10 cigarettes per day, and may have lesser effects on maternal and fetal hemodynamic parameters. The overall nicotine exposure with transdermal nicotine (as measured by maternal cotinine levels) more closely approximates cotinine levels of smoking in women who smoke at least 10 cigarettes per day. One study of transdermal nicotine for smoking cessation in pregnancy found no statistical difference in quit rates in the nicotine versus the placebo groups, however the birth weight was higher in offspring born to mothers assigned to the transdermal nicotine group. One pilot study of bupropion SR in 44 pregnant smokers showed that bupropion SR may be effective for smoking cessation (45% vs 14%  $p=.047$ ). However, this study is small and the results need to be replicated. More research regarding the safety and efficacy of pharmacotherapies is needed to better define the risk/benefit profile of each medication for use in pregnant smokers.

In summary, behavioral interventions have a consistent impact on quit rates, although the effect is modest and the majority of pregnant smokers do not quit. Moreover, the effectiveness of behavioral interventions appears to be greatest in lighter smokers. Pharmacotherapy has the potential to increase smoking cessation rates in pregnancy. However, more studies are needed to better determine the risk/benefit ratio in pregnant smokers. Treatment-matching may be useful in future studies to better determine which interventions work best for various subgroups of pregnant smokers.

This work is supported by NIDA DA15167, and the Patrick and Catherine Weldon Donaghue Research Foundation

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## Educating advocates: health professionals training

**Patrick Sandström**

National Public Health Institute, Finland

The majority of smokers would like to quit but stopping smoking is not easy because of considerable physical, psychological and social addiction. Seventy-six percent of Finnish smokers stated that they are worried about the health risks of tobacco and 61% that they would like to stop smoking in the 2006 nationwide health behaviour survey. According to the same study about 40% of the smokers try to quite smoking every year but as we know, only 3-5% succeeds in their quitting attempt.

Health professionals, especially medical doctors, have a unique opportunity in tobacco control and cessation. Even brief simple advice about quitting smoking increases the likelihood that a smoker will successfully quit.

As the main obstacles preventing them from taking up a patients smoking physicians report lack of time and regarding smoking as a private matter of the patient, as well as the fact that many physicians and nurses do not believe that smokers want to quit.

There is need to develop easy to use tools for health professionals to gain information about health effects of tobacco and the addiction process in order to provide the best possible cessation advice for patients trying to quit smoking. This educational tool has to be readily available for all groups of health professionals and students of these professions. Furthermore, the approach has to be multidisciplinary, including a clear division of tasks and a functional referral system between physicians, nurses, dentists and pharmacists.

The Finnish Current Care guideline on 'Smoking, nicotine addiction and interventions for cessation' was published in 2002 (updated 2006). As one tool in the implementation of this guideline the internet based interactive 'Tobacco Dependence and Cessation Treatment Training in Health Care' project was started at the National Public Health Institute, KTL, Finland.

A database on health effects of tobacco by medical specialty was created at the National Public health Institute, KTL, Finland in 2005. The database also includes facts on addiction and the smoking cessation process and has been built as part of the Finnish smoking cessation internet site [www.stumppi.fi](http://www.stumppi.fi).

A model for tobacco and health, tobacco addiction and tobacco cessation education for health professionals was developed as multidisciplinary collaboration between KTL, University of Kuopio and Savonia University of Applied Sciences in Kuopio. The education material has then been tailored for the education

of different groups of health professionals in order to answer to the specific needs of each group. The course was built using wiki technology ([www.wikipedia.org/](http://www.wikipedia.org/)) in the Moodle course management system (<http://moodle.com/>).

The course format includes a seminar day as well as pre- and post-seminar assignments online as individual or group work.

### 1. Pre-seminar assignment

- The students study the theory on tobacco and health included in the internet database and their knowledge is tested with interactive multiple choice questions specific for each medical speciality. The tests are designed to give feedback on wrong and right answers and that way guide the student. If the answer given by the student is wrong, he/she gets back to the theory part to study more and try again. The theory database also includes theory on tobacco addiction and the cessation process.

### 2. Seminar

- The half day seminar is concentrating on the addiction process and practical tools for effective smoking cessation as the students are already familiar with the theoretical background. A multidisciplinary approach is encouraged, including e.g. a physician speaking about medication and methods used in smoking cessation and a nurse specialised in smoking cessation speaking on the perspective of putting theory into practise. An important part of the seminar is case studies executed e.g. as role plays or small group discussions. As the last part of the seminar the resolutions to the case studies are presented and discussed in the whole class.

### 3. Post-seminar assignment

- After the seminar the students participate in internet based multidisciplinary small group assignments to reflect on what they have learned and get a comprehensive picture of tobacco control. The assignment can e.g. include planning smoking cessation in their hometown answering questions such as: How should the tasks be divided between health professionals? What to consider in order to build a functional referral system? What could be specific obstacles in the process?

The course is executed annually in medical faculties in Finland as an integrated part of the curriculum or as an optional course. A comprehensive model for nursing students' education is also built at the moment and pilot projects will take place in the cities of Seinäjoki, Lahti, Savonlinna and Kuopio during the year 2007. Based on the lessons learned from this pilot study at least six more nursing schools will join the network during the year 2007. The centre for coordination of the pharmacy students' model is at the University of Kuopio. The first seminar including pharmacy students was conducted in Kuopio in 2006 and there are ongoing negotiations with the universities in Helsinki and Turku. The first tobacco and health seminar for dental students was held in spring of 2007 in Helsinki and there are plans to include the dental schools in Turku and Oulu.

Parallel to building tailored models for education for different groups of health professionals the focus is very much on a multidisciplinary approach. The first seminar and interactive internet course for medical and pharmacy students' together was conducted at the University of Kuopio in the autumn of 2006. In November 2007 nurses' students as well as medical- and pharmacy students will be integrated in the course. The multidisciplinary approach helps the students to understand the role and opportunities that different groups of health professionals bring into tobacco cessation. This way the collaboration between health professionals will run more smoothly also in real life situations and tobacco cessation efforts will be more successful.

When tobacco and health education is solidly integrated into the curriculum of health professional students the next step is to integrate the education in the supplementary and specialist education of all these professions. A tobacco cessation internet course for specialist education in general medicine is developed at the moment.

At the same time as building models and tailored education material for tobacco and health education for health professionals and integrating these in the core curriculum, a network of professionals all around the country, with the competence and willingness to educate not only students but also their own colleagues about tobacco cessation, is created.

#### Collaboration partners:

- National Public Health Institute, KTL, Finland
- University of Kuopio, Finland
- Savonia University of Applied Sciences, Kuopio, Finland.

#### Funding source:

- Ministry of Health and Social Affairs, Finland.

## How to measure craving and withdrawal in clinical trials

### Saul Shiffman

Research Professor of Psychology, Psychiatry, and Pharmaceutical Sciences,  
University of Pittsburgh & Senior Scientific Advisor, Pinney Associates Pittsburgh, Pennsylvania, USA

This lecture discusses assessment of nicotine craving and withdrawal in the context of smoking cessation. Even though abstinence is the primary outcome in cessation trials, there are several reasons to assess craving and withdrawal: they are symptoms of concern to smokers; they are important predictors of cessation and relapse; and they may mediate the effects of treatment. While assessment of these symptoms seems simple, there are several conceptual, methodological, and practical issues to be thought through. There is ongoing debate about the dimensionality of craving and withdrawal. In the author's view, craving can be meaningfully assessed using a single index. Conversely, the nicotine withdrawal syndrome consists of several clusters of symptoms – affective disturbance, restlessness, difficulty concentrating, sleep disturbance, and weight gain – which appear to have different natural histories and likely different underlying mechanisms. There is also evidence that different symptoms are differentially affected by pharmacological treatments. Accordingly, assessment of individual symptom clusters provides useful information that may be masked by using a single composite score.

Evidence indicates that craving is highly variable and dynamic, especially during cessation. In particular, craving demonstrates an episodic course, being subject to sharp spikes that are associated with exposure to provocative stimuli, such as others smoking or emotional distress. This substantially complicates its assessment, and our ability to understand its role in cessation and relapse. Methods have been developed for assessing craving responses to provocative stimuli in the laboratory, and these have proved useful for understanding craving dynamics and for shedding light on the mechanism of action of different pharmacological treatment approaches.

Methods for assessing variations in craving in real-life natural environments have also proved useful. Assessment of craving and withdrawal have generally relied on retrospective summaries. However, research on autobiographical memory suggests that such retrospective summaries may be subject to significant biases. Moreover, evidence suggests that there are meaningful variations that are masked by the use of summaries. Data collected using Ecological Momentary Assessment – real-time data collected on repeated occasions in real-world settings – can help overcome problems of retrospection, and shed light on the temporal dynamics of craving and mood and their role in relapse. Such data suggest that intensity of tonic craving is modest, even during abstinence, and declines sharply over time. Tonic craving levels modestly predict subsequent relapse. In contrast, phasic changes in craving that occur during episodes of

exposure to provocative stimuli appear to play a very direct and immediate role in precipitating relapse, as do acute changes in affective state. The implications for assessment of craving and withdrawal are discussed.

### Funding and interests

The research reported in this lecture was funded by the US National Institutes of Health or by GlaxoSmithKline Consumer Healthcare (GSKCH), which markets smoking cessation medications. Dr. Shiffman serves as a consultant to GSKCH on matters related to smoking control and/or nicotine replacement medications. Dr Shiffman also has a financial interest in a venture to develop new nicotine replacement medications and is a co-founder of invivodata, Inc., which provides electronic diaries for research.

## Acetylcholine binding proteins: structural models of the extracellular domain of the nicotinic receptors

**A. B. Smit**<sup>1</sup>, **C. Ulens**<sup>2</sup>, **P. H. Celie**<sup>2</sup>, **D. Bertrand**<sup>3</sup>, **V. I. Tsetlin**<sup>4</sup>, **T. K. Sixma**<sup>2</sup>

1. Molecular & Cellular Neurobiology, Center for Neurogenomics & Cognitive Research, Amsterdam, Netherlands. 2. Netherlands Cancer Institute, Amsterdam, Netherlands. 3. Centre Medical Universitaire, Medical faculty, Geneva, Switzerland. 4. Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Moscow, Russian Federation.

Nicotinic acetylcholine receptors (nAChRs) are members of the ligand-gated ion channel (LGIC) family that mediate and/or modulate synaptic signaling. They are members of the pharmaceutically important subfamily of pentameric ion channels, GABAA, GABAC, 5HT3 serotonin, and glycine receptors. nAChRs play important roles in memory and learning processes and the absence of functional receptors is associated with multiple diseases including schizophrenia, Alzheimers disease, drug addiction and the autoimmune disease myasthenia gravis. nAChRs are the prime mediators of nicotine addiction in tobacco smokers. Because nAChRs have prominent roles in disease of the nervous system, they have become major targets in drug discovery programs.

nAChRs exist in subtypes with different physiological properties and pharmacology. The lack of detailed structural information about these receptors has hampered rational drug design. Structural information about the ligand-binding domains and the subunit interfaces has expanded upon discovery and crystallization of the water-soluble homologues of the ligand-binding domain of nicotinic receptors, the acetylcholine binding proteins (AChBP)(1,2) that were identified in the central nervous system of several molluscan species. The crystal structures of AChBPs (fig.1) have become established models for the extracellular domain of the pentameric LGICs and homology models for different nAChRs have been generated to analyze receptor-ligand interactions in more detail. AChBPs have a pharmacological property similar to the

homomeric alpha-7 subtype of the nAChRs, with relatively weak affinity for acetylcholine and generally a 10-fold higher affinity for nicotine. The ligand-binding site of the AChBPs is characterized by the presence of aromatic and hydrophobic residues that are contributed by the two neighboring subunits. The crystal structures of AChBP in complex with nicotine and carbamylcholine (3) have elucidated the molecular contacts between ligand and protein and are in excellent agreement with biochemical data obtained from nAChR binding studies. AChBP in complex with the nAChR agonists carbamylcholine and nicotine has revealed that both ligands bind at the same position and cause similar local conformational changes within the protein. These structures are useful tools for the development of new drugs for the nicotinic acetylcholine receptor and its family members through rational design, *in silico* and/or *in vitro* screening.

In addition to these, we determined the 2.4 Å structure of  $\alpha$ -Conotoxin PnIA (A10L D14K), a potent blocker of the  $\alpha$ -7 nAChR, bound with high affinity to *Aplysia californica* AChBP (Ac-AChBP)(4). Alpha-Ctx is buried deep within the ligand-binding site and interacts with residues on both faces of adjacent subunits. The toxin itself does not change conformation, but displaces the C-loop of AChBP and induces a rigid-body subunit movement. Moreover we revealed the 2.2-Å crystal structure of Ac-AChBP in complex with alpha-conotoxin lml (5). This toxin also forms interactions in the ligand-binding site that were not seen in the complex of Ac-AChBP with PnIA(A10L D14K). In contrast to lml, conotoxin PnIA(A10L D14K) lacks binding selectivity to AChBP homologs. Although these toxins all bind at the acetylcholine binding site, each of them has specific contacts with residues of the principal and complementary face of the binding site. The knowledge of these toxin-AChBP contacts will advance rationalized design of ligands using the Ctx framework and may lead to compounds with increased receptor subtype selectivity.

#### Reference 1:

Smit AB, Syed NI, Schaap D, van Minnen J, Klumperman J, Kits KS, Lodder H, van der Schors RC, van Elk R, Sorgedragger B, Brejc K, Sixma TK, Geraerts WP. A glia-derived acetylcholine-binding protein that modulates synaptic transmission. *Nature*. (2001) 411(6835):261-8.

#### Reference 2:

Brejc K, van Dijk WJ, Klaassen RV, Schuurmans M, van Der Oost J, Smit AB, Sixma TK. Crystal structure of an ACh-binding protein reveals the ligand-binding domain of nicotinic receptors. *Nature*. (2001) 411(6835):269-76.

#### Reference 3:

Celie PH, van Rossum-Fikkert SE, van Dijk WJ, Brejc K, Smit AB, Sixma TK. Nicotine and carbamylcholine binding to nicotinic acetylcholine receptors as studied in AChBP crystal structures. *Neuron*. (2004) 41(6):907-14.

#### Reference 4:

Crystal structure of nicotinic acetylcholine receptor homolog AChBP in complex with an alpha-conotoxin PnIA variant. *Nat Struct Mol Biol*. 2005 12(7):582-8.

#### Reference 5:

Ulens C, Hogg RC, Celie PH, Bertrand D, Tsetlin V, Smit AB, Sixma TK. Structural determinants of selective alpha-conotoxin binding to a nicotinic acetylcholine receptor homolog AChBP. *Proc Natl Acad Sci U S A*. 2006 103(10):3615-20.

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## Mortality and morbidity attributable to smokeless tobacco

### Birgitta Stegmayr

Department of Public Health and Clinical Medicine, Umeå University Hospital, Sweden

Snus (Swedish for moist snuff) is a form of smokeless tobacco and is very common used in Sweden. The use of snus was introduced in Europe in the 17th century and was then inhaled through the nostrils. Nowadays most snus is taken orally in a loose form or in tea-bag-like small packages. Smokeless tobacco was banned in European Union in 1992, except in Sweden because of the long tradition of snus use in Sweden. Around 10% of the men were using snus in 1976, a habit that have increased after that. In the last MONICA survey, performed in 2004, 30% of the men and 11% of the women in age group 25-64 years were using snus daily. Since 1990 a more low-nitrosamine snus had been produced in Sweden, compared to the moist snuff used in US.

In Sweden a declining trend in lung cancer and other smoking related mortality rates is shown. Sweden has also the lowest incidences of lip and oral cavity in the Western world. In most of the developed countries around 20% of the annual deaths are caused by smoking and about 20 times as many people have serious smoking-related illness. It is in this context smokeless tobacco is estimated to be more than 90% less harmful than cigarettes.

Several studies have been investigating the health hazards for fatal or non-fatal potential health risks of snus. The studies have focused on the risks for cardiovascular diseases, diabetes, cancer oral diseases and addiction. Many of the studies have been from Sweden and this paper will mainly consider the research of Swedish snus. One difficulty with studying snus users is that almost half of all snus users have been smokers before. Rather few studies have the possibility to have never-smoking snus users.

### Cardiovascular diseases

In reviews six well-performed studies are available about the potential risk for myocardial infarction and stroke. All studies were only on men, because so few women were using snus. One cohort study found a small elevated risk for cardiovascular and cerebrovascular death in those who used snus in the 1970s. Apart from this study, no significantly increased risks for snus users were found in five studies reporting on more later cohorts. Three of the studies were case control studies. For all this studies the estimated risk was close to 1 for non-

fatal and fatal cardiovascular disease including one study for stroke. All these studies showed consistently a two-to-three fold risk for myocardial infarction or stroke for smoking men compared to never tobacco users.

One explanation for the divergent results on mortality between the older study vs. newer ones, could be that the older cohort was associated with population and exposure characteristics specific to that cohort.

### **Diabetes**

One prospective well-conducted cohort study looked at the effect of snus use and on diabetes in men. In this study no significant risk of diabetes was found for snus users but the researchers found an increased risk for diabetes in smoking men.

### **Cancer**

The strongest risk factor for many cancers is smoking. In a recent study in *The Lancet* the elevated risk for oral cancer, lung cancer and pancreatic cancer in smokers were respectively 6.9, 10.2 and 13.0 times higher compared to non-smokers. The figures for snus users for the same cancers were 0.9, 0.8 and 2.1 respectively. (In this study the snus users had been using the older manufactured snus with a higher content of nitrosamine). There is no evidence for elevated risks for cancer in snus users, maybe with the exception for pancreatic cancer. Here a small risk can be considered.

In a recent study in researchers from Australia have estimated the health gain effects if snus were to be launched in Australia. Their conclusion was, if many current smokers switched to snus instead continue to smoke, this would realize a substantial health gain.

### **Conclusion**

The optimal, is of course, not to use any tobacco products at all. They all cause severe addiction, but if an individual has serious problem to quit smoking, a switch to snus is a much better alternative than continue to smoke. In terms of harm reduction, the use of snus has a great potential – but the problem is if many starts with snus and then switch to smoking. Therefore to introduce snus in communities that have no tradition of snus can be hazardous.

The grants supporting the me.

Grants from the Swedish Heart and Lung foundation, the County Councils of Northern Sweden (Visare Norr), the Faculty of Medicine, Umeå University, and the Swedish Medical Research Council.

## **Reimbursement for Pharmacological Treatments for Smoking Cessation. The Experiences of Smoking Cessation Services in the UK**

### **Gay Sutherland**

Research Psychologist Tobacco Research Unit. Institute of Psychiatry King's College London & Honorary Consultant Clinical Psychologist Specialist Smokers Clinic South London & Maudsley NHS Foundation Trust

*Funding from Lambeth, Southwark & Lewisham NHS Primary Care Trusts*

Until 1999 few smokers in the UK were offered formal help to stop smoking. There were only a handful of research clinics specifically treating smokers and although NRT was licensed for use it was available only by private and therefore costly prescriptions. Everything changed in 1999 when the new Government prioritized tobacco control and set aside funding for, and implemented a number of strategies including for the first time, comprehensive nationwide treatment programmes to help smokers stop. These combine various levels of intensity of behavioural/psychological support from specially trained healthcare staff (stop smoking advisors), with strong endorsement to use adjunctive stop smoking pharmacotherapy.

The Government set up an organization - the National Institute for Health & Clinical Excellence (NICE), with responsibility for making evidence-based decisions about which medications or medical procedures are effective and importantly cost effective, and should, therefore, be reimbursed and made available to the population. NICE has reviewed NRT, varenicline, and bupropion, and concluded they are all extremely cost-effective and so smokers wishing to make a serious attempt to stop smoking in the UK are in a very fortunate position, compared to those in many other countries, because the cost of these medications are covered by our National Health Service (NHS) which is funded from general taxation. Smokers above a certain income threshold pay only a small contribution towards each prescription they receive (about 10 Euros). Low income smokers receive the medication completely free of charge. This is true for all drugs in the UK. NICE guidance says that, contraindications aside, smokers preference for a particular treatment should be taken into consideration when prescribing pharmacotherapy, and that they should be encouraged to use behavioural support from the stop smoking services as this will significantly increase their chance of quitting. However, although the quit rates are lower when pharmacotherapy is used without formal support, it can still be prescribed on the NHS (reimbursed) to smokers who wish to try to stop on their own without behavioural support.

In order to ensure that stop smoking pharmacotherapy is used as cost-effectively as possible, NICE guidelines say that they should be prescribed on a number of repeated prescriptions, rather than given as a full 2-3 month course of treatment in a single prescription. The NICE regimen

encourages users of stop smoking medication to re-attend for follow-up appointments, thus increasing the likelihood they will stop successfully. Typically smokers are prescribed 1-2 weeks NRT at a time, bupropion for 4 weeks, and 2-4 week prescriptions for varenicline. If smokers are not abstinent from tobacco or making good progress towards it, after about 4 weeks, medication is often discontinued. NICE recommend that smokers who relapse should not usually be eligible for a second course of stop smoking pharmacotherapy on the NHS for 6 months or longer. This may further contribute to cost-efficacy and improve outcome in smoking cessation as it may help ensure smokers make the most of the medication as they are told they may have to wait some time before being given a subsequent course. Some stop smoking services prescribe combination NRT on the National Health Service and others prescribe only a single product but recommend the smoker purchase a second NRT over the counter.

In order to make these medications as widely and easily available as possible there is a useful legal mechanism in the UK called a Patient Group Direction, which enables healthcare staff such as nurses and pharmacists to dispense medications which are usually only prescribed by doctors. This has been extremely helpful since most of the behavioural treatment services for smokers in the UK are run stop smoking advisors rather than prescribing doctors. Smokers can therefore obtain their medication from their stop smoking advisor and do not have to make a separate appointment to see their doctor for a prescription which saves both the smoker and the healthcare system time and money.

## Smoking cessation in pulmonary patients

**Philip Tønnesen, M.D., Dr.Med.Sci.,**

Chair dept. of Pulmonary Medicine  
Gentofte University Hospital,  
Copenhagen, Denmark

Smoking cessation is a cornerstone in the therapeutically approach to patients with respiratory disorders. European Respiratory Society has recently published guidelines about smoking cessation for smokers with respiratory disorders. Drugs for smoking cessation has almost doubled the long-term abstinence rate. Cochrane meta-analysis found that nicotine replacement products (NRT), bupropionSR and varenicline increase quit rate in smokers. In COPD patients few studies have been published. In two large studies in COPD patients both nicotine sublingual tablets and bupropionSR increased quit rate. Cessation counselling and behavioural strategies are important adjuncts for maintaining long-term smoking abstinence.

We enrolled 370 COPD patients who smoked a mean of 19.6 cigarettes/day, with a mean of 42.7 pack-years and with a mean FEV1 of 56% predicted. Nicotine sublingual tablet or placebo were scheduled to be used for 12 weeks, combined with either low support (4 visits plus 6 telephone calls) or high

support (7 visits plus 5 telephone calls), provided by nurses, according to a standard guideline.

Smoking cessation rates were statistically significantly superior with sublingual nicotine versus placebo for all measures of abstinence: 6-month point prevalence 23% vs. 10%, 12-month point prevalence 17% vs. 10%. There was no significant difference in effect between low vs. high behavioral support. The SGRQ score improved significantly in abstainers vs. non-abstainers; the changes in mean scores were -10.9 vs. -2.9 for total score, and -28.6 vs. 2.3 for symptom score, respectively.

In summary, we demonstrated for the first time the long-term efficacy of NRT for cessation for the general population of COPD smokers, regardless of daily cigarette consumption. Cessation success rates were in the same range as in healthy smokers, and abstinence improved SGRQ scores. To implement these findings, NRT should be used to aid cessation in all smokers with COPD, regardless of disease severity and number of cigarettes smoked.

Patients with respiratory disorders such as COPD and asthma have a greater need to quit smoking as it affects their disease negatively. These patients are often more nicotine dependent than healthy smokers and thus need more pharmacological support. Combination therapy with NRT and bupropionSR is the options. Too low dose and too short a duration of use of these products is a common observation.

Another smoking cessation and reduction study in 220 asthmatics is reported and discussed. The main findings were that symptoms and bronchial hyper-reactivity improved in asthmatics that quit smoking.

Smoking reduction is a concept that might be useful for smokers not yet motivated to quit completely. Smoking reduction seems to be a gateway to smoking cessation as least in healthy smokers. With this approach its now possible to enrol the majority of smokers in smoking cessation support programmes.

Overall, smoking cessation intervention is a must for patients with respiratory disorders as this might prevent disease progress. Smoking cessation should be an integral component of therapy in this group of patients.

### References.

Tønnesen P, Carrozzi L, Fagerstrøm KO, Gratzou C, Jimenez-Ruiz C, Nardini S, Vieg G, Lazzaro C, Campell IA, Dagli E, West R. Smoking cessation in patients with respiratory diseases: a high priority, integral componet of therapy. *Eur Respir J* 2007;29:390-417.

Fiore MC, Bailey WC, Cohen SJ, et al. Treating Tobacco use and Dependence. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000.

Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2004;3:CD000031.

Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement

therapy for smoking cessation. *Cochrane Database Syst Rev* 2004;3: CD000146.

Tashkin DP, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomized trial. *Lancet* 2001;357:1571-75.

Jimenez-Ruiz CA, Masa F, Miravittles M, et al. Smoking characteristics. Differences in attitudes and dependence between healthy smokers and smokers with COPD. *Chest* 2001;119:1365-1370.

Hand S, Edwards S, Campbell IA, Cannings R. Controlled trial of three weeks nicotine replacement treatment in hospital patients also given advice and support. *Thorax* 2002;57:715-718.

Wagena EJ, van der Meer RM, Ostelo RJ, et al. The efficacy of smoking cessation strategies in people with chronic obstructive pulmonary disease: results from a systematic review. *Respir Med* 2004;98:805-15.

Wallström M, Nilsson F, Hirsch JM. A randomized, double-blind, placebo-controlled clinical evaluation of a nicotine sublingual tablet in smoking cessation. *Addiction* 2000;95:1161-1171

Bolliger CT, Zellweger JP, Danielsson T, et al. Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. *BMJ* 2000;321:329-33.

Wennike P, Danielsson T, Landfeldt T, et al. Smoking reduction promotes smoking cessation: Results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. *Addiction* 2003;98:1395-1402.

Rutten-Van M, Roos B van N. An empirical comparison of the St George's Respiratory Questionnaire (SGRQ) and the Chronic Disease Questionnaire (CRQ) in a clinical setting. *Thorax* 1999;54:995-1003.

Tønnesen P, Pisinger C, Hvidberg S, et al. Effects of smoking cessation and reduction in asthmatics. *Nicotine Tob Res* 2005; 7:139-148.

Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *J Am Med A* 1994;272:1497-1505.

Tønnesen P, Mikkelsen K, Markholst C, et al. Nurse-conducted smoking cessation in a lung clinic: a randomized controlled study. *Eur Respir J* 1996;9:2351-2355.

Simmons MS, Connett JE, Nides MA, et al. Smoking reduction and the rate of decline in FEV1: results from the Lung Health Study. *Eur Respir J* 2005;25:1011-1017.

Tønnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD, using nicotine sublingual tablets and behavioral support. *Chest* 2006;130:314-316.

## Smoking cessation in cardiovascular patients: Do we need different objectives, treatments and regimes?

**Serena Tonstad**

Head physician, professor  
Department of Preventive Cardiology  
Ullevål University Hospital  
Oslo, Norway

### Introduction

Admission to a coronary care or stroke unit may represent a time when smoking behavior is particularly susceptible to intervention. Conversely one-half or more of patients with cardiovascular disease do not quit successfully thus highlighting the difficulty in stopping smoking even under these circumstances. The Euroaspire II survey performed across Europe found that 48% of patients stopped smoking after a cardiac event (Scholte op Reimer et al 2006). Only 38% of those whose event was myocardial ischemia quit, a lower rate than observed among those with a coronary artery bypass graft (47%), percutaneous coronary intervention (49%) or myocardial infarction (52%). Clearly the seriousness of the event influences quit rates. Other predictors of the likelihood of quitting were increasing age, high educational level, and obesity. Notably, care by a hospital cardiologist rather than another physician also increased the likelihood of quitting.

Patients with cardiovascular disease are encountered in hospital, in cardiac rehabilitation programs and as outpatients after the acute event. Different approaches may be needed to promote smoking cessation in each of these venues. Most importantly, new treatment approaches should consider the needs of cardiovascular patients in each of these settings.

### Hospitalized patients with a cardiovascular diagnosis

Interventions for smoking cessation in hospitalized patients were reviewed in a Cochrane meta-analysis where it was found in the pooled data that intensive intervention (inpatient contact with follow up for at least one month) was associated with higher quit rates (odds ratio 1.8; 95% CI 1.5-2.2) compared to controls (Rigotti et al 2003). Contact during hospitalization without follow-up was not associated with a statistically significant increase in quit rate. Nine of 17 studies reviewed comprised patients with a cardiovascular diagnosis. In these studies the intervention increased quitting (odds ratio 1.4; 95% CI 1.2-1.7).

Results from studies published after 2002 and enrolling patients with CVD are mostly consistent with the Cochrane review. In one study conducted in Norway, 240 smokers hospitalized for coronary heart disease and given inpatient intervention followed by monthly follow-up for a minimum of 5 months had a 57% quit rate 12 months after admission versus 37% ( $P < 0.01$ ) for a control group (Quist-Paulsen & Gallefoss 2003). In another study conducted in France, 168 patients with myocardial infarction, angina, heart

failure or peripheral vascular disease were randomized to inpatient counseling with telephone follow-up, inpatient counseling or usual care. Quit rates were 42%, 30% and 20% in the groups, respectively, after 6 months ( $P=0.05$ ) (Chouinard & Robichaud-Estrand 2005). A recent study randomized 209 smokers with acute coronary syndrome or decompensated heart failure to at least 3 months of weekly counseling after discharge or no follow-up (Mohiuddin et al 2007). The intervention group had higher quit rates than the controls (39% vs 11% after 1 year and 33% versus 9% after 2 years), fewer hospitalizations and lower all-cause mortality (2.8% versus 12%). In contrast a nurse-managed cognitive behavioral relapse prevention at bedside, with telephone contact at intervals after discharge found no difference in 6-month quit rates between women with CVD who were randomized to the intervention (48%) versus usual care (42%) (Sivarajan Froelicher et al 2004).

In summary studies indicate that hospitalized smokers with CVD who receive usual care have long term quit rates of 10-40%. Inpatient intervention and follow-up after discharge boost quit rates, and should probably be continued for 3 months.

### **Pharmacological therapy in hospitalized patients with a cardiovascular diagnosis**

Evidence on the effectiveness of nicotine replacement therapy in the acute setting is limited. Several studies have focused on the safety of nicotine replacement therapy in this setting. The consensus of most experts is that nicotine replacement therapy is safer than smoking. This is in part due to the flat dose-response curve of nicotine resulting in only a modestly increased intake of nicotine compared to smoking alone.

Only one study has examined the effect of a non-nicotine medication in patients with acute cardiovascular disease (Rigotti et al 2006). The effect of 12 weeks of sustained release bupropion versus placebo was tested in 248 smokers admitted for myocardial infarction, unstable angina or other acute cardiovascular disease who were expected to have in-hospital stays of at least 24 hours. Quit rates were not significantly affected by bupropion and were relatively low after 3 months of follow-up (37% in the bupropion group versus 27% in the placebo group;  $P=0.08$ ). Adjustment for a number of factors that may influence quit rates resulted in a significant odds ratio after 3 months but not after 1 year.

### **What studies do we need in the acute setting?**

Because coronary care units are smoke free, these patients get a few days of "automatic" cessation but most relapse. Long-term treatment regimens, for example, starting drug treatment in the hospital and continued follow-up after discharge are needed. New drugs that are effective in outpatient settings should be tested in regimens that are suited to patients with acute cardiovascular disease. Few studies have been published showing the effect of interventions beyond usual care in acute stroke units.

### **Rehabilitation**

Most hospitals with cardiac care units either have their own rehabilitation programs or access to external programs. These programs provide a range from minimal intervention (pamphlets on smoking cessation) to more extensive intervention (individual or group counseling). Smoking cessation is provided as part of multicomponent interventions. A review of rehabilitation programs is beyond the limits of this lecture. Rehabilitation programs should combine the most effective pharmacological and intensive motivational support available for patients who continue to smoke after an acute cardiovascular event.

### **Outpatient settings After a cardiovascular event**

As an outpatient, the patient with CVD typically sees a generalist or specialist physician on a routine basis. This group of patients is readily available for smoking cessation studies. Despite this few studies have been done in this group.

In one study 597 patients with myocardial infarction or new onset angina during hospitalization or at a chest pain clinic were randomized to coordinated preventive care led by specialist nurses or usual care (Jolly et al 1999). Smoking rates did not differ between the two groups after 1 year. Another study recruited 385 smokers with coronary or peripheral artery disease from outpatient departments of vascular surgery, cardiology and vascular medicine in the Netherlands (Wiggers et al 2006). Patients in the control group received free nicotine replacement therapy for 8 weeks but no additional support or materials; patients in the intervention group were offered a 15-30 minute counseling session and at least one follow-up contact in addition to nicotine replacement therapy. Point prevalence abstinence rates were 14% in the usual care versus 19% in the minimal support groups after 12 months (not statistically significant).

### **Pharmacological therapy in cardiovascular outpatients**

Several studies have examined the effectiveness of nicotine replacement therapy in outpatients with a cardiovascular diagnosis (Foulds et al 1993; Working Group 1994; Campbell et al 1996; Joseph et al 1996). The first 3 studies did not find significant effects, but included small numbers of participants. The fourth and largest study included almost exclusively male veterans. Quit rates were significantly higher following a 10-week course of transdermal nicotine versus placebo at the 14 week but not at the 24 week evaluation (Joseph et al 1996). However, there is no reason to believe that nicotine replacement therapy would be ineffective in adequately powered studies.

One study of a non-nicotine containing medication in subjects with cardiovascular disease has been published. In a multicenter study conducted in seven European countries, Australia and New Zealand 629 subjects with stable cardiovascular disease defined as more than 3 months since a myocardial infarction or interventional cardiac procedure, stable angina, peripheral vascular disease or congestive heart failure (NYHA class I or II) were recruited for a study of slow release bupropion 300

mg/day versus placebo for 7 weeks with follow-up for 1 year (Tonstad et al 2003). Continuous quit rates were 22% in the bupropion group versus 9% in the placebo group ( $P < 0.001$ ). Bupropion treatment was safe and well tolerated. Media reports about the safety of bupropion arose in Europe concerning a number of adverse events. However, evaluation of existing data and further study did not find evidence of increased risk for cardiovascular events (Boshier et al 2003).

### **Before cardiac surgery**

Among patients awaiting an elective coronary artery bypass graft a nurse led intervention increased smoking rates compared to a control group (McHugh et al 2001).

### **What studies do we need in the outpatient setting?**

A minimal support program or nurse-coordinated care do not seem to be effective interventions in outpatients with a cardiovascular diagnosis. Patients that continue to smoke despite their coronary or peripheral artery disease may require more intensive and multifactorial programs. Intervention in patients awaiting a coronary artery bypass graft appears promising.

### **Patients with diabetes**

There is a dearth of studies conducted in patients with type 2 diabetes, a group that may benefit as much from smoking cessation as patients with cardiovascular disease. Because of the importance of avoiding weight gain in these patients, studies should include a weight management component.

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## **Smokeless tobacco products**

### **Inger Wahlberg**

IWG Consulting, Lyckeby, Sweden.

Smokeless tobacco forms a traditional product category, which includes products that are sucked or chewed in the mouth or inhaled through the nose. Product types sold in Europe include snus, moist snuff, chewing tobacco and nasal snuff. A ban on the marketing and sales of products intended to be sucked, i.e. snus and moist snuff was introduced in the European Union in 1992. When joining the European Union in 1995, Sweden, which has the highest consumption of smokeless tobacco in Europe, received a permanent derogation from this ban. North America has the highest use of smokeless tobacco on a volume basis. Loose leaf, which is a chewing tobacco, and oral moist snuff are the largest product types. Other types of smokeless tobacco on the US market are dry snuff (Scotch type snuff), which is used orally or nasally, and plug chewing tobacco. Most recently, snus has been introduced on the market in the USA by several manufacturers. Many African countries have a high usage of smokeless tobacco including both hand-made and industrially produced products. Algeria has an industrial production of oral and nasal snuff made from tobacco grown in North Africa. Similar products are used in Tunisia, Libya

and Egypt. Toombak, an oral moist snuff product, has a high use rate in Sudan. Various types of smokeless products are used in Nigeria and in South Africa. India and Pakistan have the highest consumption of smokeless tobacco in Asia. Many types of products are found on the market, but particularly noteworthy is the combined chewing of tobacco, betel leaf and areca nut, e.g. guthka. Various types of smokeless tobacco are also used in other countries in Asia. Thus, nass is a smokeless product of high usage in some of the former Soviet Republics. Smokeless products are either banned or of virtually no usage in Australia and New Zealand. A survey of product types used in different countries will be given.

The tobaccos used in smokeless products are commonly air-, fire- or sun-cured. Flue-cured tobacco, which is a main ingredient in the tobacco blends used for most cigarettes, is of limited use in smokeless products for taste reasons.

The manufacturing methods of smokeless tobacco products are dependent on product type and differ vastly in sophistication around the world. A few general production steps are involved: post-curing of leaf tobacco, disintegration, i.e. stripping, threshing, cutting or grinding, blending of tobaccos, processing of blended tobacco, and finishing of the product with addition of flavours and stabilizers. Swedish snus is made from a blend of ground air- and sun-cured tobaccos, which is heat-treated, i.e. pasteurized in a closed process. Snus products, additives and hygienic requirements are regulated under the Swedish Food Act. Moist snuff, as sold in the USA, contains mainly fire- and air-cured tobaccos, which are cut into different sizes, fine-cut, coarse cut or long-cut. The tobacco blend is mixed with water and fermented for several weeks. Moist snuff from other countries may be fermented or produced by simple mixing of tobacco with lime or sodium carbonate and other ingredients. Nasal snuff, which is usually a fine powder and drier than oral snuff, may be fermented or non-fermented. Loose leaf from the USA is generally made from Pennsylvania and Wisconsin tobacco. The tobacco is exposed to chemical sweating, threshed into flakes, which are treated with a sweet casing. Chewing tobacco from other parts of the world may be fermented or non-fermented and can vary in appearance from finely grated tobacco particles to blocks of compressed tobacco and thick strands of spun tobacco.

The chemical characteristics of smokeless products are dependent upon factors such as in-going tobaccos and other ingredients, manufacturing methods and storage conditions. The presence of tobacco-specific nitrosamines, TSNA, has attracted particular attention and the formation of these compounds in the tobacco raw material and during manufacture of smokeless tobacco products will be discussed.

Inger Wahlberg is a retired employee of Swedish Match AB, Stockholm, Sweden. No funding has been received to prepare this presentation.

## Proposal for a questionnaire to measure craving in a clinical setting

**Robert West**

Department of Epidemiology and Public Health, University College London

If we adopt a definition of motivation as a system of forces that energise and direct behaviour (1), it is a simple truism that smoking a cigarette after the target quit date results from the fact that, on an occasion when a cigarette is available, the motivation to smoke is stronger than the motivation to resist. There are several different scenarios. The motivation to smoke may be persistent or frequent and gradually deplete the will to resist; it may be powerful at a given moment, simply overpowering the motivation to resist; it may not be powerful but come unexpectedly, catching the would-be ex-smoker off-guard before he or she can marshal the motivation to resist; or it may be relatively modest but the motivation to resist may simply be at a low ebb at that time. Whichever of these scenarios pertains, it is clear that the strength and duration or frequency or motivation to smoke is important and that they merit assessment.

The term craving is typically used as a catch-all for the experience of the motivation to smoke which can be felt as an urge, a need or a desire to smoke. Use of the term 'craving' also usually implies that the feelings concerned are strong and compelling.

In some languages there is no direct translation of 'craving' which may be testimony to the cultural specificity of the construct and must also give pause for thought about whether it would be better to use one or more alternatives when measuring the experience of motivation to smoke. There is also an issue about whether to extend the boundaries of the concept to the various factors which may be presumed to feed into the motivation to smoke such as beliefs about whether a cigarette would alleviate withdrawal discomfort or be enjoyable (2) and also how far the experience of motivation to smoke captures all of the actual motivation, much of which may be 'automatic' (3).

Because of the difficulties and ambiguities with the term craving this paper will talk about 'experienced motivation to smoke' (EMS) which may encapsulate any single element or combination of elements of urge, desire or need.

Assessing EMS in a clinical setting can serve several purposes. Prior to the quit attempt starting, it could perhaps provide an index of the degree of addiction to cigarettes, thereby helping to determine the intensity of the treatment that may be required. Once the quit attempt has begun it could provide useful information on how far motivational forces such as nicotine dependence are under control and hence whether there needs to be a change to the treatment regimen: e.g. increasing the dose of medication. It is also clearly useful for clinical research to assess the effectiveness of a particular intervention or to identify particular kinds of smoker that may need more, or a different type of, help than another.

This then raises the question as to whether such assessment should focus on or use the term 'craving' or whether it should focus on motivation more generally or indeed specific elements of motivation such as 'urge', 'desire' or 'need'. A related question is how far it makes any difference or whether the different aspects of motivation are so intimately intertwined that measuring any element is as good as measuring any other or even all of them together.

Given all this, the question arises as to what is the optimal method of measuring EMS. There are many different measures in use, some of which focus on the term 'craving' while others focus on other terms such as desire or urge, some of which involve single ratings while others involve multiple ratings that need to be combined to give a score, some of which seek to measure a single construct while others seek to measure more than one dimension (see 4).

These different measures may in principle be differentiated in terms of how closely they relate to other indices that can be presumed to reflect motivation to smoke, most notably actual smoking behaviour. Thus one may imagine that scores of a measure of EMS would increase during abstinence and would predict relapse. If one measure does this noticeably better than another, it should be preferred. One might also imagine that scores on a measure of EMS would be able to distinguish between interventions that were designed to reduce its severity and hence aid smoking cessation. Again, if one measure were to do this better than another, it would be preferred. If there were no appreciable difference between different measures on these criteria then from an efficiency standpoint, a measure that was simpler and took less time to complete would probably be preferred.

Surprisingly, there have been very few published studies comparing measures of EMS. West et al (5) compared several of the commonly used scales in terms of sensitivity to abstinence and found little difference between them. However, the study did not include what has now become one of the most widely used scales, the Questionnaire on Smoking Urges (6), nor did it include single ratings of 'craving' and 'difficulty not smoking'. My colleagues and I have carried out a further study and have also analysed combined data from two large clinical trials that included two of the most commonly used measures. This paper does not address the very important issue of timing of measurement and just focuses on self-report measures that ask for retrospective recall of EMS over a predefined period.

Our study looked at differences in scores on EMS scales or single ratings between 30 smokers who had been randomly assigned to abstain from cigarettes for 24 hours versus 30 smokers who had been randomly assigned to continue smoking, controlling for scores on these scales or ratings at baseline, while still smoking. In each case we calculated the eta squared as an index of the effect size. Analogous to R squared for correlations, it is the proportion of variance in the target variable (in this case the EMS score) accounted for by the predictor variable (in this case abstinence versus smoking). A larger eta squared would indicate that the scale concerned was more sensitive to the effects of abstinence.

The scales we tested were: the Questionnaire on Smoking Urges (QSU) Total score (6), QSU Factor 1 score focusing on anticipated reward from smoking, QSU Factor 2 score focusing on anticipated relief from negative affect, the Mood and Physical Symptoms Scale (MPSS) combined urge to smoke score (7), MPSS strength of urges rating, MPSS amount of time spent with urges rating, a simple rating of 'craving' for a cigarette, a simple rating of difficulty not smoking, the Minnesota Nicotine Withdrawal Scale (MNWS) 'desire or craving to smoke' rating (8), the Shiffman craving scale based on 4 ratings of need to smoke, urge to smoke and 'craving' (9), the Wisconsin Smoking Withdrawal Scale (WSWS) craving subscale (10), and the Cigarette Withdrawal Scale (CWS) craving subscale (11). The results showed that the QSU Total, QSU Factor 1, QSU factor 2 and MPSS combined scales yielded eta squareds that were between 0.40 and 0.45, simple ratings of craving, difficulty not smoking, MPSS time spent with urges and MPSS strength of urges yielded eta squareds between 0.35 and 0.40. The WSWS and CWS yielded etas between 0.30 and 0.35 and the Shiffman scale and MNWS yielded eta squareds between 0.20 and 0.30. In all cases the differences between abstaining and smoking groups were significant at  $p < .0001$ .

A further question relates to whether combining different scores or ratings might give greater precision. We evaluated this by entering the different scales and ratings in a forward stepwise logistic regression with abstinent versus smoking group as the dependent variable. For this analysis we took the QSU Total score and the MPSS combined score rather than their components. The results showed that just two of the scales maximised the variance accounted for: the QSU Total Score and MPSS combined urge score which together accounted for 52% of the variance.

The other data reported here examined the effects of the nicotinic partial agonist, varenicline, on abstinence and EMS. EMS was measured using the Brief QSU Total score, Brief QSU Factor 1 score and Brief QSU Factor 2 score as well as the MNWS desire/craving rating. See (12, 13) for details of the studies from which these data were drawn. In 1818 subjects randomly allocated to receive either varenicline, bupropion or placebo who provided EMS data one week after the target quit date, the Brief QSU Total score, Brief QSU Factor 1 score and single desire/craving rating from the MNWS were equally sensitive to the effects of the medication in showing bupropion superior to placebo and varenicline superior to both placebo and bupropion.

Taken together the results suggest that single ratings of EMS focusing on general concepts such as craving, or more specific motivational elements such as urge, perform similarly to more complex multi-item scales such as the QSU in terms of sensitivity to abstinence and to medications that affect EMS. Efficiency suggests that the simpler measures be adopted as standard and it may not matter which one is used. The two items from the MPSS have an advantage in terms of being among the higher eta scores for sensitivity to abstinence while being very brief and easy to administer. It has also been found that when used while smokers are still smoking they predict relapse following a cessation attempt (14). However, when greater precision is required a combination of the QSU and the

MPSS might be best. These findings are clearly preliminary and there is much more work to do to establish the optimal choice of measures of EMS.

## References

1. West R. Theory of Addiction. Oxford: Blackwells; 2006.
2. Tiffany ST. A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. *Psychol Rev* 1990;97(2):147-68.
3. Tiffany ST, Carter BL. Is craving the source of compulsive drug use? *J Psychopharmacol* 1998;12(1):23-30.
4. Shiffman S, West R, Gilbert D. Recommendation for the assessment of tobacco craving and withdrawal in smoking cessation trials. *Nicotine Tob Res* 2004;6(4):599-614.
5. West R, Ussher M, Evans M, Rashid M. Assessing DSM-IV nicotine withdrawal symptoms: a comparison and evaluation of five different scales. *Psychopharmacology (Berl)* 2006;184(3-4):619-27.
6. Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. *Br J Addict* 1991;86(11):1467-76.
7. West R, Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology (Berl)* 2004.
8. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry* 1986;43(3):289-94.
9. Shiffman S, Khayrallah M, Nowak R. Efficacy of the nicotine patch for relief of craving and withdrawal 7-10 weeks after cessation. *Nicotine Tob Res* 2000;2(4):371-8.
10. Welsch SK, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Development and validation of the Wisconsin Smoking Withdrawal Scale. *Exp Clin Psychopharmacol* 1999;7(4):354-61.
11. Etter JF. A self-administered questionnaire to measure cigarette withdrawal symptoms: the Cigarette Withdrawal Scale. *Nicotine Tob Res* 2005;7(1):47-57.
12. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *Jama* 2006;296(1):56-63.
13. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *Jama* 2006;296(1):47-55.
14. West R. Defining and assessing nicotine dependence in humans. In: Bock G, Goode J, editors. *Understanding Nicotine and Tobacco Addiction*. London: Wiley; 2006. p. 36-51.

## Declaration of competing interest

Robert West is funded by a grant from Cancer Research UK. He undertakes research and consultancy for, and has received hospitality, travel funds and speaker fees from, manufacturers of smoking cessation medications. He has a share in a patent for a novel nicotine delivery device. The varenicline analyses were undertaken in collaboration with Pfizer.

## SESSION 1: ORAL COMMUNICATIONS ON BASIC RESEARCH

October 4th – 9.30-11.15 h

1

### **“Subtype-specific regulation of rat brain nAChRs during nicotine and cocaine self-administration”.**

Manolo Mugnaini.

Chiara Mutinelli, Paolo Repeto, Maria Pilla.

GlaxoSmithKline Medicines Research Centre. Verona. Italy.  
manolo.a.mugnaini@gsk.com

The up-regulation of native  $\alpha 4\beta 2$ -nicotinic acetylcholine receptors (nAChRs) after chronic nicotine treatment has been described extensively, but there is less and contrasting information about other relevant nAChRs, such as the  $\alpha 7$  or  $\alpha 6\beta 2^*$ . Moreover, little is known about regulation of nAChRs after self-administration of drugs of abuse like nicotine or cocaine. We have previously demonstrated that after chronic infusion with nicotine (3 mg/kg/day for two weeks), in parallel to the expected up-regulation of  $\alpha 4\beta 2$ -nAChRs (31-52% increase), there was a less pronounced up-regulation of  $\alpha 7$ -nAChRs (26-38% increase) and a down-regulation of  $\alpha 6\beta 2^*$ -nAChRs (29-45% decrease) in rat brain (Mugnaini et al.: Eur. J. Neurosci. 16,1633,2002; Neurosci. 137,565,2006). The aim of the present study was to determine the regulation of  $\alpha 4\beta 2$ -,  $\alpha 7$ - and  $\alpha 6\beta 2^*$ -nAChRs after nicotine and cocaine self-administration. Adult male Wistar rats were trained to self-administer either food (control), nicotine (0.5-1.2 mg/kg/day) or cocaine (4.6-19 mg/kg/day). After two weeks of food, nicotine or cocaine stable self-administration or after two weeks of nicotine self-administration and one month of withdrawal, the animals were killed and their brain processed for receptor autoradiography with [ $^{125}$ I]epibatidine, [ $^{125}$ I]bungarotoxin (bgtx) and [ $^{125}$ I]a-conotoxin MII (cntxMII) to respectively label all axon nAChRs or, selectively,  $\alpha 7$ - and  $\alpha 6\beta 2^*$ -nAChRs. In four (of five) cerebral cortical regions, containing mainly  $\alpha 4\beta 2$ - and  $\alpha 7$ -, but not  $\alpha 6\beta 2^*$ -nAChRs, there was a significant increase of [ $^{125}$ I]epibatidine binding after nicotine and cocaine self-administration (20-33% and 9-14%, respectively), suggesting an increase of  $\alpha 4\beta 2$ -nAChRs. No significant changes of [ $^{125}$ I]bgtx binding were found, whereas [ $^{125}$ I]cntxMII binding was absent. In the regions of mesostriatal dopaminergic pathway, which contain  $\alpha 4\beta 2$ -,  $\alpha 7$ -,  $\alpha 6\beta 2^*$ - and other less represented nAChRs, there were no significant changes of binding of either radioligand after nicotine self-administration, although a trend to a decrease of [ $^{125}$ I]cntxMII binding was observed. Following cocaine self-administration, however, there was a pronounced down-regulation (26-49% decrease) of [ $^{125}$ I]cntxMII binding in three (of five) dopaminergic regions, whereas [ $^{125}$ I]epibatidine and [ $^{125}$ I]bgtx binding remained unchanged. In summary, a smaller up-regulation of  $\alpha 4\beta 2$ - and no significant changes of  $\alpha 7$ - and  $\alpha 6\beta 2^*$ -nAChRs were observed after nicotine self-administration, with respect to chronic nicotine infusion, a difference which may reside on the lower exposure to nicotine (0.5-1.2 mg/kg/day in self-administration with respect to 3 mg/kg/day in chronic infusion). However, tiny changes of [ $^{125}$ I]epibatidine

binding and consistent changes of [ $^{125}$ I]cntxMII binding were observed after cocaine self-administration, suggesting that up-regulation of  $\alpha 4\beta 2$ -nAChRs and especially down-regulation of  $\alpha 6\beta 2^*$ -nAChRs may be common neuroadaptive events in response to prolonged exposure to both drugs of abuse.

2

### **“A differential role for dopamine in nicotine self-administration that is dependent on infusion speed”.**

Robert E. Sorge.

Paul B.S. Clarke.

McGill University, Dept. of Pharmacology and Therapeutics  
Rm. 1320 McIntyre Medical Building, 3655 Sir William  
Osler, Montreal, QC, Canada.

robert.sorge@mcgill.ca

Rationale: Recent evidence in human smokers indicates that cigarette puff-associated peaks in nicotine in the blood and brain are much more gradual and smaller than once believed. Nevertheless, animal models continue to employ rapid, high dose nicotine infusions. Objectives: To compare the standard model of nicotine self-administration, in which rats receive fast drug infusions of high doses, with our new (“slow/low”) model on measures of motivation and the contribution of dopamine (DA). Methods: In Experiment 1, rats were trained to self-administer nicotine in 3 or 30 sec infusions (15  $\mu$ g/kg/inf) on an FR1 schedule of reinforcement; an additional group was trained to self-administer cocaine (0.5 mg/kg/inf). Following training all rats were tested with each of four doses of the DA D2 receptor antagonist spiperone (0, 3, 10, 30  $\mu$ g/kg, sc) on every third day with two sessions in between. In Experiment 2 rats were trained to self-administer “fast/high” (3 sec infusion of 30  $\mu$ g/kg/inf) or “slow/low” (30 sec infusion of 3  $\mu$ g/kg/inf) infusions of nicotine, or cocaine (0.5 mg/kg/inf), on an FR1 schedule. Once intake had stabilized, rats were moved to a progressive ratio schedule (PR) and tested on every third day with the DA D2 receptor antagonists spiperone (0, 3, 10, 30  $\mu$ g/kg, sc) or sulpiride (0, 5, 10, 20 mg/kg, ip). Results: In both experiments, the intake of nicotine was greater in those rats trained on 30 sec infusions. In Experiment 1, spiperone increased the intake of cocaine and of fast infusions of nicotine, and when tested on a PR schedule (Experiment 2), spiperone and sulpiride increased intake of cocaine and “fast/high” nicotine. In striking contrast, spiperone (in Experiments 1 and 2) and sulpiride decreased intake of slow and “slow/low” infusions of nicotine. Conclusions: These results suggest that the motivational role of dopamine in nicotine self-administration depends critically on the nicotine infusion speed. Furthermore, our new model of nicotine self-administration, which more closely parallels the kinetics of nicotine in humans, may provide a better understanding of the contribution of dopamine to smoking.

3

**"The effects of non-contingent nicotine on responding for a compound light stimulus".**

Nicholas Montgomery.

Claire S Birch &amp; David JK Balfour.

*University of Dundee. Scotland. UK.*

d.j.k.balfour@dundee.ac.uk

Recent studies suggest that both contingent and non-contingent intravenous injections of nicotine, given during the session, significantly increase the salience of weakly reinforcing sensory stimuli, and that this enhances nicotine-seeking behaviour (Caggiula et al 2001, Donny et al 2003). This study tested the hypothesis that non-contingent injections of nicotine, given before each session, could also enhance the reinforcing properties of a sensory stimulus. Male Sprague-Dawley rats were trained to press an active lever for reward in a 2-lever operant chamber and then trained to press the same lever for a light stimulus presented above the active lever (Donny et al 2003). Before each 60-minute training session, groups of rats (N=6) were given subcutaneous injections of saline or nicotine (0.4mg/kg). The animals were trained initially on an FR1 schedule with a 20sec time-out signalled by extinction of the house light (FR1T020) until stable responding was achieved before the ratio was increased at weekly intervals to FR2T020 and then FR5T020. The rats showed a significant preference for the active lever which was independent of treatment ( $F(1,20)=28.1; P<0.001$ ). Only the nicotine-treated rats showed an increase in responding on the active lever as the ratio increased ( $F(2,20)=9.4; P<0.001$ ). If the previously inactive lever was made the active lever and vice versa, only the nicotine-treated rats showed diminished responding on the original active lever ( $F(2,25)=13.3; P<0.001$ ), and increased responding on the new active lever ( $F(2,25)=7.35; P<0.001$ ). This was not observed for the saline-treated rats. Withdrawal of nicotine resulted in a significant reduction in responding on the active lever ( $F(1,9)=10.5; P<0.05$ ), but this was still significantly higher even after 5 days of withdrawal than for the saline controls ( $F(1,9)=5.7; P<0.05$ ). These results support those of Donny and colleagues (2003) which suggest that nicotine can significantly increase the reinforcing properties of a sensory stimulus which is otherwise only weakly reinforcing. They further extend these observations by suggesting that this property of nicotine is seen following a single SC injection of the drug prior to the session and does not require the stimulus to be associated closely with small intravenous injections of the drug. Supported by a grant from the Wellcome Trust Caggiula, A.R., Donny, E.C., White, A.R., Chaudhri, N., Booth S., Gharib, M.A., Hoffman, A., Perkins, K.A. & Sved, A.F. (2001) *Pharmacol. Biochem. Behav.*, 70, 515-530. Donny, E.C., Chaudhri, N., Caggiula, A.R., Evans-Martin, F.F., Booth, S., Gharib, M.A., Clements, L.A. & Sved, A.F. (2003) *Psychopharmacology*, 169, 68-76.

4

**"Analysis Of Nicotine Preference In Male And Female Rats With Free Access To Oral Nicotine During Adolescence and Adulthood".**

Tanseli Nesil.

Gonca Dalkurt Mola, Lutfiye Kanit, Sakire Pogun.

*PhD student.**Ege University School of Medicine Physiology Dept.35100 Izmir /Turkey.*

tanselinesil@gmail.com

Smoking is an addiction with detrimental effects on society. Nicotine is the addictive component of tobacco and underlies the addictive properties of tobacco use. While tobacco use among adults is decreasing in developed countries, adolescent smoking, especially among girls is increasing. Tobacco use in adolescence is a major problem which has significant impact on public health. In view of these observations, the present study was designed to test voluntary nicotine consumption of rats which had free access to nicotine strating during adolescence until adulthood. Sprague Dawley rats obtained from Ege University Experimental Animal Breeding Facility were used. A total of 90 female and male rats were monitored from their birth until 4 weeks, when they were separated from their mothers and individually housed in plexiglas cages; nicotine was self administered via "two bottle free choice" method for 6 weeks, with 24 h free access. Nicotine and water consumption were recorded. Control rats received only water from both bottles. The taste of nicotine was masked by saccharin, which was also used in water. At the end of the 6 weeks nicotine administration was discontinued until the rats reached adulthood. At 4 months of age, nicotine administration was resumed and continued for 6 weeks, using the same procedure as in adolescence. At the end of the experimental period nicotine consumption data was analysed by Ward test to depict individual differences; results showed that rats were divided into 3 different groups (maximum, median and minimum) both during adolescence and adulthood. Rats were able to discriminate nicotine from water and showed individual differences in nicotine consumption both as adolescents and adults. Group means showed that nicotine consumption was higher in adolescent rats than adults ( $p<0.001$ ). Furthermore, female rats increased nicotine consumption as adults compared to their adolescent consumption rates ( $p<0.001$ ) and there was a correlation between adolescent and adult nicotine in consumption in female rats but not in males ( $p<0.001$ ). Present findings suggest that female rats are more vulnerable to nicotine as adolescents and adolescent exposure predicts higher nicotine consumption as adults in females.

5

**“The Effects of Chronic Nicotine on Fear Conditioning and Anxiety in Rats”.**

Evrım Gulbetekin 1.

Tanseli Nesil 2,3, Aysegul Keser 3,4, Sakire Pogun 3,4. Ege University, Faculty of Sciences, Psychology Dept. 1; Institute of Sciences, Biotechnology Dept. 2; Center for Brain Research 3; School of Medicine, Physiology Dept. 4; Izmir, Turkey.

evrim.gulbetekin@ege.edu.tr

The Effects of Chronic Nicotine on Fear Conditioning and Anxiety in Rats Evrim Gulbetekin1, Tanseli Nesil2,3, Aysegul Keser3,4, Sakire Pogun3,4 Ege University, Faculty of Sciences, Psychology Dept.1; Institute of Sciences, Biotechnology Dept.2, Center for Brain Research3; School of Medicine, Physiology Dept.4, and Izmir, Turkey Data on the anxiolytic effects of nicotine is controversial. While nicotine exerts sympathomimetic effects and elevates blood glucocorticoid levels, smoking is reported to regulate affect positively, possibly through the serotonergic system. The aim of the study was to observe the effects of chronic nicotine on fear conditioning, extinction of conditioned fear and behavioral despair (forced swim test: FST). Adult male (250-350g) Sprague-Dawley rats received s.c. nicotine (0.4 mg/kg base) or saline (i.e. experimental and control groups, n=6 in each group) 6 days before the experimental sessions; injections continued during the experiments. The experiments had 6 phases: (1) Habituation [rats were placed into the test chambers for 10 min for 3 consecutive days] (2) Baseline/neutral stimulus [for 2 days animals were presented with 30 (90 dB) noise bursts with 30sec interstimulus interval (ISI)]. (3) Fear conditioning [10 light (4 sec)-shock (50-V, AC) pairings, with one sec overlap, were given with 4 min ITI. (4) Pre-extinction [24 hr after fear conditioning, rats were presented with 30 noise bursts. Afterwards, in order to observe the effect of conditioned fear, additional 20 light alone, 20 noise alone and 20 noise-light trials were given in a mixed sequence and videotaped]. (5) Extinction [rats received 60 4sec light exposures without shock (ISI of 30sec). (6) Post-extinction [24hr after the extinction, rats were presented with 30 noise bursts, then 20 light alone, 20 noise alone and 20 noise-light trials were given in a mixed sequence and videotaped. Time of freezing was recorded during the 4th and 6th phases of the experiment. FST procedure was employed for two consecutive days after fear conditioning experiments: 15 and 6 minutes respectively. Freezing and struggling durations were recorded. Data was analyzed by two-way repeated measures ANOVA with group (nicotine, saline) as between-subjects, session (pre-test, post-test) and stimulus (noise alone, light alone and combined) as within-subjects factors. Significant session [F(1, 10)=5.098, p=.04] and group [F(1, 61)=16,46, p =.02] effects were observed. Our results show that nicotine treated rats showed less immobility compared to controls in both pre- and post-tests and conditioned fear of both groups showed extinction during post-test. However, all stimuli elicited similar responses in both groups. FST data was analyzed by two-way repeated measures (ANOVA). A significant group-test interaction effect

[F(1, 61)=7,77, p=.02] was found. Nicotine group displayed less freezing and more struggling behavior compared to the controls. Overall, our results suggest an anxiolytic effect of nicotine in rats. Supported by institutional funds.

6

**“Environmental tobacco smoke exposure and hair nicotine concentration in non-smoking pregnant women in Korea”.**

Yu-Jin Paek.

Hye-Mi Chang, Cheol-min Lee\*.

Dept of Family Medicine, Hallym University Sacred Heart Hospital, \*Health Care Center, SNUH.

896, Pyungchon-dong, Dongan-ku, Anyang-si, Gyeonggi-do, 431-070, South Korea.

paek@hallym.ac.kr

Objectives: Maternal environmental tobacco smoke(ETS) exposure increases the adverse birth outcomes. We explored the status of maternal ETS exposure by self-reported questionnaires and hair nicotine concentration in Korean nonsmoking pregnant women. Methods : In this cross-sectional study, we surveyed 747 pregnant nonsmokers at last visit of gestation with questionnaires about ETS exposure and their hair nicotine which measures exposure during the past 3 months (i.e., the third trimester). Results: Mean gestational age was 36 ± 1.5 weeks. 203(27.2%) women answered they were exposed to ETS both at home and outside the home, whereas 24(3.2%) at home only and 422(56.5%) outside the home only. The ETS exposure categories by hair nicotine were defined as high (nicotine concentration ≥ 0.78 ng/mg; n = 187, the top quartile), and low as the reference category (< 0.78 ng/mg; n = 559). In logistic regression analysis, controlling for confounding, the adjusted odds ratios (OR) for high nicotine level were 6.28[95% confidence interval (CI), 2.09-18.88] in ETS exposure at home only, 5.58[95% CI, 2.64-11.80] in ETS exposure at both area, and 2.49[95% CI, 1.20-5.17] in ETS exposure outside the home only, compared to unexposed women at both area. Also, the risk of high nicotine level was higher in the low monthly income group(≤2,000 dollars) than high monthly income group(≥4,000 dollars) [adjusted OR = 1.95; 95% CI, 1.13-3.35 in low income group, and 1.10; 95% CI, 0.72-1.70 in medium income group]. Conclusions : The risk of high hair nicotine level was higher in the subjects of ETS exposure at home or outside the home or both and in the low socioeconomic group in pregnant nonsmokers in Korea.

7

### **“The impact of smoking on health-related and subjective quality of life: a general population survey”.**

Hanne Heikkinen.

Piia Jallinoja, Samuli I. Saarni, Kristiina Patja.

*National Public Health Institute -KTL, Department of Health Promotion and Chronic Disease Prevention.*

*Mannerheimintie 166, 00300 Helsinki, Finland.*

hanne.heikkinen@ktl.fi

**Objective:** In addition to smoking-related diseases, tobacco use is assumed to have a direct effect on quality of life. This study examined the association between subjective and health-related quality of life and smoking in men and women of discrete smoking groups in Finland. **Methods:** The data derive from the Health 2000 Survey, conducted in Finland 2000-2001. The two-stage, stratified cluster sample, representative of Finnish population, comprised 8 028 persons aged 30 or over. The participation rate was 93%. Four categories of smoking status derived from self-reported questions were used: daily, occasional, ex- and never-smokers. Respondents' health-related quality of life (HRQoL) was measured by 15D, a generic, comprehensive, 15-dimensional, standardized, self-administered questionnaire. The 15D, covering a variety of physical, emotional and social aspects, produces both HRQoL profile and preference based, single-dimensional health utility index. Subjective QoL was assessed by a single question measure capturing the respondent's own perception and estimation of his/her quality of life. **Results:** The present study showed that daily smokers have both lower HRQoL and subjective QoL than never-smokers among the Finnish adult population. HRQoL profiles shows that daily smokers do worse than never-smokers in a considerable number of the health dimensions. Daily smoking was significantly ( $p < 0.05$ ) associated with lower scores among men on dimensions, e.g. breathing, usual activities, discomfort and symptoms and vitality. Among women, daily smokers reported scored significantly lower ( $p < 0.05$ ) than never-smokers in dimensions of mobility, usual activities, depression, vitality, breathing and distress. For the subjective QoL rating sequential models were fitted in the regression analysis. The first model contained only the smoking status, followed stepwise by age, education, income, and marital status. The final model included HRQoL in order to minimise the influence of tobacco-related chronic diseases on the association between smoking behaviour and subjective QoL. Nevertheless, an adverse association between lower subjective QoL and daily smoking was maintained in both genders. Both the HRQoL and subjective QoL of ex-smokers also approach those of never-smokers. **Conclusions:** The results of the present study suggest that improved health is not the only benefit of smoking cessation; better quality of life and more fulfilling everyday living can also be expected. As the major health consequences of smoking usually manifest themselves only after several years of smoking, both health-related and subjective QoL measurements could be used as an intervention tool for motivating people to quit.

## **SESSION 2: ORAL COMMUNICATIONS ON CLINICAL RESEARCH**

**October 4th – 11.45-13.30 h**

1

### **“The effect of baseline dependence on treatment outcomes of varenicline for smoking cessation”.**

Karl Fagerström.

Cristina Russ, Carmen Arteaga.

*\*Fagerström Consulting Smokers Information Centre  
Kavelleristen 9, Berga Alle 1, Helsingborg, Sweden S-25452.*

karl.fagerstrom@swipnet.se

**OBJECTIVES:** Extent of nicotine dependence may influence quit attempt outcomes. The objective of these post-hoc analyses was to evaluate quit rates for varenicline, an  $\alpha_4\beta_2$  nicotinic acetylcholine receptor partial agonist designed for smoking cessation, by baseline Fagerström Test for Nicotine Dependence (FTND) scores. **METHODS:** Data were pooled from 2 identically designed, randomized, double-blind, multicenter trials using varenicline ( $n=696$ ) 1-mg twice daily or placebo ( $n=685$ ) for a 12-week treatment period followed by a 40-week non-drug follow-up period to assess long-term abstinence. Outcome measures included carbon monoxide-confirmed continuous abstinence rates (CARs) for Weeks 9-12, 9-24 and 9-52. Influence of nicotine dependence levels on abstinence outcomes was assessed using a logistic regression model including treatment, study, FTND scores as a continuum, and treatment by FTND scores interaction terms. Results were compared with outcomes from models based on FTND scores as a categorical variable either  $\geq$  or  $<$  median value, or categorized as low (0-3), moderate (4-6), or high dependence (7-10). **RESULTS:** For continuum FTND scores, CARs were higher in varenicline-treated patients versus placebo for each FTND score based on the logistic regression model. Although nicotine dependence levels were inversely correlated with CARs (eg, Weeks 9-24 CARs decreased from low [FTND=1; varenicline: 43.4%; placebo: 19.4%] to high dependence [FTND=10; varenicline: 17.2%; placebo: 6.2%]), no significant FTND score by treatment interaction was detected. The other 2 approaches for assessing the influence of nicotine dependence levels on abstinence outcomes confirmed these findings. Weeks 9-24 CARs for FTND scores  $\geq$  median were lower (varenicline: 25.6%; placebo: 11.0%) than those for FTND scores  $<$  median (varenicline: 36.8%; placebo: 13.1%). Consistently, Weeks 9-24 CARs decreased as nicotine dependence levels changed from low (varenicline: 37.8%; placebo: 13.5%) to moderate (varenicline: 30.5%; placebo: 13.8%) to high (varenicline: 21.8%; placebo: 7.0%). Similar patterns were observed in Weeks 9-12 and 9-52 CARs. **CONCLUSIONS:** Compared to placebo, varenicline significantly improves CARs at end of treatment and through to Week 52 (Weeks 9-24 presented here), regardless of baseline nicotine dependence level. These analyses suggest that higher levels of baseline nicotine dependency result in lower CARs, as observed in three different approaches to analyzing FTND scores as categorical or continuous variables. As observed

with other treatment options, when treated with varenicline, smokers with higher dependence have greater difficulty in quitting than smokers with lower dependence. To further improve abstinence in this group of smokers, it is tempting to consider more intensive approaches such as higher doses.

## 2 **“Pre-cessation treatment with NRT: a randomized trial”.**

Jean-Francois Etter.

Jacques Cornuz, Philippe Huguélet, Thomas pernegger.  
*University of Geneva. 1, rue Michel-Servet. Switzerland.*  
Jean-Francois.Etter@imsp.unige.ch

**Objective.** To test whether a treatment of 4 mg nicotine gums was more effective when it started 4 weeks before the quit date than when it started on the quit date. **Participants.** 313 daily smokers recruited through the internet, by ads in newspapers and by physicians in private practice in Switzerland, in 2005-2007. **Intervention.** In the pre-cessation treatment condition, participants received by mail 4 mg nicotine gums during 4 weeks before and 8 weeks after their target quit date, and they were recommended to gradually decrease their cigarette consumption by half before quitting. In the post-cessation nicotine condition, participants received nicotine during 8 weeks after their target quit date and were instructed to quit abruptly. In both groups, participants were instructed to use 10 gums per day. Instructions were limited to booklets sent by mail. **Measurements.** Self-reported smoking abstinence during the 7 days and the 2 months before the end-of-treatment survey, that took place 2 months after the quit date. **Results.** Two months after the quit date (end-of-treatment), self-reported 7-day abstinence rates were 56.5% in the pre-cessation condition and 54.3% in the post-cessation condition ( $p=0.46$ ). Self-reported 2-month abstinence rates were 49.4% in the pre-cessation condition and 46.7% in the post-cessation condition ( $p=0.92$ ). **Conclusions.** Quit rates were high in both groups and there was no statistically significant effect of a pre-cessation treatment with 4 mg nicotine gums.

## 3 **“Cognitive and motivational predictors of relapse to smoking: A prospective study”.**

Jane Powell.

Alan Pickering, Lynne Dawkins, Robert West, John Powell.  
*Goldsmiths, University of London. Lewisham Way, New Cross, London SE14 6NW. UK.*  
j.powell@gold.ac.uk

**OBJECTIVES:** This prospective study was designed to test hypotheses derived from contemporary neurobiological models of addiction which implicate reward pathways and inhibitory control processes, determining whether cognitive and motivational impairments measured during acute abstinence predict relapse to smoking within the first three months of cessation. Relationships with clinical measures of smoking dependence, amount smoked, mood prior to cessation, and motivation to quit (StopMot) were also explored. **METHODS:** 142 smokers were assessed after 12 hours abstinence,

shortly prior to commencement of a cessation attempt. Experimental indices included cue reactivity (CueReac), attentional bias to pleasurable, aversive, and smoking-related cues (PleasBias, AversBias, and SmokeBias), response to financial reward (RewResp), motor impulsiveness (MotImp), and oculomotor response inhibition (antisaccades; AS-Accuracy). Smoking status was assessed after 7 days, 30 days, and 3 months, with self-reported abstinence verified by salivary cotinine. **RESULTS** 47% of participants relapsed within the first week, 62% within a month, and 75% by three months. Of the smoking/dependence predictors, the strongest at each point was salivary cotinine (SalCot); subjective measures of dependence such as the FTND did not explain any additional variance in outcome. Neither baseline mood nor gender was predictive; but StopMot and all of the experimental indices except RewResp were significantly associated with outcome at one week. Hierarchical logistic regression found SalCot, StopMot, SmokeBias and AS-Accuracy to make significant unique contributions, jointly accounting for approximately 30% of the variance in outcome. At one month, SalCot, SmokeBias, MotImp, StopMot, and CueReac were all individually predictive; the first three of these exerted additive influences, jointly explaining about 17% of the variance. Effects were weaker by three months, but SalCot, CueReac, and MotImp were still all significantly associated with smoking status; SalCot and MotImp together accounted for about 12% of the variance in outcome. **CONCLUSIONS** These data provide support for the hypothesised involvement of attentional biases towards motivationally salient stimuli and deficits of inhibitory control in relapse to smoking. The observed effects were partially independent of amount smoked, severity of dependence, and motivation to quit, and were not secondary to withdrawal symptoms or mood disturbance. Predictive power was greatest for outcome at 7 days, suggesting that intervention might valuably focus on early identification of would-be quitters with these specific risk factors, on equipping them with relevant strategies to combat these particular risks, and on supporting them particularly intensively during this early period.

## 4 **“Does cue induced brain activation predict outcome in smoking cessation treatment”.**

Christian G. Schütz.

*University of Bonn, Department of Psychiatry and Department of Radiology. Sigmund-Freud-tr. 25, 53105 Bonn, Germany.*  
christian.schuetz@ukb.uni-bonn.de

**Objectives:** Imaging studies on substance dependence have identified the significance of the prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and the amygdala for drug-related cue reactivity (Wilson et al., 2004). Similar findings were reported for tobacco-related cues (Due et al., 2002; Brody et al., 2002). Assuming a relevance of cue reactivity for relapse, the aim of this study was to determine whether the activity in these pre-established brain regions upon visual nicotine-related cues is able to predict the outcome of nicotine cessation treatment. **Methods:** 18 dependent smokers, consuming at least 15 cig/d and 20 healthy

controls were included in a cue-reactivity paradigm study consisting of six video sequences with smoking-related cues and six video sequences with neutral scenes. The 30 seconds videos clips were presented in random order. All participants in the study had agreed to participate in a six months nicotine dependence treatment program. Of the 18 smokers, nine (age: 38.9 +/- 6.9 yrs; 5 male, 4 female) relapsed during the treatment program ("relapse group"), while nine (age: 40.3 +/- 7.4 yrs; 3 male, 6 female) remained abstinent ("abstinence group"). The fMRI-assessments were performed on an Achieva 3.0T whole body MRI system (Philips, Best, Netherlands). Further technical details were as follows: Birdcage quadrature headcoil, GE-Single Shot EPI (TE/TR/Flip=35/3000/90°), 3.6x3.6x3.6mm<sup>3</sup>, 3 runs with each 245 dynamic scans. Preprocessing and statistical analyses were conducted with SPM2. Brain activation of relapsed smokers and abstinent smokers was compared by calculating the contrast "cue videos minus neutral videos". Results: The categorical comparison revealed enhanced activity in the "relapse group" in the DLPFC (bilateral), OFC (bilateral), ACC, supplemental motor area and parietal cortex ( $p < 0.005$ , uncorrected). Conclusion: Consistent with our hypothesis, we were able to show that brain regions associated with nicotine related cue response were differentially more activated in smokers who relapsed during the six month cessation treatment compared to smokers remaining abstinent. These findings support the known role of frontal and cingulate regions in cue responsivity. Relapsing subjects with less activation in these regions resembled reported activation patterns of non-treatment seeking substance dependent subjects (Wilson et al., 2004). These data indicate that brain activity levels in these specific regions may serve as a predictor for treatment outcome. References: Wilson SJ, et al. (2004): *Nature Neuroscience*, 7(3), 211-214 Due DL, et al. (2002): *Am J Psychiatry*, 159(6), 954-960 Brody AL, et al. (2002): *Arch Gen Psychiatry*, 59, 1162-1172.

## 5

### **"Patterns of change in reward motivation, response inhibition, mood and craving over 3 months of smoking abstinence".**

Lynne Dawkins.

Jane Powell, Alan Pickering, John Powell, Robert West.

*University of East London.*

*School of Psychology, Romford Road, Stratford, University of East London, London. UK.*

*l.e.dawkins@uel.ac.uk*

**OBJECTIVES:** We have previously demonstrated that during acute (12 hour) abstinence, smokers exhibit lowered reward motivation and impaired response inhibition relative to functioning after recent nicotine consumption (Dawkins et al., 2006; 2007). Coupled with the ubiquitously-reported increases in craving, negative mood and withdrawal symptoms during early abstinence, the smoker attempting to quit faces a daunting challenge. This prospective study explores whether these impairments recover over three months of sustained abstinence. **METHODS:** 145 smokers completed a 12-hour abstinent baseline assessment; 107

were then randomly allocated to 'quit' and 38 to 'continue smoking'. All were re-tested after 7 days, 1 month and 3 months. 34 of the 'quitters' maintained continuous (cotinine-verified) abstinence to 3 months and 31 of the continuing smokers completed all 3 follow-up assessments. Assessments included indices previously demonstrated in this cohort of smokers to be sensitive to the effect of nicotine vs. acute abstinence. These included measures of reward motivation (SHAPS, CARROT, Stroop); tasks of response inhibition (antisaccade task; CPT) and clinical indices of mood (HADS) and craving. Successful quitters' scores were compared with those of the continuing smokers, who were tested after ad libitum smoking. **RESULTS:** Abstinence-related anhedonia (SHAPS) and diminished reward responsivity (CARROT) showed significant improvement and plateaued after a month of abstinence, not differing from the scores of continuing smokers. Interference from pleasure-related words on the Stroop task did not change significantly over time in abstainers, but nor did it differ from continuing smokers. Anxiety, depression and craving all declined from acute abstinence to 1 month of cessation and by this point were equivalent or, lower than, the levels reported by continuing smokers. Response inhibition (antisaccade accuracy and CPT motor errors) did not show improvement over 3 months of abstinence. However, it is notable that most of the participants with more severe impairments on these indices at baseline (i.e. after 12 hours abstinence) went on to relapse; thus it was not possible to assess recovery of function in the smokers showing the greatest abnormalities. **CONCLUSIONS:** Smokers able to maintain continuous abstinence to 3 months showed an improvement in reward motivation, mood and craving. Response inhibition remained at baseline levels, but this reflected their relatively unimpaired functioning during acute abstinence relative to participants who went on to relapse. We conclude that appetitive processes and related affective states do appear to 'recover' in those smokers with sufficient inhibitory control to remain nicotine-free for 3 months.

## 6

### **"Long-term Abstinence is Enhanced by Immediate and Delayed Quitting with Varenicline vs Bupropion".**

David Gonzales.

Douglas E Jorenby, Carmen Arteaga, Theodore C. Lee.

*OHSU Smoking Cessation Center (Gonzales)*

*Health & Sciences University, Portland, OR 97239. USA.*

*Gonzales@ohsu.edu*

**Objective:** To analyze quitting and abstinence patterns from 2 smoking cessation studies of varenicline vs bupropion-SR, or placebo. **Methods:** Pooled data from 2 identically-designed randomized studies were analyzed from target quit date (TQD) through 12 weeks of treatment and 40 weeks of post-drug follow-up with varenicline 1mg BID (n=696), bupropion-SR 150mg BID (n=671), or placebo (n=685), plus brief behavioral treatment. Abstinence was confirmed by carbon monoxide levels of  $\leq 10$  ppm at weekly visits through Week 12 and clinic visits through Week 52. The primary endpoint was continuous abstinence rates (CARs) for Weeks 9-12. Subjects continuously abstinent for Weeks

9-12 were classified as either immediate quitters (ImQs; abstinent at all visits since TQD) or delayed quitters (DQs; smoking  $\geq 1$  visit for Weeks 2-8). Declines in the percent remaining continuously abstinent over time from Weeks 12-52 were also analyzed. Results: The 4-week CARs for Weeks 9-12 were varenicline (44.2%) vs bupropion-SR (29.7%;  $p < 0.0001$ ) or placebo (17.7%;  $p < 0.0001$ ). Of the total number in each treatment group, 24.0% of varenicline subjects were ImQs vs 18.0% for bupropion-SR ( $p = 0.0072$ ) and 10.2% for placebo ( $p < 0.0001$ ). DQs were 20.0% for varenicline vs 11.6% for bupropion-SR ( $p < 0.0001$ ) and 7.5% for placebo ( $p = 0.0092$ ). The percentage of subjects achieving continuous abstinence at each visit through Week 8 and remaining so through Week 12 accumulated with each visit regardless of treatment, with increases greater for varenicline vs bupropion-SR or placebo. The rate of decline in continuous abstinence from Week 12 was similar across treatments and quitting patterns. Both ImQs and DQs contributed to CARs for all treatment groups for Weeks 9-52 with ImQs more likely than DQs to maintain abstinence for Weeks 9-52 ( $p = 0.001$ ). Conclusions: The percent achieving abstinence increased following TQD through Week 8 suggesting a benefit for sustaining all treatments regardless of therapy. Varenicline significantly enhanced these patterns of quitting with higher percentages represented in each pattern compared with bupropion-SR or placebo. The slope of decline in continuous abstinence after treatment was unaffected by treatment type; therefore, achieving maximum levels of continuous abstinence for as few as 4 weeks at the end of treatment appears to have a significant positive effect on long-term abstinence outcomes. The more robust effects of varenicline on immediate and delayed quitting patterns may represent additional evidence of varenicline's dual agonist/antagonist mechanism of action at  $\alpha_4\alpha_2$  nicotinic receptors. The studies and analyses were supported by Pfizer.

7

**"Efficacy, safety, and effect on weight of adding a nicotine patch to rimonabant for smoking cessation: a randomized controlled trial".**

Nancy Rigotti, MD.  
 Yuchiao Chang, PhD; David Gonzales\*, PhD; Lowell Dale\*\*, MD; Daniel Lawrence\*\*\*, PhD.  
*Harvard Medical School; \*Oregon Health & Science University; \*\*Mayo Medical Center; \*\*\*University of Wisconsin, for the CIRRU Study Group. Tobacco Research & Treatment Center, Mass. General Hospital, 50 Staniford St., Boston, MA 02114, USA.*  
 nrigotti@partners.org

Objective: To improve smoking cessation outcomes while preserving reduction of post-cessation weight gain, we added the nicotine patch to rimonabant, a CB-1 receptor antagonist. Methods: A 15-site randomized double-blind placebo-controlled trial in 755 smokers tested the efficacy and safety of adding nicotine patch to rimonabant. Open-label rimonabant (20 mg/day) was given for 9 weeks. One week after starting rimonabant, 735 subjects still taking the drug were asked to stop smoking and randomly assigned to

nicotine patch (R+NRT, n=369) or placebo (R+PCB, n=366) for 10 weeks (21 mg, 8 weeks; 14 mg, 1 week; 7 mg, 1 week) followed by 13 weeks off drug. Subjects had brief cessation counseling at each visit. Primary endpoint was CO-validated sustained abstinence for weeks 6-9. Other endpoints were 7-day point prevalence abstinence (CO-validated during treatment; self-report at 24-week follow-up), sustained abstinence from week 6-24, change in body weight, and adverse events (AE). Results: Smoking cessation rates were higher for R+NRT, compared to R+PCB, by all outcome measures: CO-validated sustained abstinence for weeks 6-9 (39.0% vs 21.3%; OR 2.36; 95% CI 1.71-3.27), CO-validated 7-day abstinence at end-of-treatment (51.8% vs 28.4%, OR 2.70, 95% CI 1.99-3.67), self-reported 7-day abstinence at 24-week follow-up (42.3% vs 27.3%, OR 1.95, 95% CI 1.43-2.65), and sustained abstinence for weeks 6-24 (25.8% vs. 15.0%, OR 1.96, 95%CI 1.35-2.84). Among quitters, mean weight gain at end-of-treatment was 0.04 kg (R+NRT) vs. 0.49 kg (R+PCB)( $p = 0.15$ ); results did not change when analysis was limited to smokers with a high level of concern about weight gain. R+NRT and R+PCB groups did not differ in rates of serious AEs (2.5% vs 2.2%), or in rates of stopping drug due to AE (6.8% vs 7.2%). Conclusion: Adding nicotine patch to rimonabant increased smoking cessation rates at 24 weeks, was well tolerated, and preserved rimonabant's reduction of post-cessation weight gain, even among smokers who were concerned about weight gain. Combining rimonabant and nicotine patch may be a new treatment option for smokers who are concerned about weight gain after stopping smoking. Funding: Sanofi-Aventis. Statistical analysis by Massachusetts General Hospital Tobacco Research and Treatment Center.

8

**"Effect of Jarsin® or Cr3+ on morning saliva cortisol in quitting smokers, a stress treatment effect?"**

Mike Franklin (1).  
 Paul N Aveyard (2), Isabel Bermudez (1), Jackie Ingram (2)  
 1. School of Life Sciences, Oxford Brookes University (2) University of Birmingham. (1) Oxford OX3 0BP, UK; (2) Birmingham B15 2TT, UK.  
 mfranklin@brookes.ac.uk

Objectives Stopping smoking is difficult and causes stress. Our pilot study (1) demonstrated that the early morning rise of salivary cortisol is a good measure of stress following temporary smoking abstinence. Reduction of stress may make it easier to quit. Can SJW or chromium reduce stress and make quitting easier? Methods Studies show that morning waking salivary cortisol is a good measure of stress (2). We monitored morning salivary cortisol prior to and during treatment in four groups of quitting smokers. This is a double-blind placebo controlled trial. Subjects (n=144) aged 18+ were randomised to receive St John's wort (Jarsin, SJW) + chromium, SJW + placebo chromium, chromium + placebo SJW or placebo chromium + placebo SJW respectively. Treatment was administered 10 days prior to quitting and for up to 12 weeks after. Saliva cortisol was monitored at -10, 0 (quit day), 1, 3, 7, 14 and 28 days. Saliva samples were

collected at 15 minute intervals over 1 hour following waking. Cortisol was analysed by radioimmunoassay. Questionnaires for subjective measures of stress were also taken. This data has not been processed, but will become available and will also be presented. We may also have measures of quit success rates at the time of presentation if the data gathered has been analysed. Results Preliminary results (n=6-9 per group) show that chromium and SJW alone significantly reduce morning salivary cortisol as measured by the AUC of the time v cortisol curve (p=0.02, 0.13, 0.01, 0.03, 0.04 and 0.04 for SJW), (p=0.47, 0.013, 0.01, 0.07, 0.04 and 0.015 for chromium) respectively for days 0, 1, 3, 7, 14 and 28 versus day 0 (unpaired t-test). Whilst for SJW + chromium generally showed a reduction on all days but was significance on only some whilst placebo + placebo showed no effect. Full statistical analysis will be presented. Conclusions From initial observations we conclude that both SJW and chromium treatments on their own reduce morning salivary cortisol and probably stress levels too. We are unable to say whether the combination of SJW and chromium also reduces these measures. Placebo treatment demonstrated no measurable effect. Initial results suggest that SJW and chromium may show efficacy for smoking cessation in our trial. References 1. Franklin M et al., (2006) *Int J Neuropsychopharmacology* 9(1):S101. 2. Pruessner K et al., (1997) *Life Science* 1997 61: 2539-2549. Study was supported by CRUK and SJW extract (Jarsin) and placebo was supplied by Cassella-med GmbH and Co, KG (Berlin).

**9**  
**"Predictors of Change in Smoking following Emergency Hospitalization for Chest Pain".**

Beth Bock, PhD.  
 Raymond Niaura, PhD; Joseph Fava, PhD.  
*Brown Medical School.*  
*Miriam Hospital, Coro Building 5th floor, One Hoppin St., Providence RI 02903, USA.*  
 Beth\_Bock@Brown.edu

Objective: We examined predictors of smoking cessation among 543 adult smokers experiencing chest pain who were admitted to a hospital emergency department for 24-hour observation to rule out myocardial infarction. Methods: Smokers (n=543) were randomly assigned to one of two conditions: (1) a Tailored intervention (Tailored, n=271) with brief advice to quit from a physician, and a 45-minute counseling session given by a counselor trained in Motivational Interviewing, or (2) Usual Care (UC, n=272). All subjects choosing to quit were provided with 8-weeks nicotine patch therapy and were telephoned on their quit day and 1 and 4 weeks later. Smoking rate, nicotine dependence, motivation to quit, temptations to smoke (habit, social, mood), and other variables relevant to smoking cessation were assessed at enrollment and six month follow-up. Results: 53% of participants were men; average age was 47 years (±11.2); most participants were Caucasian (69%), 12.4% were black, 10% were Hispanic/Latino. Women were significantly older than men in our sample (p<.05). The average smoking rate at enrollment was 18.9 (±12.6) cigarettes per day. Nearly all participants

had made previous quit attempts but 59% had never used nicotine replacement medications. 17% were planning to quit in the next 30 days, 10% in the next 6 months, and 41% had no plans to quit smoking. The mean Fagerstrom score was 5.0 (moderate dependence). Using a 5-point Likert scale indicating how much participants thought their chest pain was related to their smoking, 33% said that their smoking was related to their chest pain "a little" or "not at all." A GEE repeated measures analysis showed a significant effect for treatment assignment (p=.029) for differences in 7-day point prevalence abstinence at follow-up, with the odds of abstinence higher for the Tailored group compared to Usual Care (OR=1.62, 95% CI=1.05-2.50). There were also non-significant trends for Time (p=.71) and a Time x Group interaction (p=.68). Demographic and baseline psychosocial variables were examined as potential predictors of cessation at follow-up using a multivariate logistic regression. Individuals who were older (OR=.96, CI=.93-.99), less tempted by negative affective situations (OR=.88, CI=.78-.99), more motivated to quit smoking (OR=.83, CI=.71-.96), and strongly believed their chest pain was related to their smoking (OR=.49, CI=.26-.91) were less likely to be smoking. Discussion: Each year millions of smokers are admitted to emergency departments with chest pain. Providing a brief intervention during this sentinel health event appears to boost quit rates over care as usual.

**SESSION 3: ORAL COMMUNICATIONS ON EPIDEMIOLOGY /HEALTH CARE/ OTHER RESEARCH**  
**October 5th – 9.30-11.15 h**

**1**  
**"Early onset of smoking as a predictor of cannabis use: Modifying role of behavioral symptoms".**

Tellervo Korhonen.  
 Anja C. Huizink, Danielle M. Dick, Lea Pulkkinen, Richard J. Rose, Jaakko Kaprio.  
*University of Helsinki, Department of Public Health.*  
*PO Box 41, 00014 Helsinki, Finland.*  
 tellervo.korhonen@helsinki.fi

Objectives: Early exposure to tobacco predicts cannabis use during adolescence. However, it is suggested that behavioral problems may modify this association. Our aim was to explore whether behavioral problems interact with age of smoking onset in prediction of subsequent cannabis use among Finnish adolescents. Methods: We used longitudinal data of the FinnTwin12 study with baseline at age of 12 and follow-up at age of 17, complete data being available from 1,693 boys and 1,809 girls. The outcome variable was self-reported ever use of cannabis or similar drugs. The main predictor was age of cigarette smoking initiation, categorized as early (by age of 12) and late (after age of 12) onset. Behavioral symptoms were teacher's ratings concerning inattention, hyperactivity-impulsivity and aggression. Controlling for other individual predictors

of cannabis use as confounders, we analyzed the main effect of smoking onset and interactions with behavioral symptoms as tertiles (low/medium/high scores). Results: Twelve percent of boys and 15 % of girls ( $p=.02$ ) had used cannabis or similar drugs by age 17. The adjusted main effect of early smoking onset on cannabis use was very strong both among boys (OR=29.5; 95%CI=9.2-94.8) and girls (OR=16.9; 95%CI=7.1-40.1). When the continuous behavioral symptom scores were added into the model this effect was only slightly attenuated. The effect of early smoking onset remained significant in the causal analysis among 198 twin pairs discordant for cannabis use (OR=9.7; 95%CI= 2.0-47.7). We found significant interactions between early smoking onset and all behavioral symptoms among boys, but among girls, for inattention symptoms only. The effects of early smoking were further analyzed among the subgroups with low, medium and high symptom scores. However, due to no cannabis use among never smokers within some of the subgroups, the relative influence of early versus late smoking onset on cannabis use could be tested by intensity of behavioral symptoms reliably only among subjects who had ever smoked. Thus, boys ( $n=1,356$ ) with high aggressiveness (OR=2.1; 95%CI=1.3-3.4), high inattention (OR=2.0; 95%CI=1.2-3.6) and medium impulsivity (OR=2.2; 95%CI=1.2-4.1) demonstrated two-fold risks of early smoking onset on cannabis use, whereas boys with milder symptoms did not show significant early smoking effects. Among girls ( $n=1,313$ ), similar modification was seen for inattention symptoms only, the significant influence of early smoking onset being restricted among ever smokers with medium inattention symptoms (OR=2.2; 95%CI=1.1-4.1). Conclusion: We conclude that particularly among boys behavioral symptoms seem to modify the influence of early smoking on cannabis use.

## 2

### **"Onset of tobacco use and transition to other drug use among college undergraduates in north of Iran".**

Zahra Mohtasham Amiri.

Abbas Jafari shakib.

*Department of Community Medicine, School of Medicine, Guilan University of Medical sciences, Rasht.*

*P.O Box 41635/3381 Rasht, Iran.*

mohtashamaz@yahoo.com

Objective: To estimate the cumulative probability of occurrence of first use of tobacco, and the risk of transition to illegal drugs (marijuana, cocaine, and heroine, among others), in adolescents and young adults, in Iran. MATERIAL AND METHODS: We conducted a cross sectional study of 3958 college students with mean age of  $22.2 \pm 3.5$  years selected from public and private universities by probabilistic multistage sampling in 2005. Data were collected on sociodemographic, health status, and substance abuse variables, using a validated self-applied questionnaire. Analysis was done with SPSS 11.5 software and  $\chi^2$  test and student t test were used. Results: 3700 students (93.5%) responded. 1800 students (49%) were male and 1966 students (53.1%) were from private universities. 722 students (19.5%) were current smokers. The prevalence

of illicit drug use was 7.6 % ( 282 students) that the most prevalent substances were Ecstasy (4.3%), opium (2.7%) and cannabis (2.4%). The mean age of onset of cigarette smoking was  $15.2 \pm 2.1$  years, starting of Ecstasy use  $22.6 \pm 3.1$  and other illicit drugs was  $18.6 \pm 2.8$ . Tobacco users were at greater risk of starting drug use than nonusers (OR=14.42; 95 % confidence interval [CI] = 10.62-19.74). Conclusions: Study findings suggest that interventions to decrease drug abuse should go together with efforts to delay initiation of tobacco use. The innovative method used in this study yields epidemiologic evidence relating early use of tobacco with initiation of illegal drugs in youth.

## 3

### **"Exploring personal meanings around smoking and smoking cessation strategies among health workers".**

Lumira Lagapa.

Alvin Concha, Maria Elinore Alba-Concha, Lillian Lao.

*Davao Medical Center.*

*Dept of Family and Community Medicine, Davao Medical Center, Bajada, Davao City 8000, Philippines.*

alvinconcha@yahoo.com

Objective: This study aimed to explore personal meanings around smoking and perceptions on smoking cessation strategies among health workers in a tertiary hospital. [Methods] A qualitative methodology was employed using focused group discussions and key informant interviews. Ten ever-smoker health personnel were purposively selected to share diverse vignettes around starting, sustaining and planning to quit smoking, and personal reactions to present approaches towards smoking cessation. The results of this study were based on the analysis of transcripts of two focus group discussions and two key informant interviews using the grounded theory approach. [Results] A recurring theme among the vignettes shared was the hedonistic benefits of smoking. Participants repeatedly pointed out the physical pleasure derived from the taste of cigarettes, the smell and sight of a well puffed-out smoke and the warmth that smoking affords during cold weather. These self-gratifying sensations were also claimed to accompany emotional satisfaction and bring about relief from stress, anger or boredom. Participants also expressed disinterest in smoking cessation strategies such as anti-smoking policies, ads and routine medical advice, stating that they do not gain direct benefits from these strategies, as compared to sustaining smoking. With the advent of cutting edge pharmacological approaches and far-reaching media campaigns towards a tobacco-free world, personal meanings around smoking rarely get considered in smoking cessation strategies. [Conclusion] This study exposes important considerations that focus on entrenched personal emotional attachments to smoking, and directly implicates smoking cessation strategies that offer no more than information dissemination, pharmacological treatment and behavioral interventions.

#### 4 "A qualitative evaluation of a smoke-free policy in the workplace".

Molinar Roberta\*.

Giordano\*, L., Senore\*, C. Dotti\*\*, A., Bosco\*\*, G.

\*CPO Piemonte, \*\*Spresal ASL7. Via San Francesco da Paola 31, 10123 Torino. Italy.

roberta.molinar@cpo.it

**Introduction** - In January 2006, a large Italian company introduced a smoking policy in its factory in Turin involving 500 employees, most of whom are women. **Objectives:** 1) to describe both the employees' and the management's perception of the smoke-free policy (included the cessation programme), 2) to assess the level of satisfaction and compliance with the smoke-free policy among employees and management, 3) to identify strengths and weaknesses of the smoke-free policy. **Method:** Focus group technique using a semi-structured group session, with a moderator and an assistant, was used to gather data. Participation in the focus group was voluntary. The 4 focus groups were composed as follows: a) group 1 (n = 12): smoker employees attending the cessation programme; b) group 2 (n = 12): smoker employees not attending the cessation programme; c) group 3 (n = 12): non smoker employees; d) group 4 (n = 8): management and supervisors both attending and not attending the cessation programme. The four focus groups were conducted in the workplace during normal working hours in January 2007 and averaged 90 minutes in length. All sessions were audiotaped. Data were subjected to a content analysis. A categorization scheme was developed by three independent judges. **Results:** The preliminary analysis of the transcripts revealed: a) a high overall satisfaction with the cessation programme and the temporary restoration of designed smoking areas, b) the need of more shared goals among the members of the workplace committee (Management, Labor Unions, ecc.), c) too unrealistic Management's expectations with regard to the exposure to EST in the workplace and the decrease in smoking among employees, d) insufficient enforcement and consequences of non compliance and violations, e) the need of clearness about the goals of the smoke-free policy (e.g. a smoke-free workplace vs. a smoker-free workplace; more productivity for the employer vs. a better health status for employees). Further analysis are in progress. **Conclusions:** The data from these focus groups underline the importance of: 1) helping the management in planning and designing a policy that fits his workplace situation and monitoring it periodically, 2) establishing and maintaining a clear communication with regard to smoking policy, 3) not only providing information and support to smokers but also making a real smoke-free workplace, 4) a full support to the policy by the management and the staff, 5) ensuring proper enforcement of the policy.

#### 5 "Cost-effectiveness of Varenicline for Smoking Cessation in Five European Countries".

Maureen Rutten-van Molen,1\*.

Martine Hoogendoorn 1, Andrej Rasch 2, Kristian Bolin 3.

\*Presenting author.

1 Institute for Medical Technology Assessment (iMTA), Erasmus MC, Rotterdam, The Netherlands; 2 Health Economics and Health Management (AG 5), Faculty of Health Sciences, University of Bielefeld, Bielefeld, Germany; 3 Lund University Centre for Health Economics, Lund, Sweden.

M Rutten-van Molen, Ph.D. Erasmus MC. Institute for Medical Technology Assessment -P.O. Box 1738. 3000 DR Rotterdam. The Netherlands.

m.rutten@bmg.eur.nl

**Background:** Varenicline is an innovative pharmacological treatment designed specifically for smoking cessation. As a partial agonist at the  $\alpha_4\beta_2$  nicotinic acetylcholine receptor, varenicline has the potential to reduce craving and withdrawal symptoms, while blocking the rewarding effects of nicotine through its antagonist action.

**Objective:** To evaluate the cost-effectiveness of varenicline to support smoking cessation across five European countries.

**Method:** The Benefits of Smoking Cessation on Outcomes Model (BENESCO), a model developed to simulate the consequences of smoking cessation for a nationally representative cohort of adult smokers, was used to estimate the long-term health and economic benefits of smoking cessation for smokers in the Netherlands, Sweden, Germany, the United Kingdom and Belgium making a single quit attempt at the beginning of the simulation. For varenicline, the 1-yr abstinence rate was 22.5% compared with 15.7%, 15.5% and 5% for bupropion (based on RCT's comparing varenicline and bupropion), nicotine replacement therapy (NRT) (based on meta-analysis) and unaided cessation (based on literature), respectively. Other input data were taken from national sources and analyses followed national pharmacoeconomic guidelines.

The model compared cost per quality-adjusted life year (QALY) gained over lifetime between a cohort of smokers treated with varenicline and the same cohort either untreated (unaided cessation) or treated with bupropion or NRT. In addition, the difference between the interventions in cases of smoking-related diseases prevented (lung cancer, CHD, stroke, and COPD) is presented for the Dutch model.

**Results:** Incremental costs per QALY gained for varenicline versus unaided cessation, bupropion and NRT are shown in the table below. Varenicline was both more effective and less costly as compared with bupropion and NRT. Per 1000 Dutch smokers making a quit attempt with varenicline instead of unaided, there are 32 fewer cases of smoking-related disease. The number of smoking-related diseases prevented per 1000 smokers for varenicline compared with bupropion and NRT was 12 and 14, respectively.

**Conclusion:** Varenicline is the most cost-effective treatment for smoking cessation in the countries studied.

This study was funded by Pfizer Inc.

6

**“Normalizing and Resocializing:TTC’s efforts to introduce lights and prevent smoking bans in Spain”.**

Richard D. Hurt.

Monique E. Muggli, Jon O. Ebbert, Carlos A. Jimenez-Ruiz, Juan A. Riesco Miranda.

*Mayo Clinic.*

*NDC 200 1st Street SW Rochester, MN 55905, USA.*

*mmuggli@comcast.net*

Internal corporate records from the multinational cigarette manufacturers produced during U.S based litigation discloses that the tobacco companies have long focused on developing and expanding their reach into the market in Spain. We reviewed thousands of documents at the Minnesota and Guildford, UK tobacco depositories produced by British American Tobacco (BAT) related to Spain and the Canary Islands. In the 1980’s, R J Reynolds used an elaborate marketing effort to introduce the Camel brand into the Canary Islands and in one year spent 1000 USD for every man woman and child in the islands promoting their product. In more recent years, documents show that BAT sought to increase profits and compete with the globalization of Philip Morris’ Marlboro in Spain by normalizing the Spanish market to low tar low nicotine products and engaged in “Resocialisation of Smoking” efforts by promoting ineffective ventilation technology to hospitality outlets, also known as the HORECA market, with the aim of delaying public smoking restrictions. BAT also heavily branded HORECA outlets to target young people. BAT’s corporate research carried out in markets outside of Spain noted that the company’s lights brands would “attract younger smokers” because there was a “higher propensity for younger smokers to start with Light offers,” “youth saw lights as separation from the adult world,” and “peer pressure amongst youth plays a very important role” in smoking initiation. BAT Espana’s consumer research, however, found surprising resistance to low tar cigarettes: “. the Spanish consumer does not perceive the low tar segment as an alternative. They quit instead.” Nonetheless the company continued to work toward normalizing the light segment because “establishing a success model in an underdeveloped low tar market like Spain is crucial to the geographic expansion of the [low tar low nicotine] brand.” BAT Espana’s HORECA strategies were concentrated in Madrid and Barcelona and were seen as essential to reach consumers due to the cultural uniqueness that HORECA outlets have in Spain. For example, BAT Espana reported to BAT headquarters that “the Spanish people seem to use their HORECA more than they use their homes as it seems to fill a social need of the culture. They know how to live.” Through the use of previously secret tobacco company documents, we hope to expand existing document research and inform the tobacco control community in Spain of the methods being used and propose strategies to confront these efforts.

7

**“Tobacco use in Finland and in Sweden 1988-2005”.**

Kristiina Patja.

Samu Hakala, Paul Nordgren, Margaretha Haglund.

*National Public Health Institute, KTL.*

*Mannerheimintie 166, 00300 Helsinki. Finland.*

*kristiina.patja@ktl.fi*

Objective: Sweden and Finland, neighbouring countries in Scandinavia have many common features in health and social policy and a few distinctions in tobacco policy, besides on oral tobacco. This paper analyses the differences in tobacco use between these two countries from 1988 to 2005. Methods: representative datasets from both countries with age groups 18 to 64 was used to compare tobacco use. Tobacco use included smoked tobacco and oral tobacco. The study included years 1988/89, 1996/97 and 2004/05. Results: Men in Sweden use tobacco products daily more often than men in Finland. Among women smoking prevalence has decreased significantly in Sweden, but no real change in daily smoking among women Finland. 17% of never smoking men reported daily use of snuff. In Finland, 3% of all males report daily use of snuff. Current snuff use was linked to occasional smoking in Sweden, 23% of male daily snuff users smokes occasionally, respective figure being 4% among women. Conclusions: Tobacco control activities did gain good results among women in Sweden. In Finland development is modest. Tobacco use has increased mainly due increase in snuff use and snuff seems to be appealing not only to switchers, but young males without smoking history. Snuff use seems to promote occasional smoking.

8

**“Preventing Smoking And Smoking Related Diseases In Russia: What Do The Doctors Need?”.**

Marine Gambaryan.

Anna Kalinina.

*National Research Centre for Preventive Medicine.*

*10, Petroverigsky per, 101990, Moscow, Russian*

*Federation*

*mghambarian@yahoo.co.uk*

Though Smoking (S) and Smoking-related diseases (SRD) is major public health problem the awareness of both doctors and patients is still low. E-learning course on SRD prevention was developed and introduced on professional website. This study aims to assess health practitioners’ baseline knowledge, attitudes, practices (KAP) and their needs for professional education regarding SRD prevention prior to introduction to the course. KAP and needs assessment questionnaires were sent to 58 doctors from different regions of Russia who had applied for the e-learning course. Among respondents: 17% male and 83% female - 85%, 46% and 14% were never-, ex-, and current smokers. Active and passive S was recognized by absolute majority as risk factor (RF) for cardio-respiratory diseases, but 17% and 24% respectively said only active smoking is RF for lung and other cancers, as 14% did not see S as a RF for cancers at all. All respondents believed that TC legislation should be enforced to forbid selling tobacco products (TP)

to youngsters under 18, TP advertisements, 92% said smoking should be forbidden in bars and restaurants, and 88.5% - in all public places. All respondents believed, doctors can and should influence behaviours of patients, and majority expressed the need to learn more of SRD prevention strategies: 69% and smoking cessation (SC) methods: 86%, which were not taught in under- and post-graduate trainings:83%. Though 83% accepted that disease prevention is part of their duties, only 28% consider it more and 14% as important as curative work. Only 38% practice SRD prevention and 31% SC advice at every visit of patient, 31% - in case of risk factors and 21% and 17% respectively, dependant on symptoms or if patient is interested, 17% do not offer SC advice at all. Mainly the minimal advice (86%) was mentioned as preferably used SC method. Lack of health education materials for doctors and patients mentioned by 83%, was among reasons for not practicing S prevention:21%, along with lack of knowledge/experience:17%. Lack of health education materials for doctors and patients mentioned by 83%, was among reasons for not practicing S prevention:21%, along with lack of knowledge/experience:17%. Doctors reported need for professional trainings:83%, structures for assisted S cessation:55%, and methods for patient education:59%. The suggested e-learning course was appreciated to serve a methodological aid for applying TC and SRD prevention strategies, extending the knowledge and practices in TC.

## SESSION 4: ORAL COMMUNICATIONS ON CLINICAL RESEARCH

October 5th – 11.45-13.30 h

### 1 “External Validation Of A COPD Diagnostic Questionnaire In Smokers”.

D. Kotz.

P. Nelemans, C.P. van Schayck, G.J. Wesseling.  
*Department of General Practice, Care and Public Health Research Institute, Maastricht University.*  
*P.O. Box 616, 6200 MD Maastricht, The Netherlands.*  
d.kotz@hag.unimaas.nl

**BACKGROUND** Underdiagnosis of chronic obstructive pulmonary disease (COPD) is a worldwide problem. Simple self-administered questionnaires to identify persons in whom airflow limitation is likely can be used to enhance the efficiency of early detection of COPD. The aim of the present study was to determine the external validity of the recently developed “COPD diagnostic questionnaire”[1] for identifying patients at increased risk of airflow obstruction in smokers from the general population in Dutch- and Belgian-Limburg. **METHODS** The “COPD diagnostic questionnaire” comprises a total of 8 items: age, body mass index (BMI), pack years and five respiratory symptoms. The scoring system of allows to calculate an overall COPD risk based on the weighted scores of the eight items. This sum score ranges from 0 to 38 points. According to the manual of

the questionnaire, subjects can be classified as being at “high” (>19.5 points), “moderate” (16.5 – 19.5 points) or “low” (0 – 16.5 points) risk of COPD.[1] We validated this questionnaire in a sample of current smokers aged 40 – 70 years, with a smoking history of 10 or more pack years, who reported one or more respiratory symptoms (cough, sputum production, or dyspnoea) but who had no diagnosis of a respiratory disease (COPD, asthma). Spirometry according to ATS/ERS criteria served as a reference test. **RESULTS** Six hundred seventy-six subjects entered the analyses. Of these, 398 had normal lung function and 278 had a diagnosis of COPD (postbronchodilator FEV1/FVC<0.70 with respiratory symptoms). Smokers with COPD were more likely to be older, male, and to have more pack years. The ability of the COPD diagnostic questionnaire to discriminate between subjects with and without COPD was poor: Area under the ROC-curve=0.65. Sensitivity (SN), specificity (SP) and diagnostic odds ratio (DOR) for the cut-off point 16.5 were SN=89.2%, SP=24.4% and DOR=2.67. For the cut-off point 19.5, these parameters were SN=65.8%, SP=54.0% and DOR=2.26. **CONCLUSIONS** In a high risk population consisting of middle-aged current smokers with more than 10 pack years, the COPD diagnostic questionnaire is probably not useful as a diagnostic tool to identify patients with an increased risk of airflow obstruction. This study highlights the importance of external validation of newly developed diagnostic instruments prior to the implementation in guidelines and daily practice. [1] Price DB, Tinkelman DG, Halbert RJ, et al. Symptom-based questionnaire for identifying chronic obstructive pulmonary disease in smokers. *Respiration* 2006; 73:285-295

### 2 “Piloting physical activity as an aid to smoking cessation during pregnancy”.

Dr. Michael Ussher.

Dr. Paul Aveyard, Dr. Tim Coleman, Professor Robert West, Lianne Straus, Professor Bess Marcus, Dr. St. George's, University of London.  
*Cranmer Terrace, London SW17 ORE, UK.*  
mussher@sgul.ac.uk

**Objective:** To assess the feasibility of using a physical activity intervention as an aid to smoking cessation during pregnancy. **Methods:** Pregnant smokers were recruited following their first antenatal appointment (12-14 weeks gestation) through direct telephoning, midwife referral and flyers. Two pilot studies were conducted. In the first study, 10 women were recruited and attended eight individual smoking cessation treatment sessions over seven weeks, combining behavioural support with walking or callisthenics. Based on comments made in interviews the women requested a more extensive intervention. Therefore, our second study (n= 22) included 15 treatment sessions over nine weeks; with seven sessions combining behavioural support with physical activity (treadmill walking, stationary cycling) and eight visits requiring physical activity alone. Self-reports of continuous smoking abstinence, validated by expired carbon monoxide, were measured weekly during treatment and at end-of-pregnancy. Open-ended interviews were conducted with the women at end-of-treatment and

end-of-pregnancy. Results Women were recruited from one hospital with 5000 pregnancies a year, at a rate of one woman per week. In the first study, five of the 10 women remained abstinent from smoking through to end-of-pregnancy. These women attended all of the treatment sessions. In the second study, three of 22 women (14%) remained abstinent at end-of-pregnancy and on average these women attended 12 of 15 sessions. Combining both studies, 8/32 (25%) maintained abstinence to end-of-pregnancy. In both studies, all of the women maintaining abstinence achieved the target of averaging 110 minutes of physical activity each week during the treatment programme. Ratings of desire to smoke were significantly lower after exercise compared with before exercise. The women reported that physical activity was beneficial as a distraction, for reducing cravings, for weight control, and for increasing confidence for quitting. Five of the women in the second study said that they withdrew because the number of visits was too demanding. Of the 32 women recruited 30 (94%) said that they would be willing to enter a controlled study even if they had an equal chance of not being allocated to an exercise group. Conclusions Overall, these studies demonstrate that physical activity is acceptable as an aid to smoking cessation during pregnancy and feasible to deliver to these women. Randomized studies are needed with larger samples and, to facilitate maximum compliance with exercise interventions, these may need to be between eight and 15 treatment sessions in duration. Research funding: South London Primary Care Research Network (STARNET).

### 3

#### **"Attrition in an Ongoing Trial with Low Income Postpartum Smokers: Practice and Policy Implications".**

Bradley N. Collins, Ph.D.

J. Ibrahim, K. Jaffe, N.M. Tolley, D. Nehemia, P. Wileyto, M. Hovell, J. Audrain-McGovern.

*Health Behavior Research Center, Temple University  
Department of Public Health, 1701 N. 13th St, Weiss 160  
(265-61), Philadelphia, PA, USA.*

bradley.collins@temple.edu

Objectives: Attrition is a challenge for smoking cessation interventions targeting underserved, high risk populations. No second-hand smoke (SHS) reduction trials have thoroughly examined attrition, although we confront attrition problems in our ongoing SHS trial with underserved, African American postpartum smokers. Strategies to minimize attrition are essential for examining effectiveness and determining public health impact. Philadelphia FRESH (Family Rules for Establishing Smoke-free Homes) is randomized trial designed to improve access and to minimize attrition. This study examined predictors of attrition that can inform practice and policy. Methods: To date, we have enrolled  $n = 298$  ITT participants in a two-group, randomized-controlled behavioral counseling trial. Through logistic regression, we explored baseline factors predicting retention (0=loss, 1=retained). Controlling for treatment group and recruitment site, we entered factors hypothesized to predict retention including dosage of SHS

advice from formal (e.g., pediatricians), informal (e.g., family), and media sources, maternal knowledge about SHS dangers, key child health variables, and known demographic and moderating factors of retention and smoking outcomes (e.g., maternal age, FTND, depressive symptoms.) Results. Of the 298 ITT participants, 14.7% were lost prior to 16-week end of treatment and 9% were lost in follow-up (an additional 10% are late and pending EOT; 25% are late and pending 12-month follow-up.) The resulting LR model suggested that higher maternal ratings of child health (OR 1.03,  $p = .02$ ), greater knowledge of SHS dangers (OR 1.15,  $p = .04$ ), and baby's age (OR .03,  $p = .03$ ) predict greater likelihood of retention. To understand why SHS advice dosage was not included in the model, we explored bivariate correlations between dosage types and key variables. Significant correlations suggested that decreased child health related to more Personal SHS messages, but fewer Formal SHS messages. Moreover, there was a negative correlation between Formal SHS messages and mom's perceived support for smoking cessation ( $r = -1.57$ ,  $p = .04$ .) For the presentation, these analyses will be rerun with a larger sample from our ongoing trial, along with Cox regression to examine predictors related to the timing of attrition. Currently, these results suggest a need to focus efforts on the quantity and quality of advice practitioners provide to mothers about SHS and smoking cessation. These results will help facilitate improved retention strategies to minimize effects of attrition on external validity and may inform other trials attempting to target underserved communities. This research was supported by R01 CA105183 and K07 CA93756 (Collins, PI).

### 4

#### **"Smoking behaviour and nicotine metabolism in Caucasians, Orientals and Mixed Ethnicity".**

Dr. NoorZurani Md Haris Robson, MBBS, M.Med, PhD.

Dr. Kim Wolff, PhD, Dr Alyson Bond, PhD.

*Institute of Psychiatry, Kings College London and  
University Malaya, Kuala Lumpur.*

*Dept Primary Care Medicine, Faculty of Medicine,  
University Malaya, 50603 Kuala Lumpur, Malaysia.*

noorzurani@hotmail.com

Objective: (1) To determine smoking behaviour of Caucasian, Oriental and Mixed Ethnicity smokers, and (2) To determine nicotine metabolic status of Caucasians, Orientals and Mixed Ethnicity smokers.

Method: A cross sectional study was carried out in the United Kingdom and Malaysia between September 2003 and April 2005. A total of 217 subjects, comprising 113 Caucasians, 69 Orientals and 35 Mixed Ethnicity subjects were recruited. Demographic data was assessed using self-report questionnaire, nicotine dependence was assessed using the Fagerstrom Test of Nicotine Dependence (FTND) and smoking behaviour was assessed using the Smoking Behaviour Questionnaire (SBQ). Nicotine metabolism was determined by calculating the ratio of plasma cotinine/nicotine 2 hours after chewing a piece of 2 mg nicotine gum.

Results: The subjects were mainly males (n=100), mean age 30.7 years, single, educated up to first degree or above, who smoked mean 12.7 cigarettes/day and mainly smoked filtered standard cigarettes. Caucasians started smoking at a younger age (mean age 14.8) than Orientals (mean age 16.9) (p=0.001). Caucasians (mean age 17.3) also regularly smoked at a younger age than Orientals (mean age 19.5) (p=0.002), but there was no significant difference in number of cigarettes smoked or level of nicotine dependence (according to FTND) between the ethnic groups. However, according to the SBQ, Caucasians were more nicotine dependent (p<0.001), smoked more for regulation of negative affect (p=0.008) and smoked more for hedonism (p<0.001) than Orientals. On the other hand, Orientals smoked more for social integration (p=0.03) than Caucasians. There was also wide variability in nicotine metabolism among smokers as evident from the wide range of plasma cotinine/nicotine ratios (range 0.0 – 2400). A proportion of smokers (7.4%) had a deficient capability of converting nicotine to cotinine (Poor Metabolisers (PM)). All Poor Metabolisers were Orientals. Poor Metabolisers were significantly more likely to be Orientals (p<0.001), had generally stopped smoking for > 6 months before the study (p<0.001), smoked fewer cigarettes (p=0.04), started smoking at an older age (p=0.017) and were less nicotine dependent (p=0.012).

Conclusion: Our findings suggest variability in smoking behaviour and nicotine dependence between Caucasians, Orientals and Mixed Ethnicity groups. This difference may have important implications with regard to optimising treatments in smoking cessation programmes.

## 5 **“Tobacco prevalence’s evolution in three classes from Third-year Medicine Students”.**

Adriana Jiménez-Muro Franco.

Adriana Marqueta Baile, Isabel Nerín de la Puerta.

*Unidad de Tabaquismo, Facultad de Medicina, Universidad de Zaragoza. C/ Domingo Miral s/n, Edif. A, 1 planta. Zaragoza. Spain.*

tabaquis@unizar.es; adrijmf@unizar.es

Objective: To analyze the evolution of the tobacco’s prevalence at Medical University in three different classes. Methods: Analytical and transversal study. Survey fulfilled in the room by third course medicine students in the year 1993, 2000 and 2007 correspondent to 1991-1996, 1998-2003 and 2004-2010 classes. Results: The tobacco’s prevalence in 1993 was 20%, in 2000 16% and 13.5% in 2007, with statistically significant differences among the three courses (p=0.000). The daily smoker’s prevalence has decreased by 6.5% from 1993 until 2007. The percentage of smokers at week-end in the class 2000-2001 is significantly bigger than those in the years 1993-1994 and 2006-2007 (p=0.000). In the last two classes studied, the percentage of non smokers has kept stable fixed (74%), as well as in the first class was smaller (67%) with statistically significant differences (p=0.000). Conclusions: In the last fifteen years the tendency watched is the decrease of the tobacco’s prevalence in the medicine students. Medical University is

an adequate environment so as to get deep in the risks which take the tobacco’s consumption as well as to provide the students the enough strategies and knowledge’s for the giving up of it.

## 6 **“Motivational Interviewing to Help Hispanic Parents of Children with Asthma to Quit Smoking”.**

Belinda Borrelli, PhD.

McQuaid, E., Novak, S., Hammond, K., Becker, B., Amador, J., Jusino, L, & Lee, C.

*Brown Medical School, Centers for Behavioral and Preventive Medicine. Coro-Building-West, 5th Floor, Providence, RI, 02903, USA.*

Belinda\_Borrelli@Brown.edu

Objectives: The PAQS project (Parents of Asthmatics Quit Smoking) contrasts two theory-based smoking cessation interventions for Hispanic caregivers of children with asthma. Methods: Caregivers who smoked (N=133; M age=36.8, 73% female, 58% < high school education, M=10.8 cigs/day; Fagerstrom = 3.9); had an asthmatic child, and who were receiving in-home, nurse-delivered asthma treatment, were randomly assigned to receive one of two nurse-delivered smoking interventions: 1) Behavioral Action Model (BAM), based on AHRQ guidelines, targeting self-efficacy to quit, or 2) Precaution Adoption Model (PAM), which uses Motivational Interviewing to deliver feedback on the smoker’s Carbon Monoxide exposure and the child’s Environmental Tobacco Smoke exposure to increase risk perception. Free nicotine patches were available to those wanting to quit. ETS was measured through passive air dosimeters for 7 days; one placed in the home and one worn by the child. We hypothesized that enhancing risk perception to self and child would motivate quitting smoking more than standard approaches. Results: Overall, 41.4% used the nicotine patch; 50% of PAM and 34.7% of BAM (n.s.). Intent to treat analyses showed that, at 2 months post-treatment, 20.6% of PAM and 9.2% of BAM reported continuous abstinence (chi square =3.45, p= .055). At three months post-treatment 19.1% of PAM was continuously abstinent, vs. 13.8% of BAM (p>.05). Environmental tobacco smoke (p<.05) and asthma morbidity (p<.001) significantly decreased from baseline to the two-month follow-up but there were no significant differences between treatment groups. Conclusions: Results will help tailor interventions to this population and identify mechanisms of behavior change.

7

**"Understanding Demand for Smoking Cessation Treatment Among Young Adults in the U.S."**

Susan J. Curry, Ph.D.

Amy K. Sporer, MS, Dianne C. Barker, MHS, Sherry L. Emery, PhD, George Balch, PhD.

*University of Illinois at Chicago, Institute for Health Research and Policy. 1747 W. Roosevelt Rd., Suite 558, Chicago, IL 60608, USA.*  
suecurry@uic.edu

Objectives: Although the vast majority of young adult smokers in the U.S. want to quit permanently and almost half report making a serious quit attempt in the past year, very few use evidence-based treatments to support their quit attempts. Tobacco cessation among young adults is an understudied area. Little is known about how young adult smokers approach quitting, about their awareness and knowledge of treatment options, and about the types of treatment that would appeal to them. This presentation describes six focus groups conducted with young adult smokers to explore perspectives on smoking, quitting, cessation treatment, and seeking information and help services in general. Methods: All focus group participants had smoked 100 cigarettes in their lifetime, were current smokers aged 18-24, and had intentions to quit. Groups were drawn from three U.S. sample sources: prior behavioral treatment users from the Helping Young Smokers Quit (HYSQ) cohort (n=260); young adult smokers who had not previously used behavioral treatment, drawn from the National Youth Smoking Cessation Survey (NYSCS) cohort (n=1431); and a cohort specific to this study recruited through craigslist.com, an on-line classified ad site (n=535). From each source, two groups were formed: 1) those who did or planned to attend a four-year college, and 2) those who had no intentions of attending a four-year college. The focus groups were conducted using a telephone conferencing system, which made it possible for each group to include young adult participants from across the nation. Results: Among the focus group participants (total n=42): 57% were female; 52% had or planned to attend a 4-year college. They smoked in response to common triggers including stress, boredom, and parties or social situations. They were interested in quitting for health reasons, to improve their professional image, and to save money. Common themes regarding treatment were: skepticism of seeking help; lack of awareness of treatment options, particularly behavioral treatments such as a quit-line; bias against taking medications to quit smoking; and beliefs that the government mandated tobacco companies to provide cessation treatment. When the elements of behavioral programs were described, they were interested in seeking help that provided personal interaction, gave them strategies and advice, and was delivered by former smokers. Conclusions: Implications of these qualitative findings for designing marketing tools to increase demand for cessation resources among young adult smokers will be discussed.

8

**"Reducing the number of cigarettes smoked as a harm reduction approach: Evidence from mortality data"**

Jaakko Kaprio.

Tellervo Korhonen, Ulla Broms, Markku Koskenvuo.

*University of Helsinki, Dept of Public Health.**PO Box 41, 00014 Helsinki, Finland.*

jaakko.kaprio@helsinki.fi

Objectives Smoking reduction appears to predict a higher likelihood of subsequent cessation (Broms et al, N&TR, in press), but does it result in better health outcomes? So far, two large Scandinavian longitudinal studies have examined the health outcomes of spontaneously reduced cigarette smoking with mainly negative results. The aim of this study was to examine among Finnish population whether smoking reduction over a six-year period (1975- 1981) had impact on mortality by 2003. Methods: Longitudinal questionnaire data from two surveys in 1975 and 1981 among the Finnish adult twin cohort were linked with national mortality data from Statistics Finland. For a total of 21,349 subjects with smoking data, overall mortality and disease specific mortality rates for cardiovascular and lung cancer were examined as the outcome measures. Based on smoking behaviour between 1975 and 1981, a total of 4989 (mean age 34 years) subjects were identified as current smokers at both surveys. Out of them 42% had no change, 35% had increased and 23% had decreased their amount of smoking. Of the latter, five percent had less than 25%, 13% less than 50%, 4% less than 75% and 2% at least 75% reduction in their daily cigarette consumption. There were a total of 1077 deaths by the end of year 2003. Survival analyses were conducted to estimate the risk of mortality in relation to changes in amount smoked between 1975 and 1981, adjusted for sex, age and amount of baseline smoking. Those who did not change their smoking were regarded as the reference group. Results: Baseline smoking status in the whole cohort expectedly and significantly predicted total, cardiovascular and cancer mortality, while among smokers a dose response relationship was observed between number of cigarettes smoked and mortality from lung cancer but not for cardiovascular disease. Changes in amount smoked did not impact the risk of overall, cardiovascular or lung cancer mortality. Because a decrease in smoking by 1981 may be due to disease, we accounted for possible pre-existing morbidity by excluding deaths during the five first years of mortality follow-up. This resulted in 937 deaths among 4843 subjects; results remained similar after correcting for pre-existing morbidity. Conclusion: We conclude that among continuing smokers reducing number of cigarettes as such may not provide health benefits as measured by mortality risk. Thus, the public health value of smoking reduction depends on to what degree it serves as a step for smoking cessation.

9

**"Efficacy Of Smoking Cessation Interventions For Hospitalized Smokers: A Meta-Analysis".**

Rigotti NA, Marcus Munafo\*, Lindsay Otead\*\*.  
 Harvard Medical School, USA; \*University of Bristol, UK;  
 \*\*University of Oxford, UK.  
 Harvard Medical School.  
 Tobacco Research & Treatment Center, Mass. General  
 Hospital, Boston, MA 02114 USA.  
 nrigotti@partners.org

**Objectives:** A hospital admission provides an opportunity to promote smoking cessation. Illness increases a smoker's perceived vulnerability to illness, and smoke-free hospitals require smokers to abstain temporarily from tobacco. Starting tobacco treatment during hospitalisation might promote long-term smoking cessation after discharge. We conducted a systematic review of the efficacy of smoking interventions initiated during a hospital stay. **Methods:** We identified randomized and quasi-randomized trials of behavioural or pharmacological smoking cessation interventions, conducted with hospitalised patients who were current smokers or recent quitters. The intervention had to start in the hospital but could continue after discharge. We excluded studies of patients admitted for psychiatric disorders or substance abuse and studies with less than 6 month follow-up. Quit rates were based on intention to treat analyses, with patients lost to follow up counted as smokers. Data were analyzed in 4 pre-determined strata of intervention intensity. Data were pooled for meta-analysis using the Mantel-Haenszel fixed-effect method. **Results:** 33 trials met the inclusion criteria. Counselling interventions that began during hospitalisation and continued with supportive contacts, usually by telephone, for at least 1 month after discharge increased smoking cessation rates long-term (OR 1.65, 95% CI 1.44-1.90; 17 trials). No benefit was found for less intensive counselling interventions. Adding nicotine replacement therapy (NRT) produced a nonsignificant increase in cessation over what was achieved by intensive counselling alone (OR 1.47, 95% CI 0.92-2.35, 5 trials). Similar results were found when trials were stratified by admitting diagnosis. In-hospital counselling with at least 1 month of follow-up support increased the odds of smoking cessation in trials for patients admitted to hospital with acute cardiovascular disease (OR 1.81, 95% CI 1.54-2.15, 11 trials) and for patients with any admitting diagnosis (OR 1.43, 95% CI 1.17-1.75, 6 trials). **Conclusions:** Behavioural interventions that begin during a hospital stay and include at least one month of supportive contact after discharge promote long-term smoking cessation. They are effective regardless of the patient's admitting diagnosis and should be offered to all hospitalised smokers. Interventions of lower intensity or shorter duration are not effective. The evidence to support adding NRT to counselling, though not definitive, is compatible with research in other settings showing that NRT is effective.

10

**"Adherence: The Achilles Heel of OTC Nicotine Replacement".**

Scott J. Leischow, Ph.D.  
 James W. Shaw, Ph.D., Pharm.D., M.P.H.; Myra L. Muramoto,  
 M.D., M.P.H.  
 The University of Arizona (Leischow and Muramoto),  
 The University of Illinois (Shaw). Arizona Cancer Center,  
 University of Arizona, 1515 N. Campbell Avenue, Tucson,  
 Arizona, USA, 85719.  
 sleischow@azcc.arizona.edu

**Objectives:** To assess adherence across three different studies on the effectiveness of over-the-counter (OTC) nicotine replacement therapy (NRT). **Background and Methods:** We conducted three studies to explore the effectiveness of OTC NRT, two of which have been published (Leischow et al 1999; Leischow et al 2004). The two published studies assessed the effectiveness of inhaler and patch in OTC and Health Care Provider conditions, while the unpublished study assessed the effect of cost (\$0, \$10, \$20) on OTC nicotine gum effectiveness. **Results:** Nicotine Patch. The total number of patches purchased in the OTC condition was 32.3 (sd=30.3). By week two of the study, the average number of days per week that study participants wore the patches was 4.8 (sd=2.4). By week 6, the average dropped to 4 days of use per week. Nicotine Inhaler. The number of medication boxes purchased was 3.26 (sd=4.28), and the average number of inhaler cartridges used per day at week two was 2.66 (sd=2.2), thus indicating low use and high variability. The recommended daily use of cartridges is up to 16 per day. Nicotine gum (polacrilex). In the gum cost study, the total number of boxes purchased/obtained were 11.6, 3.6, and 2.1 in the no cost, \$10/box, and \$20/box conditions, respectively (p<0.001). The average number of pieces of gum used per day at week two was 6.8, 2.3, and 1.3 in the no cost, \$10/box, and \$20/box conditions, respectively (p<0.001). Use decreased in each condition after week 2. Even the \$0 condition used less than half the recommended amount. **Conclusions:** All three studies found that adherence to recommended NRT dosing did not occur in an OTC setting, thus likely serving as a contributor to the low quit rates that we observed. Discussion of results will include the implications for public health campaigns, issues of abuse liability, and whether a new approach to OTC NRT is needed. Funding provided by DHHS Grant #DA08885 to SJL, and some medications provided by Pharmacia and Upjohn (now Pfizer).

11

**"Use Of Over The Counter Available Nicotine Replacement Products On Tobacco Cessation".**

Prof. Rama Kant 1\*

Dr. Madhu Pathak 2, Dr. Pooja Ramakant 3, Bobby Ramakant 4.

*TCC, King George Medical University and Satellite centers, Lucknow**Address: C-2211, C-Block crossing, Indira Nagar, Lucknow. 226 016. India.**ramakantkgmc@rediffmail.com*

Objectives: 1. Evaluate impact of OTC availability of Chewable powder containing Nicotine on Tobacco cessation. 2. There looks to be a sudden spurt of manufacturers in India to combine with anti tobacco activists and advertising their chewable nicotine containing pouches as NRT to achieve unprecedented sale. Setting: Tobacco Cessation clinic at King George Medical University, Lucknow, India and its 10 satellite centers. Methods: 680 patients who used OTC product were selected for this project. This includes those who took it themselves or we had advised. Their routine CRF was prepared and all demographic details,

psychological status, physical and psychological co-morbidity and severity of addiction were evaluated by Faggerstrom grading and modified FTND in SLT. They were followed up for plus 16 weeks. Results: Chewable Gutka pouches containing defined amount of nicotine are available in India. This study shows a significant increase in the fraction of smokers using chewable powder ( $P < 0.05$ ) immediately following their availability as OTC. There were also a significantly higher proportion of smokers reporting abstinence with NRT and counseling ( $P < 0.01$ ). The results of this study suggest that removing the prescription status of NRT products resulted in an increase in number of quit attempts, more sustained smoking abstinence or quitting chewable tobacco. But all these successes reached contemplation stage and repeated counseling was additionally required. Quit rate was about 28% and surprisingly it had no significant relationship with severity of addiction. Failure and addiction to SLT instead of smoking was a problem in 33% cases. Conclusions: It becomes apparent that in spite of Nicotine being available as an OTC product and its' use having some element of manufacturer's intention to sell its product like Tobacco, still it is useful in tobacco cessation.

# POSTER DISPLAY

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## POSTER DISPLAY 1

October 4th – 15.00-16.00 h

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### POSTER BOARDS FROM 1 TO 38

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#### POSTER BOARD 1.

##### **HIS and FTND: Are there differences in how they explain the dependence?**

Begoña Alonso

M. I. Santiago Pérez, M. Pérez Ríos, A. Malvar Pintos, X Hervada.

Dirección Xeral de Saúde Pública. Xunta de Galicia.

Edificio administrativo San Lázaro s/n. 15703. Santiago de Compostela. Teléfono: 981540044.

monica.perez.rios@sergas.es

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#### POSTER BOARD 2.

##### **Age Differences In Novelty Seeking In Male Mice Treated With Bupropion Alone Or Combined With Nicotine**

Carrasco MC

Gomez MC, Redolat R

Departamento de Psicobiología. Facultad de Psicología, Universitat de València

AV. BLASCO IBAÑEZ, 21, VALENCIA, SPAIN

Carmen.Carrasco@uv.es

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#### POSTER BOARD 3.

##### **CPP Effect In Adult Rats Which Had Free Access To Oral Nicotine Since Adolescence**

Gorkem Yararbas

Tanseli Nesil, Lutfiye Kanit, Sakire Pogun

Ege Univ. Center for Brain Research and Center for Drug R&D and Pharmacokinetic Applications

Ege Univ. Center for Drug R&D and Pharmacokinetic Applications ARGEFAR Bornova Izmir Turkey

gorkem.yararbas@ege.edu.tr

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#### POSTER BOARD 4.

##### **Behavioral effects of nicotine in mice with high and low levels of novelty-seeking in the hole-board**

Rosa Redolat

Asunción Pérez, Patricia Mesa

Departamento de Psicobiología. Facultad de Psicología. University of Valencia. Spain

Blasco Ibañez, 21

Rosa.Redolat@uv.es

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#### POSTER BOARD 5.

##### **The effect of nicotine on attention in a water maze place learning test: Sex differences**

Lutfiye Kanit

Tanseli Nesil, Gorkem Yararbas, Sakire Pogun

Ege University Center for Brain Research; School of Medicine, Physiology Dept., and Institute of Sci

Ege University School of Medicine, Physiology Dept. Bornova, izmir TURKEY

lutfiye.kanit@ege.edu.tr

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#### POSTER BOARD 6.

##### **Multidimensional Scaling of Craving in Virtual Reality**

Brian Carter

Amy Crunk Traylor, Susan X Day, Megan W. Paris, Patrick Bordnick

M. D. Anderson Cancer Center

PO Box 310439 - Unit 1330

bcarter@mdanderson.org

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#### POSTER BOARD 7.

##### **Exploring attention to visual cues in nicotine dependent young adults using virtual reality (VR)**

Amy C. Traylor, Ph.D.

Patrick S. Bordnick, Ph.D.; Brian Carter, Ph.D.

1) M.D. Anderson Cancer Center, 2) University of Houston, 3) M.D. Anderson Cancer Center

Unit 1330

UT MD Anderson Cancer Center

PO Box 301439

Houston, TX 77230-1439

atraylor@mdanderson.org

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#### POSTER BOARD 8.

##### **Relationship of perceived risks to withdrawal, craving, & depression over 7-day smoking abstinence.**

Andrea H. Weinberger, Ph.D.

Suchitra Krishnan-Sarin, Ph.D., Carolyn M. Mazure, Ph.D., Sherry A. McKee, Ph.D.

Yale University School of Medicine

1 Long Wharf Drive, Suite 101, New Haven, CT 06511

andrea.weinberger@yale.edu

**POSTER BOARD 9.**

**Pharmacokinetics and Local Tolerability of a New Nicotine Sublingual Tablet**

Anna C Hansson\*  
 F Nilsson\*\*, JM Hirsch\*\*\*  
 Depts for Clinical Pharmacology\* and Medical Affairs & Clinical Research\*\*, McNeil AB, Sweden \*\*\*Dept  
 Karl XI gatan 4, SE-222 20 Lund, Sweden  
 ahansson@conse.jnj.com

**POSTER BOARD 10.**

**Multiple Perspectives of Smoking Cessation Needs for Persons with Mental Illnesses**

Chad Morris  
 Jeanette Waxmonsky, Mandy Graves, Alexis Giese, Olga Belikova  
 University of Colorado at Denver and Health Sciences Center  
 Campus Box A011-11, 4455 East 12th Avenue, Denver Colorado 80220  
 chad.morris@uchsc.edu

**POSTER BOARD 11.**

**Nicotine Patch Therapy Prior to Quitting Smoking: A Meta-Analysis**

Saul Shiffman, Ph.D.  
 Stuart G. Ferguson  
 Pinney Associates  
 201 N Craig Street, Suite 320  
 shiffman@pinneyassociates.com

**POSTER BOARD 12.**

**Smoking rate and Stage of change for quitting in the patient with smoking associated disease**

Eon Sook Lee  
 Seon-Yeong Lee  
 Department of Family Medicine, Center for Health Promotion and Clinical Research Center, Ilsan-Paik  
 2240, Daewha-dong, Ilsanseo-gu, Goyang-si, Gyeonggi-do, 411-706, Korea (South).  
 leejeny@ilsanpaik.ac.kr

**POSTER BOARD 13.**

**Dependence on nicotine gums**

Jean-François ETTER  
 University of Geneva  
 1, rue Michel-Servet, Geneva, Switzerland  
 jean-francois.etter@imsp.unige.ch

**POSTER BOARD 14.**

**Cytisine for smoking cessation: a research agenda**

ETTER Jean-Francois  
 Ronald J. LUKAS, Neal L. BENOWITZ, Robert WEST, Carolyn M. DRESLER  
 University of Geneva. 1, rue Michel-Servet  
 Jean-Francois.Etter@imsp.unige.ch

**POSTER BOARD 15.**

**Type Of Reinforcement And Dependence Can Help Us To Better Diagnose Smokers.**

Carlos A. Jiménez-Ruiz  
 Noelia Amor Besada, Marisa Mayayo, Maribel Cristobal, Ana Cicero, Juan Jose Ruiz, Angel Guirao García  
 Institute of Public Health. Madrid, Spain.  
 C/ Santa Cruz de Marcenado, 9. Piso 2. Madrid 28015  
 victorina@ctv.es

**POSTER BOARD 16.**

**Assertiveness and motivation to quit smoking in cardiac patients after myocardial infarction**

Guerra, M. Prista  
 Viana, F.; Fernandes O. & Maciel, M.J.  
 Faculty of Psychology and Educational Sciences - University of Porto, Portugal  
 Rua Dr. Manuel Pereira da Silva, 4200-392, Porto, Portugal  
 mguerra@fpce.up.pt

**POSTER BOARD 17.**

**Multiple partial seizure-like symptoms in smokers**

Miroslav Svetlak  
 Petr Bob, Jana Bardonova, Michal Cernik, Robert Roman, Miloslav Kukleta  
 Department of Physiology, Faculty of Medicine, Masaryk University  
 Komenskeho nam. 2, 662 43 Brno, Czech Republic  
 svetlak@email.cz

**POSTER BOARD 18.**

**A Mixed Methods Investigation of Cigarette Smoking and the Quality of Life**

Dima M. Qato, Pharm.D.1  
 James W. Shaw, Ph.D.1; Carol S. Shaw, B.S.; Christine W. Hartmann, Ph.D.2; Frank T. Leone, M.D.3; Stephen Joel Coons, Ph.D.4; Scott J. Leischow, PhD.4  
 1University of Illinois at Chicago; 2Boston University; 3Thomas Jefferson University; 4University of Arizona  
 College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, M/C 871, RM 252, Chicago, IL 60612, USA  
 jwshaw@uic.edu

**POSTER BOARD 19.**

**Effectiveness of aromatherapy including cigarette smell in smoking cessation**

Youn Chang-Ho  
 Lee Jin-Woo, Lee Jung-Bum  
 Department of Family Medicine, Kyungpook National University Hospital  
 50 SAMDUK-2GA JUNG-GU DAEGU KOREA  
 ychfm@knu.ac.kr

**POSTER BOARD 20.**

**Impact of age of onset of cigarette smoking on heavy drug use.**

Nooshin Khasteganan  
 Zahra Mohtasham Amiri  
 Forsat quit addiction clinic, Rasht, Iran  
 Forsat quit addiction clinic,Haji Abad Ave, Rasht ,Iran  
 khasteganan@yahoo.com

**POSTER BOARD 21.**

POSTER WITHDRAWN

**POSTER BOARD 22.**

**Is It Necessary To Be Motivated For Stop Smoking?**

Adriana Marqueta Baile  
 Adriana Jiménez-Muro Franco, Isabel Nerín de la Puerta  
 Unidad de Tabaquismo. Facultad de Medicina. Universidad de Zaragoza  
 c/Domingo Miral s/n. Edificio A, 1ªplanta. Zaragoza  
 amarquet@unizar.es; tabaquis@unizar.es

**POSTER BOARD 23.**

**Differences in belief systems between smokers and non-smokers**

Fernando Calvo  
 Josefina Ramal; María Dolores Díaz; Elba Betancort  
 Universidad de Las Palmas de Gran Canaria  
 Centro de Ciencias de la Salud, Apto correos 550, 35016  
 Las Palmas de Gran Canaria  
 fcalvo@denf.ulpgc.es

**POSTER BOARD 24.**

**NicVAX Demonstrated Proof of Concept at 6 Months, an Evaluation of a Nicotine Vaccine in Smokers**

Dorothy Hatsukami, PhD  
 S.Rennard,MD; D.Gonzales,PhD; N.Rigotti,MD; A.de Vos,MD,PhD; R.Akhavain; E.Bortey,PhD; D.Jorenby,PhD  
 U. Minnesota, U. Nebraska, Oregon Health & Science U., Harvard U., U. Wisconsin, Nabi Biopharm  
 U. of Minnesota Tobacco Use Research Ctr, 2701 University Ave, SE, Suite 201, Minneapolis, MN 55414  
 hatsu001@umn.edu

**POSTER BOARD 25.**

**Passive smoking as a source of tobacco specific N-nitrosamines for delivering women**

Ewa Florek  
 Wojciech Piekoszewski, Grzegorz H. Breborowicz, Wojciech Lechowicz, Maksymilian Kulza  
 Laboratory of Environmental Research Department of Toxicology University of Medical Sciences  
 Dojazd 30, 60-631 Poznan, Poland  
 eflorek@amp.edu.pl

**POSTER BOARD 26.**

**Efficacy of distress tolerance treatment vs. standard behavioral treatment for early lapse smokers**

Richard A. Brown, Ph.D.  
 Kathleen M. Palm, Ph.D., David R. Strong, Ph.D., Carl W. Lejuez, Ph.D., Christopher W. Kahler, Ph.D., Michael J. Zvolensky, Ph.D., Elizabeth V. Gifford, Ph.D., Steven C. Hayes, Ph.D.  
 The Warren Alpert Medical School of Brown University/ Butler Hospital  
 345 Blackstone Blvd., Providence, R.I. 02906 USA  
 Richard\_Brown@brown.edu

**POSTER BOARD 27.**

**Attention To Smoking Cues Is Associated with Incentive-Related Physiological and Subjective Measures**

Andrew J. Waters  
 Brian L. Carter, Jason D. Robinson, Cho Y. Lam, David W. Wetter, & Paul M. Cinciripini  
 The University of Texas M. D. Anderson Cancer Center.  
 Department of Behavioral Science, Unit 1330, 1155 Pressler Street, Houston, TX 77030-3721, USA  
 ajwaters@mdanderson.org

**POSTER BOARD 28.**

**Active Smoking and the Incidence of Type 2 Diabetes: A Systematic Review and Meta- analysis**

Carole Willi, MD  
 Patrick Bodenmann, MD, MScPH, William A. Ghali, MD, MPH, Jacques Cornuz, MD, MPH  
 Department of Ambulatory Care and Community Medicine, University of Lausanne  
 Rue du Bugnon 44, 1011 Lausanne, Switzerland  
 carole.willi@hospvd.ch

**POSTER BOARD 29.**

**Students Using Computerized Coaching To End Smoking Successfully (Success): Preliminary Results.**

Alexander Prokhorov, M.D., Ph.D.  
 Mary Mullin Jones, M.P.H.; Salma Marani, M.S.; Tracey Yost, MS; Janice Segura; Sheryl Nelson, M.P.H.  
 University of Texas M.D. Anderson Cancer Center  
 Department of Behavioral Science; Unit 1330; P.O. Box 301439; Houston TX 77230-1439  
 aprokhorov@mdanderson.org

**POSTER BOARD 30.**

**Association of COMT Genotype with Smoking Cessation**

Marcus R. Munafò  
 Elaine C. Johnstone, Michael F. G. Murphy, Paul N. Aveyard  
 University of Bristol. Department of Experimental Psychology. University of Bristol  
 12a Priory Road. Bristol BS8 1TU. United Kingdom

**POSTER BOARD 31.**

**DRD4 gene variation and smoking cessation: a randomised controlled trial of NRT**

Sean P. David  
 Marcus R. Munafò, Michael F. G. Murphy, Maureen Proctor, Robert T. Walton, Elaine C. Johnstone  
 SPD (Brown U.), MRM (U. Bristol) MFGM, MP, ECJ (U. Oxford), RTW (MRC Laboratories, The Gambia)  
 Brown Univeristy CPCP, 111 Brewster St., Pawtucket, RI 02860, U.S.A.  
 Sean\_David@Brown.Edu

**POSTER BOARD 32.**

**Could the key to quitting lie in the genes? - A pragmatic clinical evaluation of the NicoTest**

Lisa J Miles, D.Phil.  
 Graham Mould, Ph.D; Carolyn Burden; Robert Walton, MD  
 g-Nostics Ltd., Guildford Clinical Pharmacology Unit Ltd., North East Essex NHS Primary Care Trust  
 g-Nostics Ltd., 68J Milton Park, Oxford, OX14 4RD  
 projects@g-nostics.com  
 (g-Nostics Ltd.= funder of study)

**POSTER BOARD 33.**

**Rimonabant for smoking cessation**

Kate Cahill  
 Michael Ussher  
 Cochrane Tobacco Addiction Group  
 Old Road Campus, Oxford University, OXFORD, OX3 7LF, UK  
 kate.cahill@dphpc.ox.ac.uk

**POSTER BOARD 34.**

**A comparison of German smokers' exposure to tar and nicotine using analysis of smoked cigarette filters with yields from a range of machine smoking regimes**

DC Mariner  
 M Booty, G Mullard, CJ Shepperd  
 British American Tobacco  
 Group R&D, Regents Park Road, Southampton, UK SO15 8TL  
 derek\_mariner@bat.com

**POSTER BOARD 35.**

**How negative and positive reinforcement is associated to nicotine dependence?**

Broms Ulla  
 Fagerström Karl, Madden Pamela AF Heikkilä Kauko, Kaprio Jaakko  
 Department of Public Health, University of Helsinki, Finland  
 POBox 41, 00014 University of Helsinki, Finland  
 ulla.broms@helsinki.fi

**POSTER BOARD 36.**

**BSQ (Body Shape Questionnaires) scores in smoking and non-smoking adolescent**

Ayesta, F.J.  
 Otero M, Cortijo C, De La Rosa L  
 University Of Cantabria  
 Fac. Medicine, C. Herrera Oria S/N, 39011 Santander, Spain  
 ayestaf@unican.es

**POSTER BOARD 37.**

**Differences In Cdi Scores In Smoker And Non-Smoker Adolescents**

Miriam OTERO  
Sergio VEIGA, Miriam RODRÍGUEZ, F. Javier AYESTA  
Plan Gallego Vida sin Tabaco, Conselleria de Sanidade  
Ed. Administrativo San Lázaro S/N · 15703 Santiago de Compostela  
Miriam.Otero.Requeijo@sergas.es

**POSTER BOARD 38.**

**Modelling smoking-related morbidities based on 12-versus 6-week studies of treatment with varenicline in the UK.**

Michael Metcalfe\*  
Koo Wilson, Enrico De Nigris  
Pfizer Limited. Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS, UK  
Michael.Metcalfe@pfizer.com

**POSTER DISPLAY 2**

**October 5th – 15.00-16.00 h**

**POSTER BOARDS FROM 39 TO 81**

**POSTER BOARD 39.**

**Constituent comparison in smokeless tobacco products used in Europe.**

Justine Williamson  
Helena Digard, Eian Massey  
British American Tobacco  
British American Tobacco, GR&D, Regents Park Road, Millbrook, Southampton, SO15 8TL  
justine\_williamson@bat.com

**POSTER BOARD 40.**

**A strategy for targeting smokers from high deprivation areas to a computer-tailored intervention**

Camille Alexis-Garsee  
Dr Hazel Gilbert, Prof. Stephen Sutton; Prof. Irwin Nazareth;  
Dr Richard Morris  
University College London  
Department of Primary Care and Population Sciences, Rowland Hill Street, London, NW3 2PF  
c.alexis-garsee@pcps.ucl.ac.uk

**POSTER BOARD 41.**

**Adult Cigarette Smokers' Attitudes Toward Smokeless Tobacco As Part of a Harm Reduction Strategy**

James E. Dillard III  
No Co-Authors  
Senior Vice President - Manufacturing, Science and Technology, of U.S. Smokeless Tobacco Company  
100 West Putnam Avenue, Greenwich, CT 06830, USA  
dcrighton@usthq.com

**POSTER BOARD 42.**

**Correlates of smoking outcome expectancies in Hungarian adolescent samples**

Róbert Urbán  
Edit Czeglédi  
Eötvös Loránd University, Department of Personality and Health Psychology  
Budapest, H-1064, Izabella u. 46  
urban.robort@ppk.elte.hu, or rurban@hu.inter.net

**POSTER BOARD 43.**

**Implementation of the National Current Care Guideline on Smoking Cessation in Finnish Community Pharmacies**

Terhi Kurko1  
Kari Linden2, Mari Vasama1, Kirsi Pietilä1, Vesa Jormanainen2, Marja Airaksinen1  
1 University of Helsinki, Faculty of Pharmacy, Division of Social Pharmacy, Helsinki, Finland, 2 Pfizer Inc, Helsinki, Finland  
Division of Social Pharmacy, P. O. Box 56, 00014 University of Helsinki, Finland  
terhi.a.kurko@helsinki.fi

**POSTER BOARD 44.**

**Smoking Cessation Outside Clinical Settings in Sweden - Patterns in Different Population Subgroups**

Lars M. Ramstrom  
Institute for Tobacco Studies  
Ingemarsgatan 4 B, SE-11354 Stockholm, Sweden  
Lars.Ramstrom@tobaccostudies.com

**POSTER BOARD 45.**

**Tobacco use among twins participating in a prospective study of smoking cessation in Sweden.**

Helena Furberg Barnes  
P Lichtenstein, NL Pedersen, CM Bulik, L Thornton, C Lerman, PF Sull  
University of North Carolina, USA  
UNC Department of Genetics, CB#7264, 103 Mason Farm Road, Chapel Hill, NC 27599 USA  
helena\_furberg@med.unc.edu

**POSTER BOARD 46.**

**Use of health literacy kiosks for stop smoking awareness after CO measurement (EU Help Campaign)**

Luís Saboga Nunes, MPH  
Ana Paula Cupertino  
Escola Nacional de Saúde Pública da Universidade Nova de Lisboa  
Escola Nacional de Saúde Pública - UNL, Avenida Padre Cruz, 1600-560 Lisboa Codex  
saboga@hotmail.com, saboga@ensp.unl.pt

**POSTER BOARD 47.**

**National Partnership to Help Pregnant Smokers Quit Impact Evaluation**

Leah M. Ranney  
Cathy L. Melvin  
University of North Carolina at Chapel Hill  
725 Martin Luther King Jr. Blvd  
Leah\_ranney@unc.edu

**POSTER BOARD 48.**

**The “Why do I smoke” test as predictor of failure in quitting smoking**

Salvador S. Coelho  
Rita Gerardo, Lígia C. Pires  
Pulmonology Department  
Hospital S. Marta, 1169-024 Lisboa, Portugal  
coelho.salvador@gmail.com

**POSTER BOARD 49.**

**The Prevalence of Physician-Delivered Advice to Quit Smoking among Italian Smokers**

Amy K. Ferketich  
Silvano Gallus, Paolo Colombo, Roldano Fossati, Giovanni Apolone, Piergiorgio Zuccaro, Carlo La Vecchia  
The Ohio State University College of Public Health  
B-209 Starling-Loving Hall, 320 West 10th Ave, Columbus, OH, USA  
aferketich@cph.osu.edu

**POSTER BOARD 50.**

**Hardcore and relapsed smokers and cigarette dependence: A qualitative exploration among Taiwanese**

Chih-Ling Huang  
Kuang-Chieh Hsueh, Hsiu-Hung Wang  
Department of Nursing, Chang Jung Christian University and Kaohsiung Medical University  
396 Sec. 1, Chang Jung Road, Kway Jen, Tainan 71101, Taiwan.  
chhuang@mail.cjcu.edu.tw

**POSTER BOARD 51.**

**Smoking cessation and weight gain: A prospective study on weight variation and treatment options.**

José M<sup>a</sup> Ramón  
S. Morchon, C. Masuet  
Smoking Cessation Clinic. Hospital Universitari de Bellvitge, Barcelona, Spain.  
Unidad de Tabaquismo. Preventive Medicine Department. Hospital Universitari de Bellvitge. Feixa Llar  
jmramon@csub.scs.es

**POSTER BOARD 52.**

**To be or not to be cited**

Jean-François ETTER  
University of Geneva  
1, rue Michel-Servet, Geneva, Switzerland  
jean-francois.etter@imsp.unige.ch

**POSTER BOARD 53.**

**Benefits Of Smoking Cessation Despite Weight Gain**

Juan M. Díez  
D Alvaro, S Mayoralas, R Pérez, P Rodríguez, L Serrano; V Román  
Neumology, Hospital Mostoles  
c/ Palo de Rosa, nº 3, escalera 3, 7º A Madrid - Spain  
jmdpas@hotmail.com

**POSTER BOARD 54.**

**Characteristics And Evolution Of Women On A 12-Month Smoking Cessation Program**

M.C. Pinet, MD  
N. Siñol, E. Ribalta, F. Llarger  
Addictive Behaviour Unit, Psychiatry Department. Hospital de Sant Pau  
c/ Sant Antoni M<sup>a</sup> Claret 167. 08025 Barcelona, Spain  
mpinet@santpau.es

**POSTER BOARD 55.**

**The impact of a smoking cessation programme in an Italian workplace**

Piccinelli C.  
Dotti A., Beatrice F., Molinar R., Giordano L., Senore C.  
CPO Piemonte  
via san francesco da paola 31, 10123 Torino (Italy)  
gruppo.fumo@cpo.it

**POSTER BOARD 56.**

**Health Care Professional's Attitudes Towards Giving Smoking Cessation Help: A Patients' Perspective**

Ilda de Godoy  
Suzana Erico Tanni; Paula Angeleli Bueno de Camargo;  
Nathalie Izumi Iritsu; Massaki Tani; Irma Godoy  
Department of Internal Medicine, Pulmonary Division,  
Botucatu School of Medicine, São Paulo State Un  
Alameda Sibipirunas, 231. Parque das Cascatas. Botucatu-  
SP, Brasil. CEP: 18607-330  
degodoy@fmb.unesp.br

**POSTER BOARD 57.**

**Factors associated with adherence to treatment and with short-term abstinence in smoking-cessation**

Suzana E Tanni  
Ilda de Godoy, Rosana SS. Martin, Liana S Coelho; Renata  
Ferreira, Laura MO Caram; and Irma Godoy.  
Internal Medicine and Nursing Departments, Divisions of  
Pulmonology and Community and Preventive Nur  
Faculdade de Medicina / Departamento de Enfermagem/  
UNESP. Botucatu, SP. Brasil.CEP18618-970  
degodoy@fmb.unesp.br

**POSTER BOARD 58.**

**Fagerstrom Test for Nicotine Dependence scores in smokers across countries.**

Fagerstrom Karl  
Smoker's Information Centre  
Berga Alle 1, Helsingborg, Sweden  
karl.fagerstrom@swipnet.se

**POSTER BOARD 59.**

**Depression, Smoking, Nicotine Dependence And Motivation To Smoking Cessation.**

Laura Valadés  
Carlos Catalina, José Luis Tornero, Susana García-  
Redondo, Laura González, Paloma Mata  
IBERMUTUAMUAMUR  
Calle Ramírez de Arellano, 27  
lauravalades@ibermutuamur.es

**POSTER BOARD 60.**

**Smoking cessation in primary care**

Anders Ostrem  
Hilary Pinnock, Onno van Schayck  
International Primary Care Respiratory Group  
Gransdalen Legesenter, 1054 Oslo, Norway  
andersostrem@c2i.net

**POSTER BOARD 61.**

**To Quit Smoking In Psychotic Patients: Individual Vs Group Therapy**

Antonia Raich  
Cano, M<sup>\*\*</sup>; Fernandez, T<sup>\*\*</sup>; Martinez, A<sup>\*\*\*</sup>; Borrell, O<sup>\*</sup>;  
Prat, G.<sup>\*</sup> Althaia Medical Care Network \* Cas Mataro.  
Consorti Sanitari Del Maresme \*\* Unitat De Tabaquisme.  
Dap Mollet-Granollers. Ics<sup>\*\*\*</sup>  
ALTHAIA FOUNDATION. Medical care network  
c/Dr. Llatjos, s/n. 08243 Manresa.(Barcelona) SPAIN.  
araich@althaia.cat

**POSTER BOARD 62.**

**The influence of smoking on peripheral obstructive arterial disease**

Sochor O.  
Hofirek I., Sarnik S., Rotnagl J., Hladka H., Novakova M.,  
Jancar R., Lehar F., Hejnicova L.  
Ist cardio-angiological departement, St. Ann's University  
Hospital, Brno, Czech Republic  
Pekarska 53, Brno, Czech Republic, Europe  
ondrej.sochor@fnusa.cz

**POSTER BOARD 63.**

**Comparison Of Nicotine Levels In Primary Health Centers Of The Spanish Northern Region Cantabria Prior To And After The Spanish Tobacco Law 28/2005.**

Sonia Álvarez, Blanca M<sup>a</sup> Benito, Emma del Castillo, M<sup>a</sup>  
Eugenia López, Fernando Martín and Leticia Viadero.  
Gobierno de Cantabria  
c/ Federico Vial 13. Santander 39009  
alvarsonia@gmail.com

**POSTER BOARD 64.**

**Early start of smoking may worsen anthropometric parameters including their changes after quitting**

Eva Kralikova  
Lenka Stepankova, Ludmila Pohlova, Jan Zajack  
Charles University, First Faculty of Medicine, 3rd Medical  
Dpt, Tobacco Dependence Treatment Centre  
Kralovo namesti 32, 120 00 Praha 2, Czech Republic  
eva.kralikova@lf1.cuni.cz

**POSTER BOARD 65.**

**Smoking Cessation Practises And Attitudes Towards Smoking Among Health Professionals In Finland**

Patrick Sandström  
Terhi Kurko, Markku Myllykangas, Vesa Jormanainen, Kristiina Patja, Marja Airaksinen  
National Public Health Institute, Finland  
Mannerheimintie 166, 00300 Helsinki, Finland  
patrick.sandstrom@ktl.fi

**POSTER BOARD 66.**

**Maternal smoking in Uruguay: a modifiable reality.**

Raquel Magri  
Menendez ,A , Suarez H, Miguez H, Parodi V, Bustos R, Hutson JR.  
Uruguayan study group on perinatal and drugs affaires , Hospital Pereyra Rossell; SMU.  
Br.Artigas 1515. Montevideo .Uruguay .PC 11200.  
menendez012002@yahoo.com.ar

**POSTER BOARD 67.**

**Adjustment for Selection Bias Due to Missing Data in Smoking Cessation Trials**

James W. Shaw, Ph.D.1  
Jia Luo, M.D.1; Myra L. Muramoto, M.D.2; James R. Ranger-Moore, Ph.D.2; Scott J. Leischow, Ph.D.2  
1University of Illinois at Chicago; 2University of Arizona College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, M/C 871, RM 252, Chicago, IL 60612, USA  
jwshaw@uic.edu

**POSTER BOARD 68.**

**Internet Recruitment for Cessation Research and Treatment: A Viable Strategy for Young Adult Smokers**

Amy K. Sporer, MS  
Susan J. Curry, PhD, Sherry L. Emery, PhD, Robin J. Mermelstein, PhD  
University of Illinois at Chicago, Institute for Health Research and Policy  
1747 W. Roosevelt Rd., Suite 558, Chicago, IL 60608, USA  
aksporer@uic.edu

**POSTER BOARD 69.**

**The incidence of cardiovascular events in smokers is similar to a non-smoker 8 years older: Analyse**

Jaime Fernández de Bobadilla  
Antoni Sicras, Ruth Navarro, Xavier Frías, Cristina Sánchez Maestre  
Pfizer SA, Badalona Servicios Asistenciales, Euroclin Institute  
Avda. Europa 20B, Alcobendas, Madrid  
cristina.sanchezmaestre@pfizer.com

**POSTER BOARD 70.**

**Relationship between Cigarette Smoking and Abdominal Obesity in a Population-based Study**

Carole Willi, MD  
A. Chiolero, D. Faeh, J. Cornuz, P. Marques-Vidal, F. Paccaud, G. Waeber, P. Vollenweider  
Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland  
33 Bugnon avenue, 1011 Lausanne, Switzerland  
carole.willi@hospvd.ch

**POSTER BOARD 71.**

**Tobacco Use In Immigrants: A Comparative Study With Spanish Population**

Natalia Sobradieł  
Adoración Mas, Arantxa Crucelaegui, Javier Garcia-Campayo, Hilda Wara Revollo  
USM CS Torrero-La Paz. Hospital Miguel Servet de Zaragoza.  
C/ Soleiman, 11, planta 1, Unidad de Salud Mental. 50007 ZARAGOZA - SPAIN  
nsobradieł@gmail.com

**POSTER BOARD 72.**

**THE ALTERNATIVE /a comprehensive multidisciplinary approach to Smoking Cessation: all the Know How and the 'ingredients' attractively conveyed in a BOX**

Rima Khalil  
AUB Tobacco Free Campus Initiative  
American University of Beirut Medical Center-Dale hme, Beirut Lebanon  
rkhalil@inco.com.lb

**POSTER BOARD 73.**

**Smoking in familial schizophrenia: Is this a specific phenotype?**

Nuria Lanzagorta  
Austria F Escamilla M Apiquian R Dassori A Canive J  
Ontiveros A Raventos H Medina R Jerez A Mendoza R Nicolini H  
Carracci Smoking Cessation Program, Carracci Medical  
Group, Mexico.  
Carracci 107, Extremadura Insurgentes, 03740, Mexico, DF.  
nuriaipik@yahoo.com.mx

**POSTER BOARD 74.**

**Prevalence of smoking among pregnant women in Korea: A random sample survey using self-reporting and urinary cotinine measurement**

Hong-Gwan Seo+  
Jong-Gwan Chun\*, Do-Hoon Lee+, Moon-Woo Sung+, Yoon-Dan Kang\*, Hyung-Joon Jhun¶,  
+National Cancer Center, Goyang, Korea  
\*Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, Korea  
¶Department of Occupational and Environmental Medicine, College of Medicine, Korea University, Ansan, Korea.  
Address: 809 Madu-dong Ilsandong-gu Koyang-si Kyunggi-do Rep. Of Korea  
hongwan@ncc.re.kr

**POSTER BOARD 76**

POSTER WITHDRAWN

**POSTER BOARD 77.**

**Importance of price and reimbursement on the use of smoking cessation medicines – Opinions of Finnish community pharmacists**

Kari Linden (1)  
Terhi Kurko (2), Vesa Jormanainen (1) and Marja Airaksinen (2)  
(1) Pfizer Oy, Helsinki, Finland, (2) University of Helsinki, Faculty of Pharmacy, Division of Social Pharmacy, Helsinki, Finland  
Pfizer Oy, Tietokuja 4, FI-00330 Helsinki, Finland  
kari.linden@pfizer.com

**POSTER BOARD 78.**

**Necessity for additional stimulation for quit smoking**

Doroteya Naboko  
Valentina Petkova, Zlatka Dimitrova  
Sopharma  
16, Iliensko shosse str., Sofia 1220, Bulgaria  
teja@sopharma.bg

**POSTER BOARD 79.**

**Promoting the Puerto Rico Quitline through a Community-Based Outreach Program**

Luz Mejia, MA  
Carlos A. Mazas, Ph.D., Ana Patricia Ortiz, MPH, Ph.D.,  
Virmarie Correa-Fernandez, Ph.D., William Calo-Perez, MPH, Maria Del Carmen Santos-Ortiz, Ph.D., David Warren Wetter, Ph.D., Antonio Cases, MPA and Elba Cecilia Diaz-Toro, DMD.  
University of Texas M.D. Anderson Cancer Center  
1515 Holcombe Blvd Houston TX 77030  
lmmejia@mdanderson.org

**POSTER BOARD 80.**

**How to design a training programme on tobacco treatment for clinical staff of primary care settings**

Eduardo Olano  
Blanca Matilla, Ana Esteban, Miriam Otero, Miriam Rodríguez  
11th Area of Madrid Health Service (SERMAS)  
C/ Parque Bujaruelo 33, 7º A, 28924, Alcorcón (Madrid)  
e\_oeoeoe@hotmail.com

**POSTER BOARD 81.**

**Comprehensive tobacco action plan for Andalusia 2005-2010 : A health promotion. Strategy.**

Pilar Mesa  
Marcos Garcia , Josefina Castro , Teresa Puebla  
Andalusian Health Service (Spain)  
Avda.Carlos Haya s/n 29009 SPAIN  
magarue@gmail.com

# PAPER PRESENTATIONS

## ORAL COMMUNICATIONS

Oral Communications will be presented in the following Sessions:

### SESSION 1: ORAL COMMUNICATION ON BASIC RESEARCH

October 4th from 9.30 to 11.15 h

### SESSION 2 : ORAL COMMUNICATIONS ON CLINICAL RESEARCH

October 4th from 11.45 to 13.30 h

### SESSION 3: ORAL COMMUNICATIONS ON EPIDEMIOLOGY/ HEALTH CARE / OTHER RESEARCHS

October 5th from 9.30 to 11.15 h

### SESSION 4: ORAL COMMUNICATIONS ON CLINICAL RESEARCH

October 5th from 11.45 to 13.30 h

AV equipment for Computer Projection (Power Point) will be available for all conference rooms. There will be a "Slides Preview Desk" to check and modify presentations. Authors are required to give their presentations directly to the room technician before the beginning of the Session.

## POSTERS

Poster Area will be located at Salon Roma. Posters could be posted from October 3rd (16.30 h onwards) until October 6th (before 12.00 h). The Organizing Secretariat will not be responsible of non-removed posters.

Posters will be briefly presented during the following Poster Display Sessions:

### POSTER DISPLAY 1 (Poster Boards from 1 to 38)

October 4th from 15.00-16.00 h

### POSTER DISPLAY 2 (Poster Boards from 39 to 81)

October 5th from 15.00-16.00 h

# REGISTRATION

**Members SRNT (1)**

**Non-Members**

**Students (2)**

**Accompanying person (3)**

**One day ticket**

Late registration  
(after 30/06/07)

300,00 €

425,00 €

250,00 €

125,00 €

110,00 €

*(1) Member code is required.*

*(2) A copy of your student card or a certificate issued by your University is required.*

*(3) Only includes the welcome reception. No access to scientific sessions.*

*VAT 16% not included.*

### The registration fees includes:

- Attendance to scientific sessions
- Congress Bag
- Lunch and coffee breaks
- Welcome reception

**No registration will be confirmed without the corresponding payment.**

# ACCOMMODATION

	Single Room	Double Room
<b>NH EUROBUILDING *****</b> (Venue)	190,50 €	209,70 €
<b>NH LA HABANA ****</b>	167,00 €	181,00 €

Prices per room and night.  
Breakfast and VAT included.

## METHODS OF PAYMENT

- **Bank transfer to:** Viajes y Congresos S.A.  
**Account Holder:** Viajes y Congresos S.A.  
**Bank name:** Banco Central Hispano  
**Bank address:** Banco Central Hispano, c/ Princesa 31, 28008 Madrid - SPAIN  
**Account number:** 0049 0356 56 2010595386  
**IBAN:** ES68. 0049 0356 56 2010595386  
**SWIFT CODE:** BSCHEMM

A copy of the bank transfer order is required and should be sent together with the registration form (via e-mail [vycongrema@viajesycongresos.com](mailto:vycongrema@viajesycongresos.com) or fax: +34 91 559 58 81). Do not forget to include your full name in the bank transfer order.

- **Credit Card (VISA or MASTERCARD)**

## CHANGES AND CANCELLATIONS

All changes and cancellations must be addressed by written to Viajes y Congresos S.A.  
[vycongrema@viajesycongresos.com](mailto:vycongrema@viajesycongresos.com)

### Cancellation Policies for Registrations:

- 1 Any cancellation received less than 90 days prior to the congress:  
25% cancellation fees will be applied (minus bank transfer charge)
- 2 Any cancellation received less than 60 days prior to the congress:  
50% cancellation fees will be applied (minus bank transfer charge)
- 3 Any cancellation received less than 45 days prior to the congress:  
75% cancellation fees will be applied (minus bank transfer charge)
- 4 No refund will be made for any cancellation received less than 30 days prior to the congress.

All refunds will be made after the end of the Conference

In compliance with Organic law 15/1999, dated on December, 13th, related to data protection, we inform you that the personal information provided by you in this form will be stored in a database controlled by Viajes y Congresos, S.A. and used to promote the mentioned event, or related events and future editions of this event. If you wish to exercise your rights to access, rectify, cancel and oppose the treatment of your data, please contact Viajes y Congresos, Gran Vía 71-3° ext. izdo. Madrid 28013. SPAIN

# GENERAL INFORMATION

## CONGRESS DATES

October 3rd-6th 2007

## CONGRESS WEBSITE

The official website of the Conference is [www.srnt2007madrid.com](http://www.srnt2007madrid.com). Please check the site regularly for updated information.

## VENUE

The venue will be the NH Eurobuilding Hotel, located in the most modern area of downtown Madrid and surrounded by high quality restaurants and nice shops within walking distance. It is very well connected to the airport and to the center of Madrid by underground and bus. Metro Stations: Cuzco (Line 10) or Colombia (Lines 8 and 9).

## LANGUAGE

English is the official language of the Conference although some of the Main Lectures will have simultaneous translation into Spanish.

## EXHIBITION

Conference participants are invited to visit the exhibition located at the Hall Plaza Mayor. The exhibition will be open on October 3rd at 16.30h until October 6th at 13.00h.

## INSURANCE

Participants are strongly advised to make their own arrangements in respect to health and travel insurances. The Organizer do not accept any liability for individual medical, travel or personal insurance.

## PASSPORT AND VISA

Identity card is required to entry in Spain for people from EEC Countries, For people from non EEC countries a valid passport is required. A visa may be required for some countries. For information about visa and passports contact the Spanish embassy in your country at least 3 months prior to your departure to Spain.

## TECHNICAL SECRETARIAT

The Technical Secretariat desk will be open the following times:

03/10 from 16.30h. to 19.00h.

04/10 from 08.00h to 13.30h. and from 14.30h. to 19.00h.

05/10 from 08.00h to 13.30h. and from 14.30h. to 19.00h.

06/10 from 08.00h. to 13.00h.

## LUNCHES AND COFFEE BREAKS:

Lunches: PIC NIC Lunch.

Coffee Breaks: will be served at the Hall Plaza Mayor.

# ABOUT MADRID

Madrid is an exciting and fascinating city with much to offer to the visitor in terms of art, culture and leisure, all of them within the city itself and in its surroundings.

Madrid's Museum Mile has more masterpieces per metre than anywhere else in the world: Museo del Prado, Museo Thyssen and Centro de Arte Reina Sofía, where all the history of universal painting has been collected, together with many of its most outstanding masterpieces.

There is always something to do to have fun in Madrid, and at every time of the day: a huge and delicious gastronomy, tempting shops difficult to avoid, and a vibrating nightlife. You will surely enjoy the hospitality of the inhabitants and the beautiful autumn in the city of Madrid.

Madrid Tourism Information:

<http://www.descubremadrid.com> and <http://www.munimadrid.es>

## CLIMATE

Early October daytime temperatures are around 20-25° and a bit cooler during the evenings.

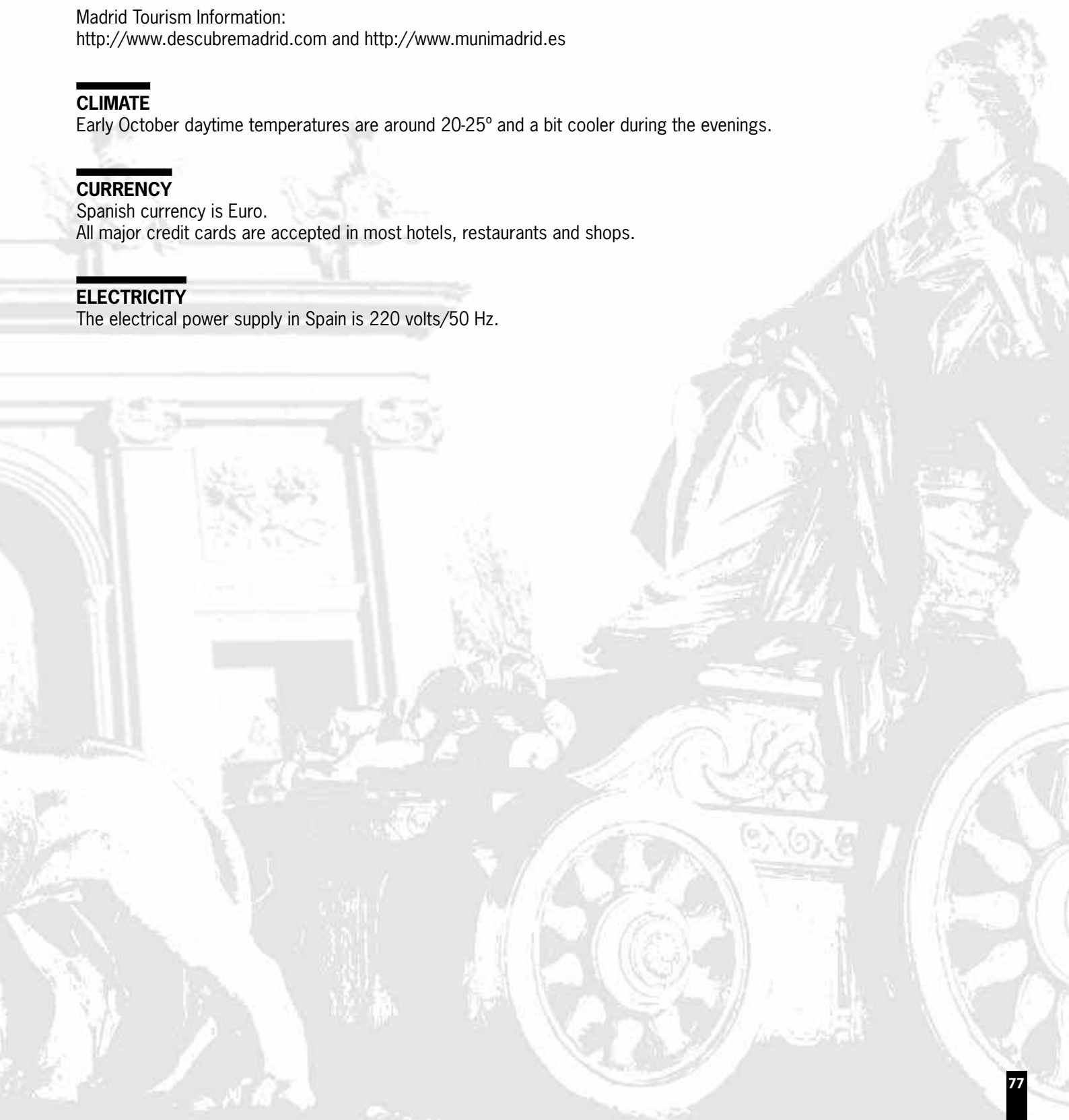
## CURRENCY

Spanish currency is Euro.

All major credit cards are accepted in most hotels, restaurants and shops.

## ELECTRICITY

The electrical power supply in Spain is 220 volts/50 Hz.



# NOTES



Congress Secretariat:



Viajes & Congresos S.A.  
C/ Gran Vía, 71, 3º Ext. Izdo. - 28013 Madrid - Spain  
Tel.: +34 91 547 37 47 - Fax: +34 91 559 58 81

[www.viajesycongresos.com](http://www.viajesycongresos.com)  
[vycongrema@viajesycongresos.com](mailto:vycongrema@viajesycongresos.com)