DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: OCT 17 2000

From: (Acting) Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification for New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient:	Cotinine
Firm:	Pharmaco Behavioral Associates, Inc.
Date Received by FDA:	August 4, 2000
90-Day Date:	November 2, 2000

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on pubic display in docket number 95S-0316 after November 2, 2000.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

RPT 79

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

OCT 17 2000

Robert M. Keenan, M.D., Ph.D.
Pharmaco Behavioral Associates, Inc.
810 Gleneagles Court, Suite 310
Towson, Maryland 21286

Dear Dr. Keenan:

This is in response to your letter, dated July 31, 2000, submitted to the Food and Drug Administration (FDA). In this letter, you make a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)). Your letter notifies FDA of your intent to market a product containing cotinine (1-methyl-5-(3-pyridinyl)-2-pyrrolidinone), an extract of the Australian Corkwood Tree (Duboisia Hopwoodii), as a dietary supplement. However, for reasons discussed below, we believe that cotinine, as presented in your submission, is a drug under 21 U.S.C. 321(g)(1)(B) (section 201(g)(1)(B) of the Act) because it is intended for treatment of nicotine addiction.

You state in your submission, "Cotinine, as a dietary supplement, will be recommended for use by cigarette smokers who want to quit smoking." You also maintain:

> Cotinine users will be instructed [to] self-administer two capsules orally every day (q a.m. and q p.m.) for two weeks prior to attempting to quit smoking cigarettes. Following this two week preparation and during their smoking cessation attempt, smokers will be instructed to self-administer two to four capsules on a daily basis as needed to help achieve tobacco abstinence.

(Submission at page 1).

Under 21 U.S.C. 321(g)(1)(B), a drug is defined as an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. You indicate in your submission that you will suggest to consumers that cotinine will enable them to quit smoking if used twice daily for two weeks before and during an attempt at smoking cessation. As a result, your product is intended as treatment for nicotine addiction and thus is a drug under 21 U.S.C. 321(g)(1)(B). See 65 F.R. 1000, 1030 (January 6, 2000). Accordingly, your product would be subject to regulation under the drug provisions of the Act. If you wish cotinine to be evaluated for its use in the treatment of nicotine addiction, you should contact FDA's Center for Drug Evaluation and Research (CDER), Office of Compliance, HFD-310, 7520 Standish Place, Rockville, Maryland 20855.

Because the information in your submission indicates that your product is a drug and not a dietary supplement, we are providing no response with respect to whether there is an adequate basis to conclude that a dietary supplement containing cotinine will be reasonably expected to be safe under 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the act). However, please note that, under 21 C.F.R. 190.6(f), failure by FDA to respond to a notification under section 350b(a)(2) does not constitute a finding by the agency that a new dietary ingredient or the dietary supplement is safe or is not adulterated under 21 U.S.C. 342 (section 402 of the Act). Therefore, not only would your product be subject to regulation as a drug if marketed, but, even insofar as it might be argued that your product is a dietary supplement, it could be deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) (section 402(f)(1)(B) of the Act). In any event, you are not prohibited from submitting a new pre-market notification for cotinine under 21 U.S.C. 350b(a)(2), if you deem such resubmission appropriate.

Your submission will be kept confidential for 90 days from the date of receipt, August 4, 2000, and after November 2, 2000, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public.

Should you have any questions concerning this matter, please contact us at (202) 205-4168.

Sincerely yours,

Felicia B. Satchell

Felicia B. Satchell
(Acting) Director
Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements
Center for Food Safety and Applied Nutrition

Robert M. Keenan, MD, PhD
Pharmaco Behavioral Associates, Inc.
810 Gleneagles Court, Suite 310
Towson, MD 21286

July 31, 2000

Office of Special Nutritionals (HFS-450)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street, SW
Washington, DC 21204

To whom it may concern:

Enclosed you will find the 75-day Premarket Notification For A New Dietary Supplement as required by 21 CFR 190.6. There is one original and two copies. Thank you for your time and consideration on this matter. If you have questions, please feel free to contact me at 410-823-5713.

Sincerely Yours,

Robert M. Keenan, MD, PhD

Robert M. Keenan, MD, PhD
Pharmaco Behavioral Associates, Inc.
810 Gleneagles Court, Suite 310
Towson, MD 21286

Received 8/4/00
RFF

July 31, 2000

PREMARKET NOTIFICATION FOR A NEW DIETARY SUPPLEMENT

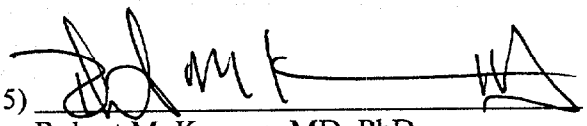
Robert M. Keenan, MD, PhD
Towson, MD 21286

410-823-5713
410-823-5734 (fax)
Corey25@erols.com

2) The new dietary supplement is the extract of the Australian Corkwood Tree (Duboisia Hopwoodii) containing only cotinine (1-methyl-5-(3-pyridinyl)-2-pyrrolidinone). Cotinine is a natural alkaloid found in significant amounts in Genus Solanaceae plants such as Duboisia Hopwoodii and several types of Nicotiana species.

3) Cotinine combined with a small amount of excipient (magnesium stearate and lactose) will be placed in #4 capsules to achieve a dose of 40 mg per capsule. Cotinine, as a dietary supplement, will be recommended for use by cigarette smokers who want to quit smoking (see Appendix A for efficacy data). Cotinine users will be instructed self-administer two capsules orally every day (q a.m. and q p.m.) for a period of two weeks prior to attempting to quit smoking cigarettes. Following this two-week preparation and during their smoking cessation attempt, smokers will be instructed to self-administer two to four capsules on a daily basis as needed to help achieve tobacco abstinence. Thus, the overall recommended daily cotinine dose will range from 80 to 160 mg of cotinine each day.

4) For a written summary of existing safety data related to cotinine use, see Appendices A-C.

5) 
Robert M. Keenan, MD, PhD
(see attached C.V.)

CURRICULUM VITAE

Robert Michael Keenan, MD PhD

ADDRESS

The Elite Center
810 Gleneagles Court, Suite 310
Baltimore MD 21286
Office: (410) 823-5483
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The Elite Center
7130 Minstrel Way, Suite LL130
Columbia MD 21046
Office: (410) 381-6205
Fax: (410) 381-6978

The Elite Center
2107 Laurel Bush Road, Suite 209
Bel Air MD 21045
Office: (410) 569-1733
Fax: (410) 569-2502

POSITIONS

Owner and Staff Physician, The Elite Center, Baltimore MD, 5-93 to present.

Biomedical Research Consultant, Pharmaco Behavioral Associates, Incorporated, Bloomington, MN, 3-93 to present.

Guest Research Fellow, Biology of Dependence Laboratory, Clinical Pharmacology Branch, Division of Intramural Research, National Institute on Drug Abuse, National Institutes of Health, Johns Hopkins Bayview Medical Center, Baltimore MD, 3-93 to 8-97.

Drug Development/Biomedical Research Consultant, LecTec Corporation, Minnetonka, MN, 3-93 to 3-96.

Senior Staff Research Fellow, Biology of Dependence Laboratory, Clinical Pharmacology Branch, Addiction Research Center, National Institute on Drug Abuse, National Institutes of Health, Johns Hopkins Bayview Medical Center, Baltimore MD, 7-91 to 3-93.

Associate Attending Physician, Center for Chemical Dependence, Johns Hopkins Bayview Medical Center, Baltimore MD, 7-92 to 7-93.

On-Duty Psychiatric Physician, Crownsville Hospital Center, Maryland State Hospital, Crownsville MD, 9-91 to 6-93.

Medical Director, Comprehensive Women's Center/ Methadone Maintenance Program, Johns Hopkins Hospital, Baltimore MD, 8-91 to 11-93.

Bariatric Physician, Dr. William J. Strowhouer Clinic, Denton MD, 8-91 to 8-93.

Staff Intern, Hennepin County Medical Center, Minneapolis MN, 6-90 to 6-91.

Post-Doctoral Research Associate, Department of Psychiatry, University of Minnesota Medical School, Minneapolis MN, 7-88 to 6-91.

Graduate Research Assistant, Department of Psychiatry, University of Minnesota Medical School, Minneapolis MN, 9-84 to 7-88.

Undergraduate Research Assistant, Department of Psychiatry, University of Minnesota Medical School, Minneapolis MN, 9-83 to 9-84.

Undergraduate Research Assistant, Department of Psychology, University of Minnesota, Minneapolis MN, 12-81 to 9-84.

EDUCATION

Graduate Fellowship:
Clinical Pharmacology Fellowship
Biology of Dependence Laboratory
Clinical Pharmacology Branch
Intramural Research Program
National Institute on Drug Abuse
National Institutes of Health
Johns Hopkins Bayview Medical Center
Baltimore, MD 7-91 to present

Medical Internship:
Rotating Transitional Internship
Hennepin County Medical Center
Minneapolis, MN 6-90 to 6-91

Medical Education:
Doctor of Medicine (MD)
University of Minnesota Medical School
Minneapolis, MN 9-85 to 6-90

Graduate Education:
Doctor of Philosophy (PhD)
Experimental Psychology
Departments of Psychology and Psychiatry
University of Minnesota Graduate School
Minneapolis, MN 9-84 to 8-88

Undergraduate:
Bachelor of Arts (BA)
Psychology and Physiology
University of Minnesota College of Liberal Arts
Minneapolis, MN 9-78 to 6-84

HONORS AND AWARDS

Young Investigator Award, November 1994, American Society ofAddiction Medicine, 7th National Conference on Nicotine Dependence.

Distinguished Contributor, October 1994, American Society of Addiction Medicine, ASAM principles of Addiction Medicne.

Rock Sleyster Scholar, 1989-90
American Medical Association Education and Research Foundation.

Summa Cum Laude, Bachelor of Arts (Psychology and Physiology), 1984.

PROFESSIONAL SOCIETIES

American Society of Addiction Medicine
Society for Research on Nicotine and Tobacco

PROFESSIONAL ACTIVITIES

EDITORIAL REVIEWER

Addictive Behaviors
Annals of Internal Medicine
Archives of Internal Medicine
Behavior Research Methods, Instruments, & Computers
Chest
Journal of Substance Abuse Treatment
Journal of the American Medical Association
Psychopharmacology
Preventive Medicine

AD HOC RESEARCH REVIEWER

Tobacco-Related Disease Research Program
University of California
Oakland, CA

Program Presentation Reviewer
Society for Research on Nicotine and Tobacco
Washington, DC

PATENTS PENDING

Inventors: Robert M. Keenan, MD PhD and Dorothy K. Hatsukami, PhD
Title: Cotinine to Alleviate the Tobacco Withdrawal Syndrome
United States Patent Application
Serial Number: 07/885,314

Inventor: Robert M. Keenan, MD PhD
Title: Human Body Weight Management
United States Patent Application
Serial Number: 07/964,277

Inventor: Robert M. Keenan, MD PhD
Title: Nicotine Metabolites, Nicotine Dependence, and Human Body Weight
United States Patent Application
Serial Number: 08/012,379

Inventor: Robert M. Keenan, MD PhD
Title: Use of Cotinine to Alleviate the Tobacco Withdrawal Syndrome
United States Patent Application
Serial Number: 08/293,585

Inventor: Robert M. Keenan, MD PhD
Title: Nicotine-Free Smoking Material
United States Patent Application
Serial Number: 08/398,528

Inventor: Robert M. Keenan, MD PhD
Title: Use of Cotinine to Treat Imflammatory Bowel Disorders
United States Patent Application
Serial Number: 08/405,607

PRESENTATIONS

Keenan RM. The effects of dose on the self-administration of nicotine gum. Behavioral Pharmacology Symposium, Monticello MN: March, 1985.

Keenan RM, Gust SW, Hughes JR. The effects of nicotine gum on smoking cessation. Conference of the Minnesota Association of Behavior Analysts, Minneapolis MN: April, 1985.

Gust SW, Keenan RM, Pickens RW. Situational control of cigarette smoking topography in the natural environment. The Annual Meeting of the Association of Behavior Analysts, Columbus OH: May, 1985.

Keenan RM, Hughes JR. The effects of tobacco withdrawal on performance. Committee on Problems of Drug Dependence Annual Meeting, Baltimore MD: June, 1985.

Hughes JR, Keenan RM. Instructions control the ability of nicotine to serve as a reinforcer. International Study Group Investigating Drugs as Reinforcers, Baltimore MD: June, 1985.

Hughes JR, Gust SW, Keenan RM, Ramlet D, Healy M, Skoog KP. The efficacy of nicotine gum in general practice. III World Conference on Clinical Pharmacology and Therapeutics, Stockholm Sweden: August, 1986.

Hughes JR, Gust SW, Keenan RM, Skoog KP, Strickler G, King D, Pickens RW, Hatsukami DK. Behavioral and physical dependence on nicotine gum. III World Conference on Clinical Pharmacology and Therapeutics, Stockholm, Sweden: August, 1986.

Hughes JR, Pickens RW, Keenan RM, Gulliver S, Amori G, Spring W. Instructions control whether nicotine is a reinforcer. III World Conference on Clinical Pharmacology and Therapeutics, Stockholm, Sweden: August, 1986.

Hughes JR, Gust SW, Keenan RM, Skoog KP, Pickens RW. The efficacy of nicotine gum in general clinical practice. Annual Meeting of the American Psychological Association, Washington DC: August, 1986.

Hatsukami DK, Keenan RM. Symptoms of smokeless tobacco withdrawal. Annual Meeting of the American Psychological Association, Washington DC: August, 1986.

Gottesman J, Burkhardt DA, Keenan RM. Sensory latency and reaction time: Dependence on contrast polarity and early linearity in human vision. Annual Meeting of the Association of Researchers on Vision and Ophthalmology, Clearwater FL: April, 1987.

Hatsukami DK, Keenan RM, Anton DJ. Situational, temporal and subjective control of smokeless tobacco use. Annual Meeting of the American Psychological Association, New York NY: August, 1987.

Keenan RM, Hatsukami DK, Pickens RW. Influences of alcohol consumption on smoking behavior. Annual Meeting of the American Psychological Association, New York NY: August, 1987.

Hughes JR, Gust SW, Keenan RM, Skoog K, Pickens RW, Ramlet D, Healy M, Higgins S. Efficacy of nicotine gum in general practice: One-year follow-up. Committee on Problems of Drug Dependence Annual Meeting,, Philadelphia PA: June, 1987.

Keenan RM, Carroll ME, Lac ST. Effects of nicotine and PBA-415 on caloric intake. Annual Meeting of the Society for Neuroscience Research, Toronto Canada: November, 1988.

Keenan RM, Hatsukami DK, Heston LL. Cigarette smoking and ethanol use: Implications for disease. Midwest Student Medical Research Forum, Omaha NE: February, 1989.

Hughes JR, Gust SW, Keenan RM, Fenwick JW. Effects of dose on nicotine's withdrawal-suppressing, adverse and discriminative effects in humans. Committee on Problems of Drug Dependence Annual Meeting, Keystone CO: June, 1989.

Hatsukami DK, Keenan RM, Colon EA, Carroll ME. Dose-related biochemical, physiological and subjective changes from smoked cocaine-base. International Study Group Investigating Drugs as Reinforcers, Keystone CO: June, 1989.

Hatsukami DK, Keenan RM, Anton DJ. Smokeless tobacco withdrawal, nicotine and performance. Annual Meeting of the American Psychological Association, New Orleans LA: August, 1989.

Keenan RM, Hatsukami DK. Dose related effects of smoked cocaine in humans. Midwest Student Medical Research Forum, Omaha NE: February, 1990.

Keenan RM. The association between chronic ethanol use and cigarette smoking topography. Behavioral Pharmacology Symposium, Brainerd MN: May, 1987.

Keenan RM, Henningfield JE. Nicotine among other addicting drugs: An update. 4th National Conference on Nicotine Dependence: American Society of Addiction Medicine. Raleigh NC: September, 1991.

Keenan RM. The pharmacological treatment of nicotine dependence. 16th Annual Conference on Alcoholism and Drug Abuse. University of Texas, El Paso: February, 1992.

Henningfield JE, White JA, Keenan RM. Cigarette smoking among other drug addictions. Eighth World Conference on Smoking or Health, Buenos Aires, Argentina: March 1992.

Keenan RM, Hatsukami DK, Pentel PR, Henningfield JE. Cotinine: An active metabolite of nicotine. College on the Problems of Drug Dependence Annual Meeting, Toronto Ontario Canada: June, 1993.

Carmona GN, Keenan RM, Goldberg SR, Schindler CW. Cardiovascular effects of smoked cocaine and methamphetamine in squirrel monkeys: Preliminary findings. College on the Problems of Drug Dependence Annual Meeting, Toronto Ontario Canada: June, 1993.

Taylor RC, Keenan RM, Heishman SJ, Neu AV, Henningfield JE. Performance effects of smoked nicotine and cocaine in humans. College on Problems of Drug Dependence Annual Meeting, Toronto Ontario Canada: June, 1993.

Pickworth WB, Keenan RM, Neu AV, Henningfield JE. Pupillary effects of intravenous and smoked cocaine in humans. College on the Problems of Drug Dependence Annual Meeting, Toronto Ontario Canada: June, 1993.

Jenkins AJ, Keenan RM, Cone EJ, Kivett JB, DeMuth K, Neu AV, Heishman SJ, Henningfield JE. A method for delivering smoked drugs of abuse in humans: Preliminary findings. College on Problems of Drug Dependence Annual Meeting, Toronto, Ontario, Canada: June, 1993.

Henningfield JE, Keenan RM, Cone EJ, Neu AV, DeMuth K, Kivett JB, Jenkins AJ, Heishman SJ. A pharmacodynamic comparison of smoked and intravenous cocaine and nicotine in humans. College on Problems of Drug Dependence Annual Meeting, Toronto Ontario Canada: June, 1993.

Heishman SJ, Francis-Wood A, Keenan RM, Chiang CN, Terrill JB, Tai B, Henningfield JE. Safety and pharmacokinetics of a new formulation of depot naltrexone. College on Problems of Drug Dependence Annual Meeting, Toronto Ontario Canada: June, 1993.

Jenkins AJ, Keenan RM, Henningfield JE, Cone EJ. Pharmacokinetics and pharmacodynamics of smoked cocaine. American Academy of Forensic Sciences, October, 1993.

Jenkins AJ, Grant TM, Keenan RM, Cone EJ. Disposition of heroin and metabolites in blood from subjects who smoked heroin. Society of Forensic Toxicology, Phoenix AZ: October, 1993.

Henningfield JE, Jenkins AJ, Steinberg K, Keenan RM, Cone EJ. The role of nicotine delivery rate in development of selectively targeted medications. College on Problems of Drug Dependence Annual Meeting, Palm Beach FL: June, 1994.

Keenan RM, Hatsukami DK, Henningfield JE. Are alcohol abuse and gender risk factors for increased cigarette-related disease? College on Problems of Drug Dependence Annual Meeting, Palm Beach FL: June, 1994.

Nelson RA, Keenan RM, Gorelick DA, Carmona GN, Covi L. Cardiovascular effects of cocaine use in outpatients taking antidepressant medications. College on Problems of Drug Dependence Annual Meeting, Palm Beach FL: June, 1994.

Henningfield JE, Keenan RM, Evans SM, Jenkins AJ, Cone EJ. Physiological basis of the addictiveness of the smoked route of administration. National Institutes of Health Research Festival, Besthesda MD: September, 1994.

Keenan RM, Jenkins AJ, Cone EJ, Henningfield JE. Smoked and iv nicotine, cocaine and heroin have similar abuse liability. 7th National Conference on Nicotine Dependence: American Society of Addiction Medicine. Cambridge MA: November, 1994.

Schuh LM, Henningfield JE, Pickworth WB, Rothman R, Ohuoha D, Keenan RM. Pharmacodynamic effects of cotinine. Society for Research on Nicotine and Tobacco Annual Meeting. San Diego CA: March, 1995.

Nelson RA, Keenan RM, Hatsukami DK. Pharmacodynamic effects of acute smokeless tobacco use. Society for Research on Nicotine and Tobacco Annual Meeting. San Diego CA: March, 1995.

Liberto JG, Kroiss SL, Keenan RM, Rolf D. Cotinine in the treatment of cigarette smoking. 8th National Conference on Nicotine Dependence: American Society of Addiction Medicine. Toronto, Ontario, Canada: October, 1995.

Jenkins AJ, Keenan RM, Henningfield JE, Cone EJ. A comparison of the pharmacokinetics of cocaine, heroin and nicotine after smoked and intravenous administration. Society of Forensic Toxicology, Baltimore MD: October, 1995.

Schuh LM, Henningfield JE, Fant R, Pickworth WB, Rothman R, Ohuoha D, Keenan RM. Pharmacodynamic effects of cotinine. College on Problems of Drug Dependence Annual Meeting, San Juan, Puerto Rico: June, 1996.

Pickworth WB, Fant R, Jenkins A, Keenan RM. Effects of intravenous and smoked nicotine on pupil size and pupillary light reflex. College on Problems of Drug Dependence Annual Meeting, San Juan, Puerto Rico: June, 1996.

Jenkins AJ, Keenan RM, Henningfield JE, Cone EJ. A pharmacologic profile of smoked heroin and cocaine in humans. College on Problems of Drug Dependence Annual Meeting, San Juan, Puerto Rico: June, 1996.

PUBLICATIONS

Hughes JR, Pickens RW, Spring W, Keenan RM (1985). Instructions control whether nicotine will serve as a reinforcer. Journal of Pharmacology and Experimental Therapeutics, 235, 106-112.

Hatsukami DK, Gust SW, Keenan RM (1987). Physiological and subjective changes from smokeless tobacco withdrawal. Clinical Pharmacology and Therapeutics, 41, 103-107.

Burkhardt DA, Gottesman J, Keenan RM (1987). Equivalence effects of negative and positive luminance contrast on human reaction time. Journal of the Optical Society of America, 4, 530-539.

Hatsukami DK, Keenan RM, Anton DJ (1987). Situational, subjective and temporal control of smokeless tobacco use. Pharmacology, Biochemistry and Behavior, 27, 589. (ABSTRACT).

Keenan RM, Hatsukami DK, Pickens RW (1987). Influences of ethanol consumption on cigarette smoking topography. Pharmacology, Biochemistry and Behavior, 27, 590. (ABSTRACT).

Gottesman J, Burkhardt DA, Keenan RM (1987). Sensory latency and reaction time: Dependence on contrast polarity and early linearity in human vision. Investigative Ophthalmology and Visual Science (supplement), 28, 363 (ABSTRACT).

Hughes JR, Gust SW, Keenan RM, Skoog K, Pickens RW, Ramlet D, Healy M, Higgins S (1988). Efficacy of nicotine gum in general practice: One-year follow-up. In LS Harris (ed), Problems of Drug Dependence 1987, NIDA Research Monograph Series No 81, DHHS Pub No (ADM) 88-1564.

Keenan RM, Carroll ME, Lac ST (1988). Effects of nicotine and PBA-415 on caloric intake. Journal for the Society of Neuroscience, 14, 208 (ABSTRACT).

Hatsukami DK, Keenan RM, Anton DJ (1988). Topographical features of smokeless tobacco use. Psychopharmacology, 96, 428-429.

Hughes JR, Gust SW, Keenan RM, Fenwick JW, Healy M (1989). Nicotine versus placebo gum in general medical practice. Journal of the American Medical Association, 261, 1300-1305.

Keenan RM, Hatsukami DK, Anton DJ (1989). The effects of short-term smokeless tobacco deprivation on performance. Psychopharmacology, 98, 126-130.

Hatsukami DK, Fletcher L, Morgan S, Keenan RM, Amble PJ (1989). The effects of varying cigarette deprivation duration on cognitive and performance tasks. Journal of Substance Abuse, 1, 407-416.

Hatsukami DK, Keenan RM, Anton DJ (1989). Smokeless tobacco deprivation, nicotine and performance. Pharmacology, Biochemistry and Behavior, 32, 1084 (ABSTRACT).

Carroll ME, Lac ST, Asencio M, Keenan RM (1989). Nicotine dependence in rats. Life Sciences, 45, 1381-1388.

Hughes JR, Keenan RM, Yellin AM (1989). Effect of tobacco withdrawal on a sustained attention task. Addictive Behaviors, 14, 577-580.

Keenan RM, Hatsukami DK, Heston LL (1989). Cigarette smoking and ethanol use: Implications for disease. Clinical Research, 37, 974a. (ABSTRACT).

Keenan RM (1989). The association between chronic ethanol exposure and cigarette smoking topography. Dissertation Abstracts. University of Michigan Press, Ann Arbor.

Keenan RM, Hatsukami DK, Pickens RW, Gust SW, Strelow LJ (1990). The association between chronic ethanol exposure and cigarette smoking behavior in the laboratory and the natural environment. Psychopharmacology, 100, 77-83.

Hughes JR, Gust SW, Keenan RM, Fenwick JW (1990). Effects of dose on nicotine's reinforcing, adverse, withdrawal-suppression and discriminative stimulus effects. Journal of Pharmacology and Experimental Therapeutics, 252, 1175-1183.

Hughes JR, Gust SW, Keenan RM, Fenwick JW (1990). Effects of dose on nicotine's withdrawal-suppressing, adverse and discriminative effects in humans. In LS Harris (ed), Problems of Drug Dependence 1989, In LS Harris (ed), NIDA Research Monograph Series No 95, DHHS Pub No. (ADM) 90-1663, (ABSTRACT).

Hatsukami DK, Keenan RM, Carroll ME, Colon EA, Geiske DJ, Wilson B, Huber M (1990). A method for delivery of precise doses of smoked cocaine-base to humans. Pharmacology, Biochemistry and Behavior, 36, 1-7.

Hughes JR, Gust SW, Skoog K, Keenan RM, Fenwick JW (1991). Symptoms of tobacco withdrawal: A replication and extension. Archives of General Psychiatry, 48, 52-59.

Hatsukami DK, Keenan RM, Halikas J, Pentel P, Hartman-Brauer L (1991). Effects of carbamazepine on the acute response to smoked cocaine-base. Psychopharmacology, 104, 120-124.

Hughes JR, Gust SW, Keenan RM, Skoog K, Fenwick JW, Higgins ST (1991). Long-term use of nicotine gum. Archives of Internal Medicine, 151, 1993-1998.

Hatsukami DK, Anton DJ, Callies A, Keenan RM (1991). Situational factors and patterns associated with smokeless tobacco use. Journal of Behavioral Medicine, 14, 383-396.

Hatsukami DK, Anton DJ, Keenan RM, Callies A (1992). Smokeless tobacco abstinence effects and nicotine gum dose. Psychopharmacology, 106, 60-66.

Keenan RM, Hatsukami DK (1992). Dose-related effects of smoked cocaine in humans. Clinical Research, (In Press).

Kozlowski LT, Henningfield JE, Keenan RM, Lei H, Leigh G, Jelinek LC, Pope MA, Haertzen CA (1993). Patterns of alcohol, cigarette, and caffeine and other drug use in two drug abusing populations. Journal of Substance Abuse Treatment, 10, 171-179.

Henningfield JE, Keenan RM (1993). Nicotine delivery kinetics and abuse liability. Journal of Clinical and Consulting Psychology, 61, 743-750.

Henningfield JE, Keenan RM (1993). The anatomy of nicotine addiction. Health Values, 17, 12-19.

Henningfield JE, Keenan RM (1993). Abuse potential of nicotine. Choices in Respiratory Management, (In Press).

Keenan RM, Hatsukami DK, Pentel P, Thompson T, Grillo MA (1994). Pharmacodynamic effects of cotinine in abstinent cigarette smokers. Clinical Pharmacology and Therapeutics, 55, 81-90.

Keenan RM, Hatsukami DK, Pentel PR, Henningfield JE (1994). Cotinine: An active metabolite of nicotine. In: LS Harris (ed), Problems of Drug Dependence 1993, NIDA Research Monograph Series No. 141, pps. 404, NIH Pub. No. 94-3749, (ABSTRACT).

Carmona GN, Keenan RM, Goldberg SR and Schindler CW (1994). Cardiovascular effects of smoked cocaine and methamphetamine in squirrel monkeys: Preliminary findings. In: LS Harris (ed), Problems of Drug Dependence 1993, NIDA Research Monograph Series No. 141, pps. 319, NIH Pub. No. 94-3749, (ABSTRACT).

Taylor RC, Keenan RM, Heishman SJ, Neu AV, Henningfield JE (1994). Performance effects of smoked nicotine and cocaine in humans. In: LS Harris (ed), Problems of Drug Dependence 1993, NIDA Research Monograph Series No. 141, pps. 402, NIH Pub. No. 94-3749, (ABSTRACT).

Pickworth WB, Keenan RM, Neu AV, Henningfield JE (1994). Pupillary effects of intravenous and smoked cocaine in humans. In: LS Harris (ed), Problems of Drug Dependence 1993, NIDA Research Monograph Series No. 141, pps. 376, NIH Pub. No. 94-3749, (ABSTRACT).

Jenkins AJ, Keenan RM, Cone EJ, Kivett JB, DeMuth K, Neu AV, Heishman SJ, Henningfield JE (1994). A method for delivering smoked drugs of abuse in humans: Preliminary findings. In: LS Harris (ed), Problems of Drug Dependence 1993, NIDA Research Monograph Series No. 141, pps. 401, NIH Pub. No. 94-3749, (ABSTRACT).

Henningfield JE, Keenan RM, Cone EJ, Neu AV, DeMuth K, Kivett JB, Jenkins AJ, Heishman SJ (1994). A pharmacodynamic comparison of smoked and intravenous cocaine and nicotine in humans. In: LS Harris (ed), Problems of Drug Dependence 1993, NIDA Research Monograph Series No. 141, pps. 376, NIH Pub. No. 94-3749, (ABSTRACT).

Heishman SJ, Francis-Wood A, Keenan RM, Chiang CN, Terrill JB, Tai B, Henningfield JE (1994). Safety and pharmacokinetics of a new formulation of depot naltrexone. In: LS Harris (ed), Problems of Drug Dependence 1993, NIDA Research Monograph Series No. 141, pps. 82, NIH Pub. No. 94-3749, (ABSTRACT).

Pickworth WB, Keenan RM, Henningfield JE (1994). Nicotine: Effects and mechanisms. In: Handbook of Neurotoxicology II. Effects and Mechanisms. Section V: Drugs of Abuse, Chang and Dyer eds., Marcel Dekker, Inc. New York, NY, pps. 801-824.

Keenan RM, Jarvik ME, Henningfield JE (1994). Management of nicotine dependence and withdrawal. In: NS Miller, JF Callahan (eds), American Society of Addiction Medicine: Principles of Addiction Medicine, Chapter 7, pps. 1-14.

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Appendix A

JULY 31, 2000

COTININE IN THE TREATMENT OF CIGARETTE SMOKING

Robert M. Keenan, M.D., Ph.D.

ABSTRACT

Cotinine, the major metabolite of nicotine, has been shown to influence the tobacco withdrawal syndrome following short-term nicotine abstinence. Hence, cotinine may have utility as a treatment for cigarette smoking. In this study using a double-blind, placebo-controlled randomized design, the safety and efficacy of oral cotinine fumarate in the treatment of cigarette smoking were examined. The results showed that cotinine is completely safe at this dose and is efficacious in the treatment of cigarette smoking. Further research must be performed to determine the optimum treatment dose and duration.

INTRODUCTION

Cigarette smoking is the most severe form of drug addiction claiming a higher death toll than all other addictions combined. Each year in the United States, over 400,000 people die as the result of tobacco-induced pathology (McGinnis and Foege, 1993). Although the role that nicotine plays in the mediation of tobacco dependence has been greatly elucidated over time, little research effort has been expended to understand the pharmacologic contribution of nicotine metabolites in this process.

Cotinine is the major metabolite of nicotine in tobacco users. The sensitivity and specificity of cotinine as a biochemical marker of daily nicotine exposure through tobacco use are excellent (Benowitz, 1983). Hence, blood and salivary cotinine concentrations are routinely used experimentally to objectively quantify nicotine intake in tobacco-related research paradigms. Until recently, cotinine was thought to be an inactive byproduct of nicotine metabolism (Benowitz et al., 1983). In contrast to this notion, intravenous cotinine compared to placebo induced subjective changes in abstinent cigarette smokers suggesting that it may contribute to the observed pharmacologic effects of nicotine *in vivo* (Keenan et al., 1994; 1995). Moreover, cotinine may play an important role in the tobacco dependence process as well as have potential utility as a treatment for this problem.

In this study, a double-blind placebo-controlled randomized comparison of the efficacy of oral cotinine (100 mg each day) in reducing the severity of the nicotine withdrawal syndrome and increasing short-term cigarette smoking cessation rates was undertaken. Cotinine decreased various symptoms of the tobacco withdrawal syndrome and increased smoking cessation rates with minimal effect on the cardiovascular system.

METHODS

Patients: 82 healthy male and female cigarette smokers who were between the ages of 21 and 65 years old; had no DSM-III-R psychiatric diagnoses (other than substance abuse); not physically dependent on drugs or alcohol (excluding nicotine or caffeine); using an acceptable form of birth control; smoked at least 20 cigarettes per day for one year; had an afternoon expired-air carbon monoxide (CO) level $\geq$ 20 ppm; had a Fagerstrom Nicotine Tolerance Questionnaire Score $\geq$ 5; and were motivated to quit smoking cigarettes. Potential volunteers were recruited using newspaper advertisements and word-of-mouth. Patients received no money for study participation.

Drug Preparation and Administration: Cotinine fumarate was obtained from the LecTec Corporation of Minnetonka, Minnesota. Cotinine was prepared by LecTec for human use under the guidelines of the FDA. Cotinine fumarate and identical placebo capsules were prepared and shipped to the Baltimore VA Hospital Pharmacy for dispensation in a double-blinded manner. The 82 participants were randomized into two groups. One group received the active drug and the other placebo for the duration of the investigation. Each morning, one cotinine capsule (0 mg or 100 mg) was orally ingested for 28 consecutive days. All patients were randomly-assigned to their respective dosing condition.

Dependent Measures: The dependent measures included heart rate, blood pressure, saliva cotinine concentration, CO, body weight, as well as self-reported cigarette use, subjective state, and symptoms of tobacco withdrawal. An adverse effects questionnaire was administered to systematically assess side effects related to cotinine use. These assessments were made during each visit. The treatment outcome measures included self-reported abstinence from cigarettes ($\leq$ 2 cigarettes per day), biochemical abstinence (CO $\leq$ 10 ppm) and CO-verified self-reported abstinence ($\leq$ 2 cigarettes per day and CO $\leq$ 10 ppm) as compared to the smoking baseline. Continuous abstinence was defined as meeting abstinence criteria at all post-cessation visits over the four weeks of treatment (visits 3 to 7).

Procedure: This outpatient study was performed over 29 days at the Baltimore VA Hospital. Patients were required to attend six experimental sessions lasting approximately 30 minutes each. Patients were monitored on day 1, 3, 8, 15, 22 and

29. All visits were held at the same time each day. Prior to study inclusion, patients attended an initial screening session during which a complete medical and drug use history as well as a physical examination was performed. Informed consent was obtained. Baseline and demographic data were also collected. If deemed healthy, to conclude this visit patients were scheduled for their next appointment which was considered a baseline session.

Prior to the baseline session, patients were instructed to continue to smoke their own brand of cigarettes in an ad libitum fashion. During the baseline session, all dependent measures were assessed. A pamphlet supplied by the National Cancer Institute entitled "Clear The Air" which gives behavioral tips to aide in a smoking cessation attempt was distributed to patients. The patients received medication to use until their next visit and were instructed to quit smoking the following morning. At 8 am each morning, patients were instructed to ingest their medication. Patients returned to the VA for evaluation at 2, 7, 14, 21 and 28 days following their cessation attempt. At each visit, all dependent measures were assessed and medication to use until the next visit was given to the patient. To end the last session, patients were offered a prescription for an approved nicotine replacement treatment medication (e.g., nicorette gum or nicotine patches), if so desired.

Statistical Analyses: All questionnaires were administered using pencil and paper. All recorded data were entered blindly into a computer for later analysis using SPSS. Missing data were replaced by substituting the previously recorded data collected at the most recent prior session for the subject. Statistical significance was defined as a p-value of ≤ 0.05.

For the treatment outcome measures, a chi-square analysis across dose was performed. For the continuous measures, a one-between (dose) one-within factor (time) two-way repeated measures ANOVA was performed.

RESULTS

Treatment Outcome: Cotinine tended to improve continuous abstinence rates as measured by self-reported cigarette use in smokers undergoing smoking cessation treatment as compared to placebo ($p \leq .09$). Twenty-seven percent of the cotinine group was abstinent compared to 12 percent of the placebo group.

Using CO, cotinine significantly improved continuous abstinence rates when compared to placebo ($p \leq .02$). Thirty-seven percent of the cotinine group was abstinent compared to their smoking baseline throughout the study versus 15 percent of the placebo group.

Using the combination of self-reported cigarettes smoked verified by CO, cotinine tended to improve continuous abstinence rates when compared to placebo ($p \leq .06$). Twenty-two percent of the cotinine group versus seven percent of the placebo group. Hence, it appears that cotinine is efficacious when used to induce abstinence from cigarettes during short-term treatment.

Subjective Effects: The symptoms of tobacco withdrawal measured included craving for cigarettes, irritable/angry, anxious/tense, difficulty concentrating, restlessness, need to smoke, impatience, hunger, fatigue, depressed, stress, insomnia, increased eating, desire to smoke, tired, unusual dreams, headache, and somatic symptoms rated on a 0 to 5 Likert scale with 0=none and 5=severe. A total score was calculated by summing the ratings of craving for cigarettes, irritable/angry, anxious/tense, difficulty concentrating and restlessness. Cotinine produced significantly decreased ratings of need to smoke ($p \leq .03$) and stress ($p \leq .02$), while interacting with time to produce slightly increased ratings of fatigue ($p \leq .01$).

Physiologic Effects: Cotinine (versus placebo) produced no significant effects on body weight, heart rate or blood pressure.

DISCUSSION

In this study using a double-blind, placebo-controlled randomized design, the safety and efficacy of oral cotinine fumarate in the treatment of cigarette smoking were examined. The results showed that cotinine is completely safe and non-toxic at this dose and is efficacious in the treatment of cigarette smoking. Furthermore, cotinine also affected certain symptoms of the tobacco withdrawal syndrome which may help to explain it's pharmacological mechanism of action.

Limitations of this study include the single-dose design, missing data, small sample size, limited measurement duration and large variability of the responses. Moreover, oral cotinine has little, if any, potential toxicity for patients at this dose.

In conclusion, these data suggest that cotinine has efficacy as a pharmacological treatment for cigarette smoking and a beneficial effect on some of the observed symptoms of the tobacco withdrawal syndrome during abstinence. Further research must be performed to determine the optimum treatment dose and duration.

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APPENDIX B REMOVED

CONTAINED
CONFIDENTIAL
INFORMATION
CONSIDERED NOT TO BE
RELEASABALE

Appendix C
See pages 12-18

United States Patent **5,612,357**
Keenan **, et al.** **March 18, 1997**

Use of ***cotinine*** to assist in the cessation of tobacco smoking

Abstract

A pharmaceutical composition is provided that is useful to alleviate various symptoms of tobacco withdrawal syndrome comprising an amount of ***cotinine*** or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier, which amount is effective to reduce or eliminate at least one of the symptoms of tobacco withdrawal syndrome in a human.

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Assignee: **Pharmaco Behavioral Associates, Inc.** (Minneapolis, MN)

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Filed: **August 22, 1994**

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Intern'l Class: A61K 031/44
Field of Search: 514/343,810,813

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Parent Case Text

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. patent application Ser. No. 07/885,314, filed May 18, 1992, which is incorporated by reference herein.

Claims

1. A pharmaceutical composition useful to assist in the cessation of smoking comprising an amount of ***cotinine*** or a pharmaceutically acceptable salt thereof sufficient to deliver a dose of ***cotinine*** to a human subject of from about 1.0 mg/kg to about 100 mg/kg in combination with a pharmaceutically acceptable carrier.

2. The composition of claim 1 wherein the ***cotinine is (-)-cotinine***.

3. The composition of claim 2 wherein the ***cotinine*** is a salt of ***(-)-cotinine***.

4. The composition of claim 1 which is a pharmaceutical unit dosage form.

5. The composition of claim 4 wherein the pharmaceutical unit dosage form is adapted to oral administration.

6. The composition of claim 5 wherein the pharmaceutical unit dosage form is a chewing gum.

7. The composition of claim 4 wherein the pharmaceutical unit dosage form is adapted to parenteral administration.

8. The composition of claim 7 wherein the pharmaceutical unit dosage form comprises a transdermal delivery system.

9. The composition of claim 7 wherein the pharmaceutical unit dosage form is adapted to intraocular administration.

10. The composition of claim 9 wherein the pharmaceutical unit dosage form is an intraocular insert.

11. The composition of claim 7 wherein the pharmaceutical unit dosage form is adapted to intravenous administration.

12. The composition of claim 11 which comprises ***cotinine or the cotinine*** salt dissolved in a liquid vehicle.

13. The composition of claim 7 wherein the pharmaceutical unit dosage form is adapted to intranasal administration.

14. The composition of claim 7 wherein the pharmaceutical unit dosage form is adapted to administer the ***cotinine or the cotinine*** salt by inhalation.

15. A unit dosage form useful to assist in the cessation of smoking comprising about 40 mg to about 1000 mg of ***cotinine*** in combination with a pharmaceutically acceptable carrier.

16. A pharmaceutical composition useful to maintain tobacco abstinence comprising an amount of ***cotinine*** or a pharmaceutically acceptable salt thereof sufficient to deliver a dose of ***cotinine*** to a human subject of from about 0.4 mg/kg to about 15 mg/kg in combination with a pharmaceutically acceptable carrier.

17. A unit dosage form useful to maintain tobacco abstinence comprising about 40 mg to about 1000 mg of ***cotinine*** in combination with a pharmaceutically acceptable carrier.

18. A pharmaceutical composition useful to alleviate the craving associated with the cessation of tobacco smoking comprising an amount of ***cotinine*** or a pharmaceutically acceptable salt thereof sufficient to deliver a dose of ***cotinine*** to a human subject of from about 0.4 mg/kg to about 15 mg/kg in combination with a pharmaceutically acceptable carrier, which amount is effective to alleviate craving for at least one of cigarettes, tobacco or nicotine.

19. A unit dosage form useful to alleviate the craving associated with the cessation of tobacco smoking comprising about 40 mg to about 1000 mg of ***cotinine*** in combination with a pharmaceutically acceptable carrier.

Description

BACKGROUND OF THE INVENTION

Cigarette smoking continues to be the major preventable cause of death in the United States resulting in nearly 400,000 deaths per year due to cancer and heart disease. Despite the potential adverse health effects, grave consequences, the vast majority of cigarette smokers are unable to cease smoking.

The lack of smoking cessation success is thought to be related to the tobacco withdrawal syndrome or tobacco abstinence syndrome that most smoker experience during their attempts to quit. See, Office of Smoking and Health, The Health Consequences of Smoking: Nicotine Addiction. A Report to the Surgeon General, U.S. Govt. Print. Off., Washington, D.C., DHHS Pub. No. (CDC) 88-8406 (1988). The most common effects are similar to those in almost all abstinence syndromes, and include decreased heart rate, anxiety, difficulty concentrating, impatience, irritability and restlessness. See, American Psychiatric Assoc., Diagnostic and Statistical Manual, Washington D.C. (3rd ed. 1980) at pages 159-160, 176-178. Most withdrawal effects occur within 24 hours, peak in the first 1-2 weeks and significantly decrease at one month. It is widely believed that the effects of abstinence from tobacco are due to nicotine deprivation, and that abstinence effects from smoking prevent smokers from stopping. See, J. R. Hughes et al., in Research and Advances in Alcohol and Drug Problems, Vol. 10, L. T. Kozlowski et al., eds., Plenum Pub. Corp. (1990) at pages 317-398.

Of the pharmacological approaches to aiding cessation of smoking nicotine replacement, e.g., via transdermal nicotine patches or nicotine gum is the most widely used. Nicotine gum decreases abstinence discomfort, especially anxiety, decreased memory and irritability. On the other hand, nicotine gum does not reliably decrease weight gain or craving. Also, discontinuing use of nicotine gum leads to some of the same symptoms as the cigarette withdrawal syndrome. Furthermore, nicotine is toxic, and the availability of nicotine gum or patches poses a risk of poisoning to children and pets.

Other studies have demonstrated that alpha-2 agonists, such as clonidine, decrease postcessation anxiety, irritability and difficulty concentrating. Decreased sympathetic activity has been postulated to be the mechanism by which these drugs decrease abstinence effects. Although tobacco abstinence has some effects that could be attributed to sympathetic activity, it lacks the typical signs and symptoms of sympathetic overactivity, such as tachycardia, diaphoresis and hypertension. Thus, the mechanism by which alpha-2 agonists exert their effects is unclear.

Presently, Dynagen, Inc., published PCT application WO/92/19241 disclosed drug delivery systems said to deliver a controlled, sustained release of lobeline for the treatment of nicotine dependency. While a number of other pharmacological treatments, such as use of doxepin, ACTH, and corticotrophins, for abstinence symptoms have been tested, none of the studies reported baseline and postcessation values for abstinence symptoms. See, for example, S. J. Bourne (U.S. Pat. No. 4,621,074).

Therefore, a continuing need exists for pharmacological treatments that will facilitate smoking cessation, e.g., by blocking or relieving tobacco withdrawal syndrome, or reducing the symptoms of nicotine withdrawal.

SUMMARY OF THE INVENTION

The present invention provides a therapeutic method of treatment to (a) alleviate symptoms of the tobacco withdrawal syndrome (TWS), or (b) alleviate the similar abstinence effects due to cessation of nicotine alone, comprising administering to a human in need of such treatment, i.e., a smoker or abstinent smoker, an amount of ***cotinine*** or a pharmaceutically acceptable salt thereof, in an amount effective to significantly reduce or eliminate at least one of the symptoms of TWS or of nicotine withdrawal. As discussed above, the symptoms of both tobacco and nicotine withdrawal are similar and are art recognized to include craving for nicotine, depressed mood, anxious/tense, irritable/angry, impatience, restlessness, difficulty concentrating, increased eating, weight gain and drowsiness. See

FIG. 1. The present method is effective both to alleviate the TWS acutely and to permit patients to maintain abstinence from nicotine for extended periods of time.

In a preferred embodiment, the present invention also provides a therapeutic method to alleviate the craving for cigarettes, tobacco and/or nicotine that is associated with cessation of tobacco or nicotine use, e.g., by chewing or smoking, by the administration of an effective amount of ***cotinine*** or a pharmaceutically acceptable salt thereof, to a human in need of such treatment. However, the present invention is also useful to treat the symptoms of nicotine withdrawal which are due, for example, to cessation of use of nicotine gum or a nicotine transdermal patch.

The present invention is exemplified by a study in which ***(-)cotinine*** base was orally administered to abstinent cigarette smokers in a double-blind placebo controlled study. The results of this study demonstrate that: (1) ***cotinine*** fumarate up to at least 160 mg is safe, (2) ***cotinine*** fumarate at the 80 mg dose suppresses specific withdrawal symptoms, and (3) at the 40 and 80 mg dose, ***cotinine*** fumarate suppresses total withdrawal discomfort. These effects occur at doses of ***cotinine*** which do not cause significant effects on heart rate and blood pressure.

Cotinine has many qualities which can enhance its value as a smoking cessation aid. ***Cotinine*** has a long in vivo half-life, complete oral bioavailability, minimal effect on the cardiovascular system, and has not been reported to be harmful even at very high doses in many species including man. Also, became ***cotinine*** has no significant effect on the heart, a combined pharmacologic treatment approaching ***cotinine*** and nicotine may be possible.

The present invention also provides an article of manufacture comprising packaging material, such as a box, bottle, tube, sprayer, insufflator, intravenous (i.v.) bag, envelope and the like; and at least one unit dosage form of a pharmaceutical agent contained within said packaging material, wherein said pharmaceutical agent comprises ***cotinine*** or a pharmaceutically acceptable salt thereof in an amount effective to alleviate the tobacco withdrawal syndrome or the symptoms of nicotine withdrawal, and wherein said packaging material includes instruction means which indicate that said ***cotinine*** or said pharmacologically acceptable salt thereof can be used for alleviating tobacco withdrawal syndrome, or the symptoms of nicotine withdrawal. Suitable instruction means include printed labels, printed package inserts, tags, cassette tapes, and the like.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 depicts the Minnesota Withdrawal Symptom Checklist.

FIG. 2 is a graph depicting mean blood ***cotinine*** levels of the test subjects.

FIG. 3 is a graph depicting the odds ratio of no irritability to severity by dosage.

FIG. 4 is a graph depicting the odds ratio of no anxiety to some anxiety by dosage.

FIG. 5 is a graph depicting the odds ratio of no difficulty concentrating to level experienced.

FIG. 6 is a graph depicting odds of experiencing no impatience to some impatience.

FIG. 7 is a graph depicting odds ratio of no increased appetite to level experienced.

FIG. 8 is a graph depicting the change in the total withdrawal symptom score.

DETAILED DESCRIPTION OF THE INVENTION

Cotinine

Cotinine (1-methyl-5-(3-pyridinyl)-2-pyrrolidinone) has the formula shown below: ##STR1##

The physiologically active form is the (-)-isomer, so as used herein, the term "***cotinine***" includes ***(-)-cotinine,*** or the racemic form, (+)-***cotinine***. The free base, depicted above, can be employed in the practice of the invention, as can the pharmaceutically acceptable salts. These include the amine-acid addition salts of nontoxic or organic acids or inorganic acids, such as the tartarate, fumarate ("scotine"), citrate, maleate, malate, hydrobromide, hydrochloride, sulfate, phosphate and the like. For example, see F. Vaitekunas, J. Amer. Chem. Soc., 79, 149 (1957). E. R. Bowman et al., in J. Pharmacol. and Exp. Ther., 135, 306 (1962) report the preparation of ***(-)-cotinine*** free base from (-)-nicotine. The preparation and purification of ***(-)-cotinine*** fumarate is described by N. L. Benowitz et al., Clin. Pharmacol. Ther., 34, 604 (1983).

Cotinine is the major metabolite of nicotine which accumulates in the body as a result of nicotine exposure and has previously been believed to be pharmacologically inactive. For example, see N. L. Benowitz, "The use of biologic fluid samples in assessing tobacco smoke consumption", in Measurement in the Analysis and Treatment of Smoking Behavior, J. Grabowski et al., eds., NIDA Research Monograph No. 48, U.S. DHHS, PHS, ADAMHA (1983). In contrast to nicotine, ***cotinine*** has a relatively long terminal elimination half-life (two versus sixteen hours, respectively). Due to this pharmacological characteristic, ***cotinine*** has become the principally used objective biochemical marker of nicotine exposure in cigarette smoking and/or cessation-related research paradigms.

While ***cotinine*** is a well-known metabolite of nicotine and is routinely measured in many laboratories, no systematic investigation of the physiological and subjective effects produced by intravenous ***cotinine*** administration has been performed in humans. K. I. Yamamoto et al., International J. Neuropharmacol., 4, 359 (1965) reported that intravenous ***cotinine*** produced increases only slightly in EEG activity and behavioral arousal in cats with only a slight decrease in blood pressure. In squirrel monkeys, intramuscular ***cotinine*** injections increased rates of responding on fixed interval schedules of reinforcement over a wide range of doses (M. E. Risner et al., J. Pharmacol. and Exp. Ther., 234, 113 (1985); S. R. Goldberg et al., Psychopharmacology, 97, 295 (1989)). These findings, taken together, suggest that ***cotinine*** is behaviorally active. However, the pharmacologic mechanism of action has yet to be determined.

In two recent human studies, the pharmacokinetic profiles of intravenous and orally administered ***cotinine*** were examined without emphasis on measuring the subjective and/or physiological changes induced by this compound (N. L. Benowitz et al., Clin. Pharmacol. and Therapeutics, 34, 604 (1983); P. J. DeSchepper et al., Eur. J. Pharmacol., 31, 583 (1987)). Moreover, using an uncontrolled experimental design, Benowitz et al., Clin. Pharm. and Ther., 34, 604 (1988), found that intravenous ***cotinine*** infusion over 60 min. produced no cardiovascular changes and significant decreases in subjective ratings of desire to smoke, irritability, low energy and anxiety/tension. These changes were comparable to placebo-induced changes found in other experiments with nicotine. Using a rapid infusion of ***cotinine*** over 5 minutes, no significant changes in the subjective ratings were observed. Consequently, Benowitz and his colleagues concluded that ***cotinine*** lacked significant pharmacologic activity in humans.

Administration and Dosaaes

While it is possible that, for use in therapy, ***cotinine*** and/or its salts may be administered as the pure chemicals, as by inhalation of a free powder via an insufflator, it is preferable to present the active ingredient as a pharmaceutical formulation. The invention thus further provides a pharmaceutical formulation comprising ***cotinine*** and/or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be `acceptable` in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral or parenteral (including intramuscular, subcutaneous and intravenous) administration. Forms suitable for parenteral administration also include forms suitable for administration by inhalation or insufflation or for nasal, or topical (including buccal, rectal, vaginal and sublingual) administration. The formulations may, where appropriate, be conveniently presented in discrete unit dosage forms and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with liquid carriers, solid matrices, semi-solid carriers, funely divided solid carriers or combinations thereof, and then, if necessary, shaping the product into the desired delivery system.

Pharmaceutical formulations suitable for oral administration may be presented as discrete unit dosage forms such as hard or soft gelatin capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or as granules; as a solution, a suspension or as an emulsion; in a chewable base such as a synthetic resin or chicle for ingestion of the ***cotinine*** from a chewing gum. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art, i.e., with enteric coatings.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g., by injection, for example, bolus injection or continuous infusion) and may be presented in unit dosage form in ampules, prefilled syringes, small volume infusion containers or multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

For topical administration to the epidermis, the ***cotinine*** may be formulated as ointments, creams or lotions, or as the active ingredient of a transdermal patch. Suitable transdermal delivery systems are disclosed, for example, in A. Fisher et al. (U.S. Pat. No. 4,788,603), or R. Bawa et al. (U.S. Pat. Nos. 4,931,279; 4,668,506; and 4,713,224). Ointments and creams may, br example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

The active ingredient can also be delivered via iontophoresis, e.g., as disclosed in U.S. Pat. Nos. 4,140,122; 4,383,529; or 4,051,842.

Formulations suitable for topical administration in the mouth include unit dosage forms such as lozenges comprising active ingredient in a flavored base, usually sucrose and acadia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; mucoadherent gels, and mouthwashes comprising the active ingredient in a suitable liquid carrier.

When desired, the above-described formulations can be adapted to give sustained release of the active ingredient employed, e.g., by combination with certain hydrophilic polymer matrices, e.g., comprising natural gels, synthetic polymer gels or mixtures thereof.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in molds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

For administration by inhalation, the compounds according to the invention are conveniently delivered from an insufflator, nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoromethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example, a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or, e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

For intra-nasal administration, the compounds of the invention may be administered via a liquid spray, such as via a plastic bottle atomizer. Typical of these are the Mistometer.RTM. (Wintrop) and the Medihaler.RTM. (Riker).

For topical administration to the eye, the ***cotinine*** can be administered as drops, gels (see, S. Chrai et al., U.S. Pat. No. 4,255,415), gums (see S. L. Lin et al., U.S. Pat. No. 4,136,177) or via a prolonged-release ocular insert (see A. S. Michaels, U.S. Pat. No. 3,867,519) and H. M. Haddad et al., U.S. Pat. No. 3,870,791).

The pharmaceutical compositions according to the invention may also contain other adjuvants such as flavorings, colorings, antimicrobial agents, or preservatives.

It will be further appreciated that the amount of ***cotinine,*** or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route

of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 1 to about 100 mg/kg, e.g., from about 10 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day, calculated as ***(-)-cotinine*** in the free base form.

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 40-50 to 100-500 mg of active ingredient per unit dosage form.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 .mu.M, preferably, about 1 to 50 .mu.M, most preferably, about 2 to about 30 .mu.M. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1-100 mg, preferably about 25-95 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

The invention will be further described by reference to the following detailed Example.

EXAMPLE I

Oral Administration of ***(-)-Cotinine*** Fumarate

To investigate the effects of oral ***cotinine*** on the symptoms of the tobacco withdrawal syndrome (TWS) as experienced by abstinent smokers, under controlled conditions, the following double blind, placebo controlled study was conducted at the University of Minnesota. More specifically, the study was conducted to (1) determine the safety of various doses of ***cotinine*** fumarate; (2) determine blood ***cotinine*** concentrations attained from various doses of ***cotinine*** fumarate; and (3) determine effects of various doses of ***cotinine*** fumarate on withdrawal signs and symptoms including physiological and subjective symptoms. Preliminary analysis of the data from this study demonstrate the: (1) ***cotinine*** fumarate up to 160 mg is safe, (2) ***cotinine*** fumarate at the 80 mg dose suppresses specific withdrawal symptoms, and (3) at the 40 and 80 mg dose, ***cotinine*** fumarate suppresses total withdrawal discomfort. These effects occur at doses of ***cotinine*** which do not cause effects on heart rate and blood pressure.

Methods

A. Subjects: Subjects (N=37 male and female smokers) were recruited from the Minneapolis/St. Paul metropolitan area via newspaper advertisements. Subjects were initially screened over the telephone. If they met the telephone screening criteria, then they were seen by the research coordinator and physician. At this screening session, informed consent was obtained. Subjects were required to complete a smoking history and Fagerstrom Nicotine Tolerance Questionnaire. In addition, an

alveolar carbon monoxide sample and blood samples to measure ***cotinine*** and nicotine levels were obtained. The physician then obtained a medical and concomitant medication history and conducted a physical examination that included a 12-lead electrocardiogram (ECG) and laboratory screening of blood and urine specimens. Subjects were included if they: (a) smoked at least one pack of cigarettes/day for at least one year; (b) submitted a CO>10 ppm; and (c) were in good health (e.g., no history of myocardial infarction, angina pectoris, sustained or episodic cardia arrhythmias, symptomatic peripheral vascular disease) as verified by medical history, screening examination, and screening laboratory tests. Subjects were excluded if they: (a) required any form of regular psychotropic medication; (b) chronically used systemic steroids or antihistamines; (c) abused alcohol or any other recreational or prescription drug; (d) used any other tobacco products including smokeless tobacco. To maximize compliance and completion of the study, subjects were paid $700 for their participation.

B. Procedure: This study used a between-subject design with one of the doses of ***cotinine*** or placebo as the across subject variable. The study was run at the University of Minnesota General Clinical Research Center, Minneapolis, Minn. U.S.A., a federally funded inpatient research ward. Total participation in this study was 10 days. See Table 1 for experimental procedures.

TABLE 1

Experimental Procedure									
Cue Exposure .vertline.		Cue Exposure .vertline.		Cue Exposure .vertline.					
1	2	3	4	5	6	7	8	9	10
Ad Lib									
	Placebo		***Cotinine***		Placebo		Discharge		

Subjects were admitted to research ward at noon. During the first two days of the study, baseline measure were obtained while the subject smoked cigarettes on an ad libitum basis. Subjects were required to be abstinent from cigarettes beginning in the rooming of the third day. All subjects were given placebo at this time to allow some clearance of nicotine. On the morning of the fourth day, subjects were given placebo or one of the following oral doses of ***cotinine*** fumarate: 40 mg, 80 mg, and 160 mg. Nine subjects were to be run per each condition. Doses of ***cotinine*** were tested in ascending order. The subjects who are assigned to placebo were interspersed across the active dose conditions so that the blind would be maintained. If no adverse effects were detected for a particular dose, then the next higher dose was tested with the next group of subjects. Subjects were given one of the oral doses of ***cotinine*** fumarate/placebo for the next 3 days. Three days of ***cotinine*** dosing were chosen since the maximum tobacco withdrawal effects are observed during 24-72 hours of abstinence. See Hughes et al., Res. Adv. in Alcohol & Drug Problems, 10, Kozlowski et al., eds., Plenum Pub. (1990) at pages 317-398. Beginning on the eighth day, all subjects were required to take placebo again for three more days. This placebo condition would allow observation of withdrawal signs and symptoms from ***cotinine*** fumarate. To minimize experimenter bias, the investigators and nurses involved with assessment, however, were led to believe that subject during this placebo phase were randomly assigned to continue to take the medication given to them prior three days or assigned to placebo. Subjects were discharged in the morning of the tenth day if medical and psychological status were considered normal.

Abstinence was confirmed by biochemical verification (e.g., alveolar carbon monoxide) obtained at random times three times/day, evenly distributed across the day. Weight (after voiding) in the hospital gown was recorded and a sleep scale completed every rooming. See Table 2.

TABLE 2

NICOTINE METABOLITE STUDY - TEST CHECKLIST

TEST	DAYS TESTED	0630	0830	0930	1000	1200	1500	1800	2100
PHYSICAL TESTING									
WEIGHT	PE, D0-10	X							
BLOOD PRESSURE	PE, D0-10	X	X	X	X	X	X	X	
HEART RATE	PE, D0-10	X	X	X	X	X	X	X	
SKIN TEMPERATURE	DAY 1-9	X		X	X	X			
EKG	PE, D1-9	X			X				
PSYCH TESTING									
MWSC- MN.W/DRAWAL	DAY 1-9	X		X	X	X			
SX. CHECKLIST									
POMS	DAY 1-9	X		X	X	X			
VISUAL ANALOG SCALE	DAY 1-9	X		X	X	X			
VISUAL ANALOG SCALE-	DAY 3-9	X		X	X	X			
DRUG EFFECTS									
ADDICTION RESEARCH	DAY 1-9	X		X	X	X			
CENTER INVENTORY									
ADVERSE EFFECTS	DAY 1-9	X		X	X	X			
QUESTIONNAIRE OF	DAY 1-9	X		X	X	X			
SMOKING URGES									
RECORD OF OBSERVED	DAY 1-9	X		X	X	X			
W/DRAWAL SX'S									
SLEEP DIARY	DAY 1-10	X							

Subjects were required to complete subjective measures at the same times in the morning and afternoon throughout the study. See Table 2. These measures included the Addiction Research Center Inventory (Martin, Sloan, Sapira and Jasinski, Clin. Pharmacol. Ther., 1, 245 (1971)) which measures drug-like effects; the Profile of Mood States (McNair et al., Manual Profile of Mood States, San Diego Educational and Industrial Testing Service (1971)) which measures various moods such as depression-dejection, tension-anxiety, confusion, anger-hostility, vigor and fatigue; a VAS (which measures nicotine-like effects as well as how much an individual likes ***cotinine***); the modified Minnesota Withdrawal Symptom Checklist (see FIG. 1; Hughes and Hatsukami, Arch. of Gen.

Psychol., 43, 289 (1986)) comprised symptoms of nicotine withdrawal as described in the DMS-IV (APA, 1994) which subjects rated on a 0 to 4 scale with 0=none, 1=slight, 2=mild, 3=moderate, 4=severe; and the Smoking Urges Questionnaire (Tiffany & Drobes, Brit. J. Addiction, 86, 1467 (1991)) which measured two factors, one reflecting intention, desire and anticipation to smoke, and the other factor reflecting anticipation of relief from negative affect, nicotine withdrawal and urgent or overwhelming desire to smoke.

Subjects were also measured at these times for vitals (sitting and standing blood pressure and heart rate), skin temperature, respiratory rate, assessed for adverse events, and a 12-lead EKG was obtained. Caloric intake was carefully monitored throughout the study. Meals, similar to ones normally ingested by the subjects, were planned by the registered dietician who then supervised the careful measurement and preparation of all the foods eaten by the subjects. Meal and snack trays (foods of various macronutrients made available to the subjects all day) were returned to the kitchen where all uneaten food and beverages were remeasured after each meal, thereby all the eaten food was recorded by type and amount. Food content was later analyzed and calculated for daily amount of carbohydrate, protein, fat, and calories. Caffeine intake was controlled and maintained at the same level throughout the study. The amount of caffeine intake allowed for each individual was based on the levels of intake prior to the study. Alcohol intake was prohibited. Serum nicotine/cotinine samples were obtained at noon throughout the study. On days 2 and 6, blood samples were obtained to measure corticosteroids. On days 7 and 10, routine lab tests were taken. An internist monitored the subjects for a period of 30 minutes after the subjects took the medication to assess for any signs of toxicity.

Subjects were exposed to smoking related cues on Days 2, 5 and 9 since tobacco withdrawal symptoms may be minimized in an inpatient hospital setting when all normal cues for smoking are minimal. This cue involved exposure to their own brand of cigarettes and ashtray. Subjects were asked to look at their cigarettes, ashtray and matches for 15 seconds, light their cigarettes for 5 seconds, observe their lit cigarettes for another 15 seconds, then extinguish their cigarettes. During the study, subjects are free to engage in activities provided by the unit. Their exposure to smoking related stimuli were minimized during these activities in order to maintain consistency in cue exposures across subjects.

(S)-***Cotinine*** was synthesized and converted into its fumarate salt by the method of McKennis and Bowman, Biochemical Preparation, 1963, 10, 36 (1963). The crystalline material was purified and found to be greater than 98% pure with no nicotine contamination. This material was characterized by elemental analysis, proton and carbon NMR, gas chromatography, and DSC. The drug substance was formulated into capsule dosage form at the Research Pharmacy at the University of Minnesota. The doses prepared were placebo (0 mg) and 40 mg, 80 mg, and 160 mg of ***cotinine*** fumarate. These were tested for uniformity of content, stability and drug release rate by standard USP dissolution testing. The doses were coded to assure a double blind clinical experiment and provided to the research staff as needed.

Statistical Analysis

Only results on selective withdrawal measures will be reported and the data should be considered preliminary. Demographic and smoking history variables were analyzed using oneway analysis of variance for continuous measures and chi square tests for categorical measures. When the between groups analysis of variance indicated a significant difference, multiple comparisons between treatment groups were performed using Tukey's HSD to determine which of the groups were significantly different from each other.

For the total withdrawal symptom score, a reliability analysis of the scale using Cronbach's alpha indicated that the craving and increased appetite items were not highly correlated with the other items on the scale. Consequently, these items were eliminated in the computation of the total withdrawal symptom score to increase the internal consistency of the scale.

The primary statistical analysis for the present study was performed using unbalanced repeated measure analysis. A between groups analysis comparing differences in withdrawal by treatment condition was conducted for all available subjects. Due to baseline differences between groups, ***cotinine*** level and number of cigarettes smoked daily were used as covariates in the analysis. Likelihood radio tests and Wald tests were used to determine the significance of each term in the model.

A. Effect of ***Cotinine*** on cigarette withdrawal. A repeated measures analysis was performed for the three days the subject was on medication. In addition to ***cotinine*** level and number of cigarettes smoked daily, the average score of the two baseline smoking days was used as covariate. For continuous measures, terms included in the regression model were an intercept, the three covariates, main effects for time of day, day on medication, medication dosage, and interaction of day on medication by medication dosage. For categorical measures, terms included in the logit or probit model were an intercept, the three covariates, main effects for time of day, medication dosage and day on medication.

Results

A. Demographics, smoking history and ***cotinine*** levels. Thirty-seven subjects entered the study and 35 subjects completed the study. Two of the subjects were discharged prior to assignment to the medication. One subject experienced family problems while on the unit, and the other experienced a reoccurrence of an ulcer. Nine subjects completed the protocol in each group except the 160 mg group, in which 8 subjects completed the study. The demographic and smoking history variables are shown in Table 3.

TABLE 3

Dose Variable	Placebo	40 mg	80 mg	160 mg	P value
Females	55.6	55.6	55.6	50.0	
Age	27.3	26.6	30.9	33.8	.05
Number of Cigarettes	23.0	26.6	28.3	33.8	.02
Years of Smoking	11.4	11.0	15.4	20.3	.02
Fagerstrom Score	5.3	6.6	6.2	6.9	.04
Serum ***Cotinine***	228.4	288.1	263.9	350.2	.00

Significant differences were observed in age, number of cigarettes, years of smoking, Fagerstrom Tolerance Questionnaire Score, and serum ***cotinine***. Post hoc analyses showed significant differences

between the 160 mg and placebo groups. Due to these differences among groups, ***cotinine*** level in mg/ml serum (shown in previous studies to be correlated with nicotine withdrawal symptoms) and number of cigarettes (which showed significant correlations with the other variables showing significant differences between treatment groups) were used as covariates. FIG. 2 shows the mean ***cotinine*** level attained for each of the three days on the medication. Significant differences were observed across the doses of ***cotinine*** ($p<0.001$).

B. Safety of ***cotinine***. No adverse effects were noted by the subjects that would warrant termination from the study. Ten subjects, however, experienced elevated liver function tests with 4 of these subjects in the placebo group, 1 subject in the 40 mg group, 3 subjects in the 80 mg group, and 2 subjects in the 160 mg group. Two subjects (one in the 40 mg and 80 mg group) were considered to have clinically insignificant elevations. For the 6 out of 8 subjects who complied with the follow-up visit(s) to obtain repeat liver function tests, the levels had decreased to normal.

C. Effect of ***cotinine*** on cigarette withdrawal symptoms.

1. Subjective effects:

FIGS. 3-7 show the cigarette withdrawal symptoms that showed significant differences across groups. For irritability/frustration/anger (FIG. 3), anxiety (FIG. 4), difficulty concentrating (FIG. 5) and impatience (FIG. 6), the 80 mg dose group scored experienced significantly less severe symptoms than the placebo group. For irritability, the odds were 2.6 times greater to experience no irritability than slight irritability, and 6.9 times greater to experience no irritability than mild to severe irritability. For anxiety, the odds were 2.6 times greater to experience no anxiety than any anxiety. For difficulty concentrating, the odds were 4.3 times greater in experiencing no difficulty than to experience slight difficulty in concentrating and 18.5 times greater in experiencing no difficulty concentrating than to experience mild to severe difficulty concentrating. For impatience, the odds were 13.7 times greater to experience no impatience than to experience any impatience.

For increased appetite (FIG. 7) and total withdrawal score (FIG. 8), the 40 and 80 mg groups experienced significantly lower scores than placebo. For increased appetite, in the 40 mg condition, the odds were 2.7, 7.2 and 19.2 times greater in reporting no increased appetite than to have experienced slight, mild or moderate to severe increases in appetite, respectively. In the 80 mg condition, the odds were 2.8, 7.9, and 22.4 times greater in experiencing no increased appetite than to have experienced slight, mild or moderate to severe increase in appetite, respectively. The results for the total withdrawal score showed that there was a significant dose effect ($p<0.007$), with the 40 mg ($p=0.012$) and 80 mg ($p<0001$) dose groups reported experiencing significantly lower composite withdrawal syndromes than placebo. No significant differences were observed across doses for craving, restlessness and depressed mood, or for the two main factors measured by the Smoking Urges Questionnaires. No significant differences were observed for caloric intake and specific macro nutrients.

2. Physiological effects:

No significant effects of ***cotinine*** were observed for any of the physiological measures (heart rate, systolic and diastolic blood pressure).

3. Effects of ***cotinine*** during cue exposure:

No significant effects of ***cotinine*** were observed for any of the physiological (heart rate, systolic and

diabolic blood pressure) and subjective withdrawal measures assessed during cue exposure conditions.

All publications and patents are herein incorporated by reference to the same extent as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

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