National Institute on Drug Abuse

RESEARCH

MONOGRAPH SERIES

Problems of Drug

Dependence 2004:

Proceedings of the

66th Annual Scientific

Meeting

The College on Problems

of Drug Dependence, Inc.

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Virginia Commonwealth University

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Novel compounds as antagonists for cocaine-induced effects in mice
    A.J. Daniels, E. Ayala, B. Pouw, W. Chen, A. Coop, and R.R. Matsumoto, University of Oklahoma Health Sciences Center, Oklahoma City, OK; University of Maryland, Baltimore, MD
Trifluoromethoxyl-substituted analogs of BD1008 as sigma receptor-selective ligands
    M.D. Metcalf, X. Yang, B. Pouw, R.R. Matsumoto, and A. Coop, University of Maryland School of Pharmacy, Baltimore, MD; University of Oklahoma College of Pharmacy, Oklahoma City, OK
Synthesis and structure-activity relationships of chiral 2-substituted GBR 12909 derivatives
    L. Hsin, T. Prisinzano, C.M. Dersch, R. Horel, R.B. Rothman, A.E. Jacobson, and K.C. Rice, School of Pharmacy, National Taiwan University, Taipei, ROC; NIDDK, NIH, Bethesda, and NIDA Intramural Research Program, NIH, Baltimore, MD

Exploration of the effect of stereoselective incorporation of a chroman unit in the GBR 12909 series on DAT selectivity and affinity
    T.L. Boos, E. Greiner, T.E. Prisinzano, C.M. Dersch, R.B. Rothman, A.E. Jacobson, and K.C. Rice, NIDDK, NIH, DHHS, Bethesda, and NIH/NIDA, DHHS, Baltimore, MD

Identification of a GBR12909 analog that is a partial inhibitor of [125I]RTI-55 binding to theserotonin transporter
    B. Nightingale, C.M. Dersch, T. Boos, E. Greiner, W.J. Calhoun, A.E. Jacobson, K.C. Rice and R.B. Rothman, NIH/NIDA Intramural Research Program, Baltimore, and NIDDK, NIH, Bethesda, MD

STIMULANTS

Ondansetron for the treatment of methamphetamine dependence
    B.A. Johnson, R.A. Rawson, A. Elkashef, E.V. Smith, J. Campbell, W. Haning, B. Carlton, J. Mawhinney, R. Donovick, and D. Weis, University of Texas Health Science Center, San Antonio, TX; University of California, Los Angeles, CA; NIDA, Bethesda, MD

The pharmacokinetics of intravenously administered methamphetamine enantiomers in humans
    N. Uemura, D. Harris, R.P. Nath, E. Fernandez, P. Jacob, E.T. Everhart, R.T. Jones, and J.E. Mendelson, University of California, San Francisco, CA

Effect of bupropion on pharmacokinetics of methamphetamine
    C.N. Chiang, H. Boxenbaum, T. Newton, J. Roache, A. Elkashef, E. Smith, R.L. Hawks, and F. Vocci, NIDA, Bethesda, MD; BRCI, Ann Arbor, MI; University of California, Los Angeles, CA; University of Texas, San Antonio, TX

2004 update of NIDA Phase II medications development program for treatment of cocaine dependence
    A. Montgomery, A. Elkashef, D. Ciraulo, J. Grabowsky, R.J. Malcolm, E. Somoza, S. Shoptaw, and F. Vocci, DHHS/NIH/NIDA, Baltimore, MD; Boston University, Boston, MA; University of Texas, Houston, TX, Medical University of South Carolina, Charleston, SC; University of Cincinnati, Cincinnati, OH; University of California, Los Angeles, CA

A double-blind, placebo-controlled trial of modafinil for cocaine dependence
    C.A. Dackis, K.M. Kampman, K.G. Lynch, L. Klein, M. McAllister, H. Pettinati, and C.P. O'Brien, University of Pennsylvania School of Medicine, Philadelphia, PA

Qualitative and quantitative analysis of signal-averaged electrocardiogram in chronic cocaine users
    R.A. Nelson, M.L. Copersino, S.J. Boyd, R.C. Ziegelstein, and D.A. Gorelick, NIH/NIDA Intramural Research Program and Johns Hopkins University School of Medicine, Baltimore, MD

EEG changes after short-term abstinence in cocaine abusers
    R.I. Herning, W. Better, K. Tate, and J.L. Cadet, NIH/NIDA Intramural Research Program, Baltimore, MD

Temporal dissociation of delta power and total sleep-time impairment in cocaine abstinence
    P.T. Morgan, E.F. Pace-Schott, R. Stickgold, Z.H. Sahul, V. Coric, and R.T. Malison, Yale University School of Medicine, New Haven, CT, and Harvard University School of Medicine, Boston, MA

Baseline urine results as predictor of response to desipramine for cocaine dependence in buprenorphine patients
    K. Gonsai, M. Sofuoglu, A. Oliveto, and T. Kosten, Yale University School of Medicine and VA Connecticut Healthcare System, West Haven, CT

Predictors of outcome in cocaine-dependence treatment trials
    K.M. Kampman, H. Pettinati, K.G. Lynch, C. Dackis, M. Atzram, M. McAllister, and C.P. O'Brien, University of Pennsylvania School of Medicine, and Philadelphia Veterans Affairs Medical Center, Philadelphia, PA

Initial studies of the Treatment Services Review-Second Edition
    J.S. Cacciola, A.I. Alterman, J.M. Martin, and A.T. McLellan, University of Pennsylvania School of Medicine and Treatment Research Institute, Philadelphia, PA; Butler University, Indianapolis, IN

A fidelity study of a psychosocial approach for the treatment of methamphetamine dependence implemented at eight sites
    P. Marinelli-Casey, F. Cosmineanu, J. Obert, A. Hamilton-Brown, A. Weiner, and The Methamphetamine Treatment Project Corporate Authors, UCLA Integrated Substance Abuse Programs and Matrix Institute on Addictions, Los Angeles, CA

Internal consistency and validity of the drug and alcohol version of the IPA measure
    W.H. Zywiak, D. Rohsenow, R.M. Martin, C. Eaton, and C. Neighbors, Brown University and VA Medical Center, Providence, RI

Outcomes among methamphetamine users seeking substance abuse treatment in California
    Y. Hser, E. Evans, and D. Huang, UCLA Integrated Substance Abuse Programs, Los Angeles, CA

The role of treatment experience in outpatient interventions for cocaine use
> S. Sayre, A.L. Stotts, M. Mooney, P. Hokanson, and J. Grabowski, University of Texas, Houston, TX

Early and longer-term cocaine abstinence in outpatients
> S.T. Higgins, S.H. Heil, R. Dantona, R. Donham, and G.J. Badger, University of Vermont, Burlington, VT

Urge-specific coping strategies: Effects on cocaine use outcomes after treatment
> D.J. Rohsenow, R.A. Martin, and P.M. Monti, VA Medical Center and Brown University, Providence, RI

The therapeutic workplace: A partial failure to engage
> T.W. Knealing, C.J. Wong, K.N. Diemer, J. Hampton, and K. Silverman, Johns Hopkins University School of Medicine, Baltimore, MD

Salary-based abstinence reinforcement in the treatment of persistent cocaine use in injection drug-using methadone patients
> K. Silverman, C.J. Wong, M. Needham, K.M. Godfrey, D.E. Crone-Todd, and M. Fingerhood, Johns Hopkins University School of Medicine, Baltimore, MD

Affective and situational antecedents of crack cocaine relapse risk assessed by EcologicalMomentary Assessment
> M.J. Freedman, K.M. Lester, D. Roth, C. McNamara, and J.B. Milby, University of Alabama, Birmingham, AL

Potential barriers to improved substance abuse treatment outcomes for women receiving welfare
> K.M. Eyrich, M.A. Gutman, J.R. McKay, and A.T. McLellan, University of Pennsylvania School of Medicine, and Treatment Research Institute, Philadelphia, PA

Reflections on childhood suffering: A qualitative exploration of childhood abuse in methamphetamine users' lives
> A. O'Brien, M.-L. Brecht, and C. Casey, UCLA Integrated Substance Abuse Programs, Los Angeles, CA

History of physical abuse predicts outcome in men in cocaine-dependence treatment trials
> N.M. Maullin, K.M. Kampman, H. Pettinati, R. Ndubaku, K. Nesbitt, J. Jowers, and C.P. O'Brien, University of Pennsylvania School of Medicine and Philadelphia Veterans Affairs Medical Center, Philadelphia, PA

Reliability and validity of the Amphetamine Cessation Symptom Assessment scale
> C. McGregor, M. Srisurapanont, A. Mitchell, and J.M. White, University of Adelaide and Drug and Alcohol Services Council, Adelaide, SA, Australia, and Chiang Mai University, Chiang Mai, Thailand

Which came first, the craving or the use? Examining patterns of change over time in cocaine craving and cocaine use
> K.A. DeLaune, J.M. Schmitz, M. Mooney, and S. Sayre, University of Texas Medical School, Houston, TX

Demographic and behavioral profiles of crack users who do and do not initiate treatment
> W.K. Lam, G.V. Bobashev, K.S. Riehman, B. Levine, W.A. Zule, and W. Wechsberg, RTI International, Research Triangle Park, NC

Characterization of individuals seeking treatment for caffeine dependence
> B.D. Richards, L.M. Juliano, and R.R. Griffiths, Johns Hopkins University School of Medicine, Baltimore, MD; American University, Washington, DC

Motivational enhancement to decrease drug use among cocaine users: Six-month follow-up results
> E.A. Wells, B. Beadnell, D.A. Calsyn, D.B. Rosengren, D. Nahom, E. Ricardo-Bulis, P.L. Peterson, and T.R. Jackson, University of Washington, Puget Sound Health Care System of the VA, Evergreen Treatment Services, Seattle King County Public Health Department, Seattle, WA

Brief motivational interviewing with psychophysiologic feedback for the treatment of cocaine abuse
> A.L. Stotts, G. Potts, G. Ingersoll, J.M. Schmitz, and J. Grabowski, University of Texas Medical School and Rice University, Houston, TX

A randomized controlled trial of CBT and motivational interviewing with amphetamine users
> A. Baker, N. Lee, M. Claire, T. Grant, T. Pohlman, J.B. Saunders, T. Lewin, F. Kay-Lambkin, and P. Constable, University of Newcastle, Newcastle; Turning Point Alcohol and Drug Centre, Melbourne; and Queensland Health, Brisbane, Australia

Oral Communications V - DEVIATING FROM THE SCRIPT: MISUSE OF PRESCRIPTION DRUGS
Chairs: Brent A. Moore and Sidney H. Schnoll
Post-marketing surveillance of modafinil abuse and misuse
> S.R. Calhoun, S. Romanoff, N. Wolfe, G.P. Galloway, D.E. Smith, Haight Ashbury Free Clinics, Inc., and University of California, School of Medicine and School of Pharmacy, San Francisco, CA

Interest of the French health reimbursement system in the monitoring of the potential of abuse and dependence of a drug: The trihexyphenidyl case
  E. Frauger, X. Thirion, C. Chanut, F. Natali, D. Debruyne, C. Saillard, V. Pradel, P. Reggio, C. Gatignol, and J. Micallef, CEIP Marseille (PACA-Corse,Centre Associé), DRSM PACA Corse (CNAM), CEIP Caen Nord-Ouest, Afssaps, Pharmacologie Clinique - CHU Timone, France
Prescription drug abuse among club drug users
  S.P. Kurtz, J.A. Inciardi, H.L. Surratt and L. Cottler, Center for Drug and Alcohol Studies, University of Delaware, Coral Gables, FL; Washington University, St. Louis, MO
Trends in the diversion of prescription drugs in a large midwestern city
  J.A. Inciardi, S.P. Kurtz and H.L. Surratt, University of Delaware, Coral Gables, FL
Societal burden of prescription drug misuse and abuse: A prevalence study of prescription analgesics and anxiolytics
  R. Manjunath, S. Kim, X. Zhou, and S. Schnoll, RTI Health Solutions, Research Triangle Park, NC; Purdue Pharma, Stamford, CT
Who's misusing analgesics in the general population of the US?
  K.M. Dowling, C.L. Storr and H.D. Chilcoat, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Are prescription opiate users different from heroin users?
  A.C. Camilleri, D. Carise and A.T. McLellan, Treatment Research Institute, Philadelphia, PA
Use of non-medical prescription opiates predicts outcome in office-based buprenorphine treatment
  B.A. Moore, D.A. Fiellin and R.S. Schottenfeld, Yale University School of Medicine and The APT Foundation, New Haven, CT
Should codeine be available without a prescription?
  B.A. Sproule, H. Kameh, U.E. Busto, E.M. Sellers, Centre for Addiction and Mental Health, Faculty of Pharmacy, University of Toronto, Toronto, Canada
Trends in the nonmedical use of pain relievers, other prescription and illicit drugs among youths and young adults in the U.S.: 1999-2002
  M. Smith and S. Schnoll, Purdue

Oral Communications VI -- STIMULANTS AT WORK
Chairs: Evaristo O. Akerele and Drake Morgan
The role of CREB in mediating stress-induced changes in acquisition and expression of cocaine-conditioned place preference
  A.S. Kreibich and J.A. Blendy, University of Pennsylvania, Philadelphia, PA
Effect of AME-359, a modified variant of the human butyrylcholinesterase enzyme, on cocaineself-administration in rats
  F. Gomez, Y.G. Shi, J.D. Pancook, G.Pecht, M. Ader, M. Mosko, E.M. Conner, C.-H. Park, M.-A. Campbell, J.D. Watkins, G.Winger and J. Woods, University of Michigan, Ann Arbor, MI; Applied Molecular Evolution Inc, San Diego, CA
GABAergic mediation of the discriminative stimulus effects of methamphetamine
  M.B. Gatch, M. Selvig, and M.J. Forster, University of North Texas, Fort Worth, TX
Modulation of (+)amphetamine stimulus effects by the 5-HT6 antagonist MS-245
  R. A. Glennon, R. Young, M. Pullagurla and T. Bondareva, VCU, Richmond, VA
Kappa agonist modulation of cocaine priming-induced reinstatement: Kappa opioid and serotonergic mechanisms
  D.M. Platt, J.K. Rowlett and R.D. Spealman, Harvard Medical School, New England Regional Primate Research Center, Southborough, MA
Effects of extended-access self-administration and deprivation on "motivation" to self-administer cocaine
  D. Morgan, Y. Liu and D.C.S. Roberts, Wake Forest University School of Medicine, Winston-Salem, NC
Reduction of cocaine self-administration in rhesus monkeys by a selective DAT piperidine analogue of GBR12935
  P.M. Beardsley, M.E.A. Reith, and A.K. Dutta, Virginia Commonwealth University, Richmond, VA; NYU School of Medicine, New York, NY; Wayne State University, Detroit, MI
Effects of naltrexone on the subjective response to amphetamine in healthy volunteers N. Jayaram-Lindstrom, P. Wennberg, Y.L. Hurd and J. Franck, Karolinska Institutet, Stockholm, Sweden

Acute effects of cortisol and cocaine administration on attention, recall and recognition task performance in cocaine-dependent individuals

J.W. Hopper, E.A. Macklin, K.H. Karlsgodt, S.E. Lukas, and I. Elman, McLean Hospital and Harvard Medical School, Belmont, and New England Research Institutes, Watertown, MA

A pilot study of olanzapine/risperidone for the treatment of cocaine/marijuana use disorder in individuals with schizophrenia

E.O. Akerele, L. Biderman, and F.R. Levin, Columbia University and New York State Psychiatric Institute, New York, NY

Oral Communications VII -- IMAGES OF AN ADDICTED BRAIN
Chairs: Chris-Ellyn Johanson and Julie K. Staley

Brain activation patterns related to nicotine craving using fMRI

C. Johanson, D. Fitzgerald, M. Kilbey, S. Posse, L. Phan and M. Greenwald, Wayne State University, Detroit, MI

[I-123] 5-IA-85830 SPECT imaging of beta2 nicotinic acetylcholine receptors in human tobacco smokers

J.K. Staley, S. Krishnan-Sarin, S. O'Malley, K. Cosgrove, R.M. Baldwin, G.D. Tamagnan, J.P. Seiby, P. Jatlow, E.D. London and C.H. vanDyck, Yale University School of Medicine and the VA Connecticut Healthcare System, West Haven, CT

Do the brain substrates differ for "attempted" vs. "successful" inhibition of cue-induced craving?

A.R. Childress, Z. Wang, J.J. Wang, J. Listerud, N. Sciortino, J. Detre, A.V. Hole, M.R. MacDougall, A. Fornash and C.P. O'Brien, University of Pennsylvania School of Medicine and VA Medical Center, Philadelphia, PA

Compromised orbitofrontal white matter tract integrity in chronic intravenous methamphetamine users: the Consecutively Varying Threshold Tractography study

I.K. Lyoo, A.I. Chung, J.W. Hwang, J.S. Oh, I.C. Song, Y.H. Sung, and P.F. Renshaw, Seoul National University Hospital, Seoul, Korea, McLean Hospital Brain Imaging Center, Belmont, MA

Moderate doses of alcohol modulate neural networks underlying inhibitory control and learning: Evidence from event-related fMRI

C.M. Easdon and M.T. Fillmore, Rotman Research Institute, Toronto, ON, Canada and University of Kentucky, Lexington, KY

Symposium IV -- NEUROIMAGING STUDIES OF COGNITIVE DYSFUNCTION IN SUBSTANCE DEPENDENCE
Chairs: Thomas Kosten and Nora Volkow

Cognitive dysfunction associated with dopamine receptor abnormalities and incomplete recovery of brain metabolism in abstinent methamphetamine abusers

Nora Volkow, NIDA, Bethesda, MD

Neuroimaging 5-HT neurons in MDMA users: Strengths, limitations, and relationship to cognitive deficits

George Ricaurte, Johns Hopkins Bayview Medical Center, Baltimore, MD

Innovative treatments for brain perfusion deficits and cognitive impairment in cocaine dependence

Thomas Kosten, Yale University, West Haven, CT

Oral Communications VIII -- CANNABIS-NESS
Chairs: Aron H. Lichtman and Lance R. McMahon

Cannabinoid effects on appetite regulation in mice

J.J. Burston, B.R. Martin, R.K. Razdan, and J.L. Wiley, Virginia Commonwealth University, Richmond, VA, and Organix, Inc., Woburn, MA

Interactions between the CB1 receptor agonist delta-9-THC and the CB1 antagonist SR-141716 in rats: Munchies and tolerance development

T.U.C. Järbe and N.V. DiPatrizio, Temple University, Philadelphia, PA

Effects of cannabinoid agonists and an N-(1-octyl) amide analog of SR 141716A in delta-9-THC-treated monkeys discriminating SR 141716A

L.R. McMahon, B.F. Thomas, and C.P. France, University of Texas Health Science Center, San Antonio, TX; RTI, Research Triangle Park, NC

The endocannabinoid system modulates extinction in mice

A.H. Lichtman and S.A. Varvel, Virginia Commonwealth University, Richmond, VA

Cannabis exposure to rats during adolescence alters subsequent heroin self-administration M. Stridh-Ellgren, M.S. Spano, D.C. Roberts, J. Franck and Y.L. Hurd, Karolinska Institute, Stockholm, Sweden; Wake Forest University School of Medicine, Winston-Salem, NC

Symposium V -- THE CANNABINOID SYSTEM: PHARMACOLOGIC AND IMMUNOLOGIC EFFECTS
Chairs: Thomas W. Klein and Herman Friedman
Physiological function of the endogenous cannabinoid system
  Sandra P. Welch, Virginia Commonwealth University, Richmond, VA
Cannabinoid-mediated modulation of intracellular signaling cascades
  Norbert Kaminski, Michigan State University, East Lansing, MI
Cannabinoid-induced immunomodulation and altered susceptibility to infection
  Thomas W. Klein, University of South Florida College of Medicine, Tampa, FL

Marian W. Fischman Memorial
Award Lecture
Presentation of the Marian W. Fischman Memorial Award to Nancy K. Mello
  Introduction by Jack Bergman
Marian W. Fischman Memorial Award Lecture
  Nancy K. Mello, Mclean Hospital, Harvard Medical School

EARLY CAREER INVESTIGATOR AWARDS LUNCHEON

Symposium VI -- TRANSDISCIPLINARY RESEARCH ON TOBACCO DEPENDENCE
Chairs: Dorothy Hatsukami and Lucinda Miner
Transdisciplinary research: Nature and process
  Glen Morgan, National Cancer Institute, Bethesda, MD
Initiation of tobacco use: From basic science to behavior
  Frances Leslie, University of California, Irvine, CA
Tobacco dependence treatment: Mechanisms and outcomes
  Stephanie O'Malley, Yale University, New Haven, CT
Reducing tobacco toxin exposure: A viable treatment alternative?
  Dorothy Hatsukami, University of Minnesota, Minneapolis, MN
Discussant
  William Corrigall, Corrigall Consulting, Thornhill, Ontario, Canada

Symposium VII -- TARGETED LIPIDOMICS AND DRUGS OF ABUSE
Chairs: Rao S. Rapaka and Alexandros Makriyannis
Recent developments in understanding lipid-signaling molecules related to drug abuse
  Michael Walker, Brown University, Providence, RI
Linking the metabolome to the proteome by lipid profiling
  Benjamin Cravatt, The Scripps Research Institute, La Jolla, CA
Lipid signaling during implantation
  S.K. Dey, Vanderbilt University Medical Center, Nashville, TN
The role of lipid rafts in immune cell signaling
  Susan Pierce, National Institute of Allergy and Infectious Diseases/NIH, Rockville, MD
Discussant
  Rao S. Rapaka and Alexandros Makriyannis, NIDA, Bethesda, MD and University of Connecticut, Storrs, CT

Oral Communications IX -- THERE'S NO SUBSTITUTE FOR TREATMENT
Chairs: Leslie Amass and Lisa A. Marsch
Training rural practitioners to use buprenorphine
  D. McCarty, T. Rieckmann, C. Green, S. Gallon, Oregon Health & Science University, Portland, OR
The temporal process of buprenorphine induction at an outpatient clinical program
  E.W. Gunderson, F.R. Levin, M.M. Rombone, D.M. McDowell, and H.D. Kleber, Columbia University and New York State Psychiatric Institute, New York, NY

Assessment of patients in office-based buprenorphine treatment. Comparison of prescribers' evaluations and patient direct self-reports
  J-P. Daulouède, L. Cattan and M. Auriacombe, BIZIA Treatment Center, Bayonne, Addiction Medicine Clinic, Noisy-le-Sec, Université Victor Segalen Bordeaux, Bordeaux, France
Buprenorphine tablet treatment for opioid dependence in patients with comorbid chronic severe pain
  R. Chavez and L. Amass, UCLA School of Medicine, Los Angeles, The Pain Institute at Little Company of Mary, Redondo Beach, and Friends Research Institute, Inc., Los Angeles, CA
Monitoring for adequacy of heroin detoxification with buprenorphine or clonidine: A comparison of objective, subjective, and analog measures
  A.J. Saxon, M.R. Oreskovich, C.A. Malte, M.K. Ellis, J.P. Reoux and P.C. Knox, University of Washington School of Medicine, VA Puget Sound Healthcare System, Seattle, WA
Comorbidity of psychiatric disorders and other drug use among opioid-dependent adolescents in combined behavioral-pharmacological treatment
  L.A. Marsch, W.K. Bickel, G.J. Badger, M.E. Stothart, K.J. Quesnel and C.S. Stanger, University of Vermont, Burlington, VT; NDRI, New York, NY
Comparative safety and side-effect profiles of buprenorphine vs. methadone in the outpatient treatment of opioid dependence
  M.R. Lofwall, E.C. Strain, M.L. Stitzer, G.E. Bigelow, Johns Hopkins University, Baltimore, MD
Early clinical experience with buprenorphine-naltrexone detoxification
  A.S. Reece, Southcity Medical Centre, Brisbane, Australia
Buprenorphine-naloxone tablet treatment for brief withdrawal from opioids: Initial experience in a therapeutic community
E.D. Collins, T. Horton, K. Reinke, E.V. Nunes and L. Amass, Columbia University, NY State Psych. Institute and Phoenix House, NY; Friends Research Institute, Inc., Los Angeles, CA
Assessing buprenorphine/naloxone's withdrawal precipitation potential in methadone-maintained volunteers
  J. Rosado, E.C. Strain, S.L. Walsh, and G.E. Bigelow, Johns Hopkins University School of Medicine, Baltimore, MD; Harvard Medical School, Boston, MA

Symposium VIII -- D3: DOPAMINE RECEPTOR AND DRUG ABUSE   obal
Chairs: James H. Woods and Amy H. Newman
Medicinal chemistry of D3 ligands
  Amy Hauck Newman, NIDA, ARC, Baltimore, MD
Insights into D3 receptor: From computational modeling to ligands with outstanding selectivity
  Shaomeng Wang, University of Michigan, Ann Arbor, MI
Selective effects of D3 antagonists on drug-seeking and -taking behavior
  Eliot Gardner, NIDA Intramural Research Program, Baltimore, MD
Cocaine self-administration and D3 selective compounds in D3 knockout mice
  S. Barak Caine, Harvard Medical School, McLean Hospital, Belmont, MA
Discussant
  Pierre Sokoloff, INSERM, Centre Paul Broca, Paris, France

Oral Communications X -- WHEN MARS MEETS VENUS, THERE'S SMOKE
Chairs: Stephanie L. Collins and Stephanie O'Malley
Sex differences in the conditioning effect of nicotine in rats
  S. Pogun, G. Yararbas, A. Keser, and L. Kanit, Ege University, Izmir, Turkey
Chronic nicotine differentially alters amphetamine-induced locomotor activity in male vs. female adolescent and adult rats
  S.L. Collins, R. Montano, S. Izenwasser, University of Miami School of Medicine, Miami, FL
Gender differences in delay discounting: Heavy, light, and nonsmokers
  M.W. Johnson, W.K. Bickel and F. Baker, University of Vermont, Burlington, VT
Male, but not female, tobacco smokers more likely to be depressed, in a sample of African American college seniors
  Y. Wang, F.A. Wagner and D.C. Browne, Drug Abuse Research Program/Morgan-Hopkins Center for Health Disparities Solutions, Morgan State University, Baltimore, MD

Inpact of negative affect by sex and reproductive status on abstinence in a controlled clinical trial for nicotine addiction
> C.N. Epperson, S. McKee, S. Krishnan-Sarin, C. Mazure, and S. O'Malley, Yale University School of Medicine, New Haven, CT

Symposium IX -- EARLY LIFE STRESS AND DRUG ABUSE: IS THERE A CONNECTION?
Chairs: Therese A. Kosten and David A. White
Neonatal isolation alters mesolimbic DA and behavioral responses to cocaine in rats of both sexes
> Therese A. Kosten, Yale University School of Medicine, New Haven, CT

Early postnatal separation of rat pups and dams results in long-term changes of both behavioral and drug responsiveness
> Stephen G. Holtzman, Emory University School of Medicine, Atlanta, GA

Discussant: Future directions and clinical implications
> Kathleen T. Brady, Medical University of South Carolina/CTN, Charleston, SC

Oral Communications XI -- DRUG THRILLS, MEDICAL ILLS
Chairs: Steven L. Batki and Arthur J. Siegel
EKG QT-prolongation effects of methadone, LAAM and buprenorphine in a randomized controlled trial
> E.F. Wedam, M.C. Haigney, G.E. Bigelow, and R.E. Johnson, Johns Hopkins University School of Medicine, Baltimore, and Uniformed Services University of the Health Sciences, Bethesda, MD; Reckitt Benckiser, Richmond, VA

Menstrual function during methadone maintenance
> J. Schmittner, J.R. Schroeder, D.H. Epstein and K.L. Preston, NIDA Intramural Research Program, Baltimore, MD

Bone health in methadone maintenance treatment
> T.W. Kim, D.P. Alford, A.O. Malabanan and J.H. Samet, Boston University School of Medicine, Boston, MA

Substance use and access to hepatitis C treatment in methadone patients
> S.L. Batki, A.K. Srinath, M.E. Cornell, M. Bowman, R.M.H. Peek, M. Wade, J.A. Dimmock, and M. Abdul-Hamid, SUNY Upstate Medical University and Crouse Chemical Dependency, Syracuse, NY

Acute and chronic effects of cocaine on inflammatory and immune responses
> A. Siegel, J.H. Mendelson, N.K. Mello, M.B. Sholar, J. Halpern, M. Kaufman, and P. Renshaw, McLean Hospital, Belmont, MA

Training Grant Mixer Las Olas Workshop -- SEX, DRUGS, & NO ROCK N ROLL!
Chairs: Rachel L. Peltier and Therese Kosten

Workshop -- WHAT'S NEW AT NIDA AND NIH: HOW WILL IT AFFECT YOU?
Chairs: Mark R. Green, Teri Levitin, and Mark Swieter

Workshop -- SUBSTANCE ABUSE IN SPECIAL POPULATIONS
Chairs: Evaristo Akerele and Woodburne O. Levy

Workshop -- FIVE EASY PIECES: EXAMPLES OF SCIENCE-BASED CLINICAL INTERVENTIONS DESIGNED FOR PRACTICAL APPLICATION IN REAL-WORLD SETTINGS
Chair: A. Thomas McLellan

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TUESDAY, JUNE 15, 2004
POSTER SESSION II

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ABUSE LIABILITY
Development of a denominator for calculating rates of opioid abuse
> S. Schnoll, M. Smith, R. Colucci, and A. Munoz, Purdue Pharma L.P., Stamford, CT

Researched Abuse, Diversion and Addiction-Related Surveillance system
> A. Kline and S. Schnoll, Purdue Pharma L.P., Stamford, CT

Gender differences and similarities in the nonmedical use of prescription stimulants among college students: Results from a national survey
  S.E. McCabe, J.R. Knight, C.J. Teter, and H. Wechsler, University of Michigan Substance Abuse Research Center, Ann Arbor, MI; Harvard Medical School and Harvard School of Public Health, Boston, MA
Misuse of drugs: The French hits
  C. Gatignol, E. Frauger, J. Arditti, S. Djezzar, M. Lapeyre Mestre, and X. Thirion, CEIP Marseille, CEIP Paris, CEIP Toulouse, CEIP Marseille (PACA- Corse, Centre associé), and Afssaps, France
Misuse of modafinil: Where is the reality?
  F. Haramburu, M. Mallaret, E. Frauger, N. Richard, and C. Gatignol, CEIP Bordeaux, CEIP Grenoble, Afssaps, France
Use of diverted methadone
  B. Brands, M. Lester, B. Sproule, and H. Kameh, University of Toronto, Toronto, Canada
Aberrant drug-related behaviors in opioid clinical trials 7
  M.-A. Zalman, E.D. Kramer, R.D. Colucci, and C. Wright IV, Purdue Pharma L.P., Stamford, CT
Development of objective qualifying day measures for abuse liability studies
  L.C. Fernandes, H.L. Kaplan, and E.M. Sellers, Ventana Clinical Research Corporation and University of Toronto, Toronto, Canada
Subjective and psychomotor effects of a prescription hydrocodone/acetaminophen combination product in non-drug-abusing volunteers
  J.P. Zacny and S. Gutierrez, University of Chicago, Chicago, IL
Is addiction an occupational hazard for anesthesiologists?
  M.S. Gold, K. Frost-Pineda, R. Pomm, and R.J. Melker, University of Florida College of Medicine, Gainesville, FL

MARIJUANA AND CANNABINOIDS

Trajectories of marijuana and cocaine use; A latent class analysis
  R.A. Miech and H.D. Chilcoat, Johns Hopkins University, Baltimore, MD
Opportunities and transition to using drugs among Hispanic Americans
  F.A. Wagner, D.C. Brown, and J.C. Anthony, Morgan State University, Baltimore, MD; Michigan State University, East Lansing, MI
Associations between marijuana and tobacco smoking among college freshman
  L.C. Dierker, S. Tiffany, B. Flay, M. Stolar, and R. Clayton, Wesleyan University, Middletown, CT; University of Utah School of Medicine, Salt Lake City, UT; University of Illinois, Chicago, IL; Yale University School of Medicine, New Haven, CT; University of Kentucky, Lexington, KY
Individual and neighborhood-level predictors of drug use in low-income women
  P.K. Sunder, J.J. Grady, and Z.H. Wu, The University of Texas Medical Branch, Galveston, TX
Neurobehavior disinhibition predicts multiple episodes of marijuana use: Multiple failure time approach
  L. Kirisci, M. Vanyukov, M. Habeych, M. Reynolds, and R. Tarter, University of Pittsburgh School of Pharmacy, Pittsburgh, PA
One-year follow-up of voucher-based interventions for marijuana dependence: Patterns of abstinence
  A.J. Budney, B.A. Moore, H.R. Rocha, and S.T. Higgins, University of Vermont, Burlington, VT
Dronabinol reduces signs and symptoms of idiopathic intracranial hypertension: A case report
  K.H. Murtaugh, W. Raby, P. Modica, and E.V. Nunes, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, and State University of New York, New York, NY
Dronabinol (oral THC) attenuates cannabis withdrawal symptoms
  R.G. Vandrey, A.J. Budney, B.A. Moore, and J.R. Hughes, University of Vermont, Burlington, VT
Marijuana and cocaine abuse and dependence in the general population
  D.S. Hasin, T. Harford, and B. Muthen, Columbia University, New York, NY; Boston University, Boston, MA; and University of California, Los Angeles, CA
Assessing the reinforcing effects of oral THC in humans
  C.L. Hart, M. Haney, S.K. Vosburg, S.D. Comer, and R.W. Foltin, Columbia University and New York State Psychiatric Institute, New York, NY
The relationship between drug usage by batterers and domestic violence
  T. Jospitre, C.S. Lewis, S. Griffing, R.E. Sage, M. Chu, L. Madry, and B.J. Primm, Urban Resource Institute, Brooklyn, NY

Cognitive functioning and MET+CBT treatment outcome in marijuana users
    E. Aharonovich, A. Brooks, D. Hasin, and E. Nunes, Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute, New York, NY
Effects of monetary incentive on cognitive dysfunction in marijuana withdrawal
    A. Liguori, N.C. Caino, G.S. Bauer, C.P. Gatto, and T.W. Brown, Wake Forest University School of Medicine, Winston-Salem, NC
Acute marijuana effects on human working memory: Separating initial discriminability from forgetting
    L.M. Lieving, S.D. Lane, D.R. Cherek, O.V. Tcheremissine, and S. Nouvion, University of Texas Health Science Center, Houston, TX
Drug-taking behavior under a fixed-ratio schedule of intravenous self-administration of anandamide and R(+)-methanandamide in monkeys
    Z. Justinova, G.H. Redhi, and S.R. Goldberg, NIH/NIDA Intramural Research Program, DHHS, Baltimore, MD

STIMULANTS IN ANIMALS: PHARMACOLOGY AND BEHAVIOR

Effects of the 5-HT1A agonist 8-OH-DPAT on cocaine choice in group-housed cynomolgus monkeys
    C. McCabe, P.W. Czoty, M. Dickens, C.L. Hubbard, and M.A. Nader, Wake Forest University School of Medicine, Winston-Salem, NC
Effects of T34 and T75 point mutations of DARPP-32 on cocaine self-administration in mice
    Y. Zhang, P. Svenningsson, R. Picetti, S.D. Schlussman, E.R. Butelman, A. Ho, P. Greengard, and M.J. Kreek, The Rockefeller University, New York, NY
DARPP-32 mRNA and protein regulation by chronic cocaine in mouse striatum during postnatal development
    M. Niculescu, M.E. Ehrlich, and E.M. Unterwald, Temple University School of Medicine and Thomas Jefferson University, Philadelphia, PA
Mu opioid receptor modulation of psychostimulant-induced reinforcement
    M. Hummel, J.A. Schroeder, R. Sheikh, J.E. Pintar, and E.M. Unterwald, Temple University School of Medicine, Philadelphia, PA, and University of Medicine and Dentistry of New Jersey, Piscataway, NJ
Co-occurring dose-dependent cocaine-induced aversions and preferences conditioned in C57BL/6J mice
    J.F. Randall-Thompson, F.S. Hall, G.R. Uhl, and A.L. Riley, American University, Washington, DC, and NIH/NIDA Intramural Research Program, DHHS, Baltimore, MD
The role of D1 and D2 receptors in cocaine conditioned place preference of male and female rats
    A. Nazarian, S.J. Russo, E.D. Festa, and V. Quiñones-Jenab, Hunter College and City University of New York, New York, NY
Behavioral and neurochemical effect of monoamine transporter inhibitors in nonhuman primates: Pharmacokinetic considerations
    H.L. Kimmel, P.D. Martin, A.C. Murnane, J.A. O'Connor, J.M. Ojeda, F.I. Carroll, and L.L. Howell, Yerkes National Primate Research Center, Emory University, Atlanta, GA; Research Triangle Institute, Research Triangle Park, NC
Dopamine transporter inhibitors increase striatal vesicular dopamine uptake
    K.S. Rau, E. Birdsall, F.I. Carroll, J.W. Gibb, G.R. Hanson, and A.E. Fleckenstein, University of Utah, Salt Lake City, UT; Research Triangle Institute, Research Triangle Park, NC
Ephedrine decreases plasmalemmal and vesicular dopamine transport
    A.E. Fleckenstein, J.E. Hanson, M.A. Crosby, K.S. Rau, and G.R. Hanson, University of Utah, Salt Lake City, UT
Monoclonal anti-(+)methamphetamine [(+)METH] IgG reduces hemodynamic effects of subsequent (+)METH intravenous bolus doses in rats
    W.B. Gentry, E.M. Laurenzana, T. Terlea, R.J. Berg, J.R. West, and S.M. Owens, University of Arkansas for Medical Sciences, College of Medicine, Little Rock, AR
Synthesis and comparative pharmacological activities of lobelane isomers at VMAT2
    G. Zheng, S.D. Norrholm, L.P. Dwoskin, and P.A. Crooks, University of Kentucky, Lexington, KY
Lobelane, a potent lobeline analog, inhibits methamphetamine-evoked dopamine release from rat striatal slices
    S. Krishnamurthy, S.D. Norrholm, G. Zheng, P.A. Crooks, and L.P. Dwoskin, University of Kentucky, Lexington, KY
Effects of lobelane on methamphetamine self-administration and sucrose-maintained responding N.M. Neugebauer, S.B. Harrod, D.J. Stairs, G. Zheng, P.A. Crooks, L.P. Dwoskin, and M.T. Bardo, University of Kentucky and Yaupon Therapeutics Inc., Lexington, KY
Interaction of neurotoxic and non-neurotoxic amphetamines and phenylpiperazines at the vesicular monoamine transporter

R.B. Rothman, A.G. Budzynski, M.H. Baumann, and J.S. Partilla, NIH/NIDA Intramural ResearchP rogram, Baltimore, MD

The trace amine receptor: A novel indirect target of cocaine?
B.K. Madras, C.D. Verrico, and G.M. Miller, Harvard Medical School, New England Primate Research Center, Southborough, MA

Effect of psychostimulants on dopamine and serotonin dynamics in mouse brain C.E. John and S.R. Jones, Wake Forest University School of Medicine, Winston-Salem, NC

Effects of monoamine-releasing agents on extracellular dopamine and serotonin in rat nucleus accumbens: Relationship to locomotor activation
R.D. Clark, M.H. Baumann, B.E. Blough, and R.B. Rothman, NIDA Intramural Research Program, Baltimore, MD; RTI International, Research Triangle Park, NC

Telenzepine alters the behavioral and neurochemical effects of cocaine
G. Tanda, E.L. Ebbs, T.A. Kopajtic, and J.L. Katz, NIH/NIDA, DHHS, Baltimore, MD

Role of the dopamine D3 receptor in the discriminative stimulus effects of cocaine in rhesus monkeys
J.T. Ross, C.J. Bennett, A.H. Newman, and M.A. Nader, Wake Forest University Health Sciences, Winston-Salem, NC; NIDA Intramural Research Program, Baltimore, MD

The influence of dopamine D2 and D3 receptors in cocaine- and food-maintained responding under a second-order schedule in monkeys
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Cocaine self-administration and food-maintained responding under a concurrent choice schedule of reinforcement in rats
A.C. Barrett, S.S. Negus, and S.B. Caine, Harvard Medical School, Belmont, MA

Choice between cocaine and food in rhesus monkeys can be systematically altered by reinforcement delay
K.G. Anderson and W.L. Woolverton, University of Mississippi Medical Center, Jackson, MS; West Virginia University, Morgantown, WV

Intra-accumbal shell administration of the D1-like dopamine receptor agonist, SKF-81297, reinstates drug-seeking behavior
H.D. Schmidt and R.C. Pierce, Boston University School of Medicine, Boston, MA

Administration of the D2 dopamine receptor antagonist, sulpiride, into the nucleus accumbens shell, attenuates cocaine-priming-induced reinstatement
S.M. Anderson, A.A. Bari, and R.C. Pierce, Boston University School of Medicine, Boston, MA

PERINATAL DRUG EXPOSURE

Amphetamine-induced locomotor activity in rats prenatally exposed to toluene
M.H. Mohammadi, J.H. Hannigan, and S.E. Bowen, Wayne State University, Detroit, MI

Ethanol preference in rats after variations in maternal separation
K.J. Zurich, D.D. Francis, M.J. Kuhar, and J.N. Jaworski, Yerkes Primate Center of Emory University, Atlanta, GA

Early life maternal separation in rodents: What about moms?
D.D. Francis and M.J. Kuhar, Yerkes National Primate Research Center of Emory University, Atlanta, GA

Estimated differences between prenatally cocaine-exposed and non-exposed children on continuous performance tests
A.J. Amado, C.E. Morrow, V.H. Accornero, J.C. Anthony, and E.S. Bandstra, University of Miami, Miami, FL; Johns Hopkins University, Baltimore, MD; Michigan State University, East Lansing, MI

Prenatal cocaine use: 6-year longitudinal maternal mental health outcomes
S. Minnes, L. Singer, K. Farkas, and M.O. Min, Case Western Reserve University, School of Medicine and Social Work, Cleveland, OH

Recovery of function: Arousal modulation after stressors in 8-year-olds with prenatal cocaine exposure
J.A. Kable, C.D. Coles, M.E. Lynch, K.A. Platzman, and S.J. Schmeiding, Emory University School of Medicine, Atlanta, GA

Perinatal nicotine treatment: Organizational change and clinical practice
M.A. Jessup and J. Guydish, University of California, San Francisco, CA

Buprenorphine and methadone in pregnancy: Effects on the mother and fetus/neonate
  A.L. Gordon, H. Stacey, V. Pearson, R.R. Haslam, O.V. Lopatko, and J.M. White, University of Adelaide, Adelaide; Women's & Children's Hospital, Drug & Alcohol Services Council: South Australia, Australia
Maternal methadone administration and fetal neurobehavior
  L. Jansson, A. Elko, and J. DiPietro, Johns Hopkins University, Baltimore MD
Preliminary evaluation of the acceptability and efficacy of a computer-based brief motivational intervention for perinatal drug use
  S.J. Ondersma, S.K. Chase, D. Svikis, and C.R. Schuster, Wayne State University, Detroit, MI; Virginia Commonwealth University, Richmond, VA
Predictors of treatment response among cocaine-dependent mothers
  D.T. Barry, B.A. Moore, M.C. Chawarski, M.V. Pantalon, and R.S. Schottenfeld, Yale University School of Medicine and The APT Foundation, Inc., New Haven, CT
Factors associated with lifetime history of drug abuse treatment among drug-dependent, pregnant women
  B.J. Walton-Moss and M.E. McCaul, Johns Hopkins University, Baltimore, MD
Sex work by pregnant, drug-dependent women
  M. Tuten, H. Jones, and E. Fitzgerald, Johns Hopkins University School of Medicine, Baltimore, MD

GENETICS
Comparison of motor-activating effects of cocaine in fifteen mouse strains and in rats
  S.B. Caine and R.J. Ralph-Williams, McLean Hospital - Harvard Medical School, Belmont, MA
D1 and D2 receptor agonist effects on motor activity in fifteen mouse strains and rats
  R.J. Ralph-Williams and S.B. Caine, McLean Hospital-Harvard Med School, Belmont, MA
CART mRNA expression is regulated by D3 receptors in the rat nucleus accumbens
  R.G. Hunter and M.J. Kuhar, Emory University and Yerkes National Primate Research Center, Atlanta, GA
Effects of "binge" pattern and "escalating dose" cocaine administration on striatal preprodynorphin mRNA levels
  S.D. Schlussman, Y. Zhou, A. Bailey, A. Ho, and M.J. Kreek, The Rockefeller University, New York, NY
Acute withdrawal from chronic "binge" cocaine administration increases mu-opioid receptor mRNA levels in rat frontal cortex
  A. Bailey, V.P. Yuferov, J. Bendor, S.D. Schlussman, Y. Zhou, A. Ho, and M.J. Kreek, The Rockefeller University, New York, NY
Gene expression profile in the rat hypothalamus after acute and repeated "binge" cocaine administration: A triplicate microarray study
  V.P. Yuferov, Y. Zhou, K.S. LaForge, A. Ho, and M.J. Kreek, The Rockefeller University, New York, NY
Fra-2, a critical immediate early gene, is involved in the anti-cocaine effects induced by a sigma receptor antagonist
  Y. Liu, G.-D. Chen, and R.R. Matsumoto, University of Oklahoma Health Sciences Center, Oklahoma City, OK
Matrix metalloproteinase 9: A possible target for the development of anti-methamphetamine therapeutic agents
  E.C. Nguyen, Y. Liu, D.J. Brackett, M.R. Lerner, and R.R. Matsumoto, University of Oklahoma Health Sciences Center, Oklahoma City, OK
Mexneurines: A novel neuropeptide system cloned from the CNS of mammals coding an endomorphin-like peptide sequence
  B. Anton, P. Leff, C. Allen, H. Gompf, M. Matus, J.C. Calva, C. Torner, C. Martinez, A. Salazar, P. De los Heros, G. Roldan, B. Peng, A. Alagón, G. Gamba, and J. Pintar, National Institute of Psychiatry, National Institute of Nutrition, and Institute of Biotechnology, Mexico; CROET and Portland University, Portland, OR; New York University, New York, NY
Dynorphin/kappa gene expression in mesolimbic and striatal brain structures in human heroin abusers
  P. Zarnegar, E. Keller, and Y.L. Hurd, Karolinska Institute, Stockholm, Sweden; Semmelweis University, Budapest, Hungary
Single nucleotide polymorphisms of the human preproenkephalin gene: Significant association with opiate addiction
  K.S. LaForge, D. Proudniko, J. Ball, S.M. Leal, F. Nyberg, and M.J. Kreek, The Rockefeller University, New York, NY; Uppsala Universitet, Uppsala, Sweden; Baylor College of Medicine, Houston, TX
Associations between dopamine D2 and D4 receptor alleles with heroin dependence in Spanish individuals
  J. Pérez de los Cobos, M. Baiget, J. Trujols, E. Bañuls, N. Siñol, E. Luquero, and E. Del Río, M. Gómez-Pardo, and E. Álvarez, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
Single nucleotide polymorphisms of the catechol-O-methyltransferase gene: Ethnic and gender distributions, and vulnerability to develop opiate addiction
  K.S. LaForge, A. Ho, G. Bart, S.M. Leal, and M.J. Kreek, The Rockefeller University, New York, NY

Delta opioid receptor and not dopamine and serotonin receptor gene polymorphism is associated with club drug use in Chinese youth

    J.S.K. Lee, L.N. Wan, H.L. Choi, B.K.L. Cheung, F.Y.K. Leung, and A. Stadlin, Chinese University of Hong Kong; Substance Abuse Assessment Clinic, Kwai Chung Hospital, Hong Kong

The multivariate relationship between licit and illicit drugs in female twins

    A. Agrawal, M.C. Neale, K.C. Jacobson, C.A. Prescott, L.J. Eaves, and K.S. Kendler, Virginia Commonwealth University, Richmond, VA

Serotonin transporter promoter polymorphism is associated with personality traits and illegal drugs use among adolescents

    G. Gerra, L. Garofano, L. Castaldini, A. Zaimovic, F. Brambilla, and C. Donnini, University of Parma, Parma, Italy

Genetic influences on quantity of alcohol consumed by adolescents and young adults

    C.J. Hopfer, D. Timberlake, B. Haberstick, J.M. Lessem, M. Ehringer, A. Smolen, and J.K. Hewitt, University of Colorado Health Sciences Center, Denver, and Institute for Behavior Genetics, Boulder, CO

An association study of a prodynorphin gene promoter polymorphism and opiate dependence

    R.J. Gianotti, K.S. LaForge, A.C. Chen, B.E. Oosterhuis, A. Ho, S.M. Leal, and M.J. Kreek, The Rockefeller University, New York, NY

Consent rates for sharing genetic data with the NIDA gene bank

    K. Bell, E. Ducat, S.H. Kellogg, D. Melia, K.S. LaForge, and M.J. Kreek, The Rockefeller University and New York Presbyterian Hospital, New York, NY

POLYDRUG ABUSE: EPIDEMIOLOGY AND PREVENTION

Alcohol and substance use disorders as risk factors for injury

    G. Borges, L. Mondragon, M. Medina-Mora, R. Orozco, J. Zambrano, and C. Cherpitel, National Institute of Psychiatry and Metropolitan Autonomous University, Mexico City, Mexico

Alcohol and other drug prevalence among male and female students of the São Paulo University in 2001 - São Paulo Campus

    V.A. Stempliuk, L.P. Barroso, S. Nicastri, J. Litivoc, A. Malbergier, and A.G. Andrade, São Paulo University, Sao Paulo, Brazil

Use of bootstrapping and the t-test to estimate the statistical difference of within-group survival curves

    S. Poremba, M.M. Maldonado-Molina, T.A. Ridenour, E. Spitznagel, and L. Cottler, Pennsylvania State University, University Park, PA, and Washington University, St. Louis, MO

DRAMES : Let's try a better assessment of drug abusers deaths

    N. Richard, J. Arditti, M. Deveaux, V. Dumestre, H. Eysseric, J.M. Gaulier, J.P. Goulle, P. Kintz, G. Lachatre, J.C. Mathieu-Daude, P. Mura, G. Pepin, A.Turcan, J.P. Counil, and C. Gatignol, CEIP Marseille. Forensic toxicologists, OCRTIS and forensic laboratories (Lille, Lyon, Marseille, Paris, Toulouse), Afssaps, France

Homelessness is associated with cocaine and crack dependence, but not heroin dependence, among street-recruited drug users in New York City

    D.C. Ompad, S. Galea, C.M. Fuller, D. Nash, M. Rivera, and D. Vlahov, New York Academy of Medicine and Mailman School of Public Health, Columbia University, New York, NY

Drug dependence enviromics: Job strain in the work environment and risk of becoming drug-dependent

    P.L. Reed, C. Storr, and J.C. Anthony, Michigan State University, East Lansing, MI; Johns Hopkins University, Baltimore, MD

Substance use and misuse in Texas colonias

    R.T. Spence and L.S. Wallisch, University of Texas, Austin, TX

Drug-use patterns and problems on the Texas-Mexico border

    L.S. Wallisch and R.T. Spence, University of Texas, Austin, TX

Drug-use patterns among new admissions to a substance treatment center in Rio de Janeiro,Brazil

    F. Bastos, A. Simoes, M. Malta, and D. Metzger, Office of the State Health Secretary and Oswaldo Cruz Foundation, Rio de Janeiro, Brazil; University of Pennsylvania, Philadelphia , PA

Epidemiologic evidence of health disparities in doctor-patient communications about tobacco, alcohol, and other drug problems

    A. DelaTorre, C.F. Rios-Bedoya, C.L. Storr, and J.C. Anthony, Michigan State University, East Lansing, MI; Ponce School of Medicine, Ponce, PR; Johns Hopkins University, Baltimore, MD

Patterns of initial subjective reactions to marijuana and cocaine, and their associations with abuse/dependence
    J.D. Grant, R.J. Neuman, A.A. Todorov, R.K. Price, and K.K. Bucholz, Washington University School of Medicine, St. Louis, MO
Predictors of needle exchange utilization post-drug treatment entry among injection drug users
    J. Havens, C. Latkin, S. Huettner, D. Bishai, L. Cornelius, E. Pilibosian, and S.A. Strathdee, Johns Hopkins Bloomberg School of Public Health and University of Maryland School of Social Work, Baltimore, MD
African American mother-daughter drug-using patterns
    V.A.S. Krishna, C.C. Ostella, C. Meeks, W. Reich, A. Ben Abdallah, and L. Cottler, Washington University School of Medicine, St. Louis, MO
Williams Life-Skills training in a therapeutic community
    L. Durant, V. Williams, R. Williams, C. Edwards, and L. Handelsman, Duke University Medical Center, Durham, NC
General intelligence, g, as a protective factor against drug use
    H. Nyborg and H. Albeck, University of Aarhus, Aarhus, Denmark

TREATMENT FOR OPIOID DEPENDENCE
Challenges in increasing buprenorphine treatment access
    J.C. West, T. Kosten, J. Wilk, D. Svikis, E. Triffleman, D. Rae, W.E. Narrow, F.F. Duffy, and D.A. Regier, American Psychiatric Institute for Research and Education, Arlington, and Virginia Commonwealth University, Richmond, VA; Yale University, New Haven, CT
Factors associated with medication adherence in office-based buprenorphine maintenance
    M.V. Pantalon, D.A. Fiellin, P.G. O'Connor, M.C. Chawarski, and R.S. Schottenfeld, Yale University School of Medicine and the APT Foundation, New Haven, CT
Office-based buprenorphine: Long-term follow-up in primary care
    D.A. Fiellin, L.E. Sullivan, P.G. O'Connor, M. Chawarski, M.V. Pantalon, B. A. Moore, and R.S. Schottenfeld, Yale University School of Medicine and The APT Foundation, New Haven, CT
Office-based buprenorphine: A means of decreasing HIV/AIDS risk behavior?
    L.E. Sullivan, M.C. Chawarski, P.G. O'Connor, R.S. Schottenfeld, and D.A. Fiellin, Yale University School of Medicine and The APT Foundation, New Haven, CT
Network therapy and buprenorphine maintenance for the treatment of heroin addiction
    M. Galanter, H. Dermatis, L. Glickman, R. Maslansky, M. Brealyn Sellers, and C. Rahman-Dujarric, New York University and New York University Medical Center, New York, NY
Impact of the discontinuation of LAAM on a narcotic treatment program in New York City: Taper, methadone or buprenorphine
    P. Casadonte, E. O'Donnell, J. Kendrew, N. Lynch, J. Rotrosen, and A. Starosta, Department of Veterans Affairs Medical Center and New York University Medical School, New York, NY
Doctor-shopping for buprenorphine in France: Method for assessment and trends from 2000 to 2002
    V. Pradel, X. Thirion, C. Coudert, A. Masut, and J. Micallef, Centre for Evaluation and Information on Pharmacodependence and Social Security System, Marseille, France
Advances in substance abuse treatment: Client and counselor attitudes toward the use of medication
    T. Rieckmann, D. McCarty, B. Fuller, C. Thomas, and M. Daley, Oregon Health and Science University, Portland, OR
The role of motivation in treatment outcome: Analysis of a behavioral naltrexone therapy study
    A. Lebowitz, E. Akerele, and E. Nunes, Columbia University and New York State Psychiatric Institute, New York, NY
A motivational intervention for dramatically enhancing treatment enrollment of syringe exchange participants
    M. Kidorf, E. Disney, K. Kindbom, J. Blucher, L. Williams, J. Depo, and R.K. Brooner, Johns Hopkins University School of Medicine, Baltimore, MD
A comparison of heroin injectors and snorters seeking methadone treatment
    D. Highfield, R.P. Schwartz, R.J. Battjes, J.M. Callaman, K. O'Grady, C. Butler, C. Rouse, J.H. Jaffe, and J.V. Brady, Friends Research Institute, Institute for Behavioral Resources, University of Maryland School of Medicine, Baltimore, MD
Buspirone attenuates withdrawal symptoms in heroin addicts
    L. Buydens-Branchey and M. Branchey, VA New York Harbor Healthcare System, Brooklyn, NY

Evaluation of precipitated withdrawal in volunteers physically dependent on opioids given hydrocodone and naltrexone
> D.R. Jasinski, R.D. Colucci, R.F. Kaiko, C. Wright IV and J.C. Messina Jr., Johns Hopkins Bayview Medical Center, Baltimore, MD; Purdue Pharma L.P., Stamford, CT

Probuphine™ provides sustained serum buprenorphine concentration and long-term control of withdrawal symptoms and cravings
> J. Bell, J.M. White, J. Saunders, F. Bochner, P. Williamson, M. Makowska, D. Lissin, and A. Jacobs, University of Adelaide, Adelaide, The Langton Center, Sydney, and University of Queensland, Brisbane, Australia; Titan Pharmaceuticals, South San Francisco, CA

A novel HPLC method suitable for the routine determination of buprenorphine concentrations in serum
> E.J. Dunn, E. Giesbrecht, B. Brands, A. Elkader, and B. Sproule, University of Toronto, Toronto, Ontario, Canada

Capillary blood or saliva as a substitute for venous blood in therapeutic monitoring of opioid
> A. Christophersen, L. Olsen, H. Waal, and J.G. Mørland, Norwegian Institute of Public Health and University of Oslo, Oslo, Norway

Blood morphine concentrations and clinical impairment in a population of suspected drugged drivers
> L.C. Bachs, J.G. Bramness, S. Skurtveit, and J.G. Mørland, Norwegian Institute of Public Health, Oslo, Norway

ALCOHOL

Motives for smoking and drinking: Country and gender differences in samples of Hungarian and US high-school students
> T.A Wills, B. Piko, and C. Walker, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY; The University of Szeged, Szeged, Hungary

The relationship of conduct disorder to substance use disorders across gender in Chinese-, Korean-, and White-American college students
> S.E. Luczak and T.L. Wall, University of California, San Diego, CA

Reducing alcohol-exposed pregnancy risk in college women: 4-month outcomes
> S.D. Ceperich, K.S. Ingersoll, and M.D. Nettleman, Virginia Commonwealth University, Richmond, VA; Michigan State University, East Lansing, MI

Social construction of alcoholism in women in a rehabilitation process
> M.J. Gomez, S. Tortajada, A. Vidal, J. Aguilar, M. Castellano, and J.C. Valderrama, University of Valencia, Fundación de Ayuda contra la Drogadicción, and Generalitat Valenciana, Valencia, Spain

Domestic violence and risky sexual behaviors among college students
> J. Gross, L. Simons, B. Okeke, D. Dempsey, M. Browne, N. Millwood, L.Wright, and S. Rowe, Widener University, Chester, PA

Neurocognitive function in alcohol-dependent domestic violence offenders
> T.M. Neavins, C.J. Easton, K.A. Sacco, and T.P. George, Yale University School of Medicine, New Haven, CT

The effects of alcohol and risk status on behavioral activation and inhibition
> P.R. Finn and M.E. Rickert, Indiana University, Bloomington, IN

Random breath sample collection to detect alcohol use in homeless alcoholics
> C.J. Wong, K.N. Diemer, L. Webb, C. Taylor, T.W. Knealing, M. Fingerhood, G.E. Bigelow, D. Svikis, and K. Silverman, Johns Hopkins University School of Medicine, Baltimore, MD

Contingency management for attendance in a pharmacotherapy clinical trial for alcohol dependence
> F.R. Levin, J.J. Mariani, S. Shagrin, and S. Evans, Columbia University and New York State Psychiatric Institute, New York, NY

Assessing severity: Predicting DSM-IV dependence diagnoses from ASI composite scores
> S. Rikoon, J. Cacciola, D. Carise, and A.T. McLellan, University of Pennsylvania, Philadelphia, PA

Social drinkers underestimate additive behavioral impairment from alcohol and visual deficit sources
> E.L.R. Harrison and M.T. Fillmore, University of Kentucky, Lexington, KY

Alcohol and drug-related problems and fitness to drive: Assessment following the European Union legislation rules in the clinical setting
> J. Alvarez, University of Valladolid, Valladolid, Spain

Oral ethanol intake in rhesus macaques using an ethanol fading procedure
> S.N. Katner, M. Cole, C.T. Flynn, A.J. Kirsten, S.N. VonHuben, S.A. Davis, C.C. Lay, A.J. Roberts, H.S. Fox, and M.A. Taffe, The Scripps Research Institute, La Jolla, CA

IMPULSIVITY, RISK-TAKING

Impulsivity and compulsivity in pathological gambling
> C. Blanco, J. Grant, M.N. Potenza, A. Ibáñez, R. Zaninelli, J. Sáiz-Ruiz, and S.W. Kim, Columbia University, New York, NY; University of Minnesota, Minneapolis, MN; Yale University, New Haven, CT; Hospital Ramón y Cajal, Madrid, Spain

Characterizing the role of context on a delayed discounting task among pathological gamblers
> T.W. Fong, L. Mechanic, B. Clemente, H. Vanyo, T. Chan, C. Oto, and T. Newton, University of California, Los Angeles, CA

Disinhibition in adolescents with serious substance and conduct problems
> L.L. Thompson and T.J. Crowley, University of Colorado School of Medicine, Denver, CO

Adolescents with serious substance and conduct problems take more risks on the Balloon Analogue Risk Task
> T.J. Crowley, K. Raymond, S.K. Mikulich-Gilbertson, L.L. Thompson, and C.W. Lejuez, University of Colorado School of Medicine, Denver, CO; University of Maryland, College Park, MD

Evaluation of a behavioral measure of risk-taking propensity with inner-city adolescents
> C.W. Lejuez, W.M. Aklin, M.J. Zvolensky, C.W. Kalher, M. Gwadz, and F. Tyler, University of Maryland, College Park, MD; University of Vermont, Burlington, VT; Brown University, Providence, RI; National Development and Research Institutes, New York, NY

Influence of the home-rearing environment on adolescent sensation-seeking
> H.B. Moss, T.L. Hardie, and K.G. Lynch, University of Pennsylvania School of Medicine, Philadelphia, PA; University of Delaware, Newark, DE

Effects of tobacco deprivation and subsequent tobacco smoking in high- and low-impulsive sensation-seeking smokers
T.H. Kelly, A. Yingling, G. Robbins, C.A. Martin, N.G. Harrington, M.J. Bardo, C.R. Rush, and Perkins, University of
> Kentucky, Lexington, KY; University of Pittsburgh, Pittsburgh, PA

Behavioral and self-reported impulsivity in a cocaine- and alcohol-dependent sample: An argument for multi-method assessment
> J.A. Schumacher and S.F. Coffey, Research Institute on Addictions, University at Buffalo, Buffalo, NY

Cocaine users display impaired discrimination-reversal learning in a model of behavioral control
> M.T. Fillmore and C.R. Rush, University of Kentucky, Lexington, KY

Impulsivity (delay discounting) as a predictor of acquisition of i.v. cocaine self-administration in male (vs. female) rats
> J.L. Perry, J.P. German, G.J. Madden, and M.E. Carroll, University of Minnesota, Minneapolis, MN; University of Wisconsin, Eau Claire, WI

Effects of chronic nicotine on impulsive choice in rats
> M.L. Locey, B. Raiff, J. Marusich, and J. Dallery, University of Florida, Gainesville, FL

CRIMINAL JUSTICE

What role does substance use play for the criminal carrier?
> M. Stenbacka and H. Stattin, Karolinska Hospital, Stockholm; Örebro University, Örebro, Sweden

Criminal career patterns among long-term cocaine users
> E. Evans, Y. Hser, and D. Huang, UCLA Integrated Substance Abuse Programs, Los Angeles, CA

Enhancing employment: Outcomes from a 12-month randomized trial
> C.G. Leukefeld, M. Staton, J.M. Webster, A. Matayoke-Scriver, and T.K. Logan, University of Kentucky, Lexington, KY

Treatment outcomes for court-referred patients
> T.K. Killeen and K.T. Brady, Medical University of South Carolina, Charleston, SC

Diversion of prison-bound offenders to residential treatment: Effects on post-program drug use
> S. Belenko, C. Foltz, and M. Lang, University of Pennsylvania, Philadelphia, PA; Samaritan Village, Inc., New York, NY

County strategies designed to engage and retain clients in California's Substance Abuse and Crime Prevention Act program (Proposition 36)

    M. Hardy, C. Teruya, J.C. Yang, E. Evans, C. Grella, and Y. Hser, UCLA Integrated Substance Abuse Programs, Los Angeles, CA

Impact of Proposition 36 on local treatment systems and their linkages to the criminal justice system: Perspectives of county stakeholders

    C. Teruya, M. Hardy, J.C. Yang, Y. Hser, and E. Evans, UCLA Integrated Substance Abuse Programs, Los Angeles, CA

Drug dependence and treatment experience among Manhattan arrestees

    A. Golub and B.D. Johnson, National Development and Research Institutes, Inc., New York, NY

Naltrexone treatment for opiate-dependent parolees

    D.M. Coviello, J.W. Cornish, A.I. Alterman, D. Reyes, L. Sugar, M. Feeley, M. Alegria-Poyraz, K. Williams and C.P. O'Brien, University of Pennsylvania, Philadelphia, PA

Effects of acute administration of Flumazenil on aggressive responding of male parolees with history of conduct disorder

    O.V. Tcheremissine, D.R. Cherek, S.D. Lane, L.M. Lieving, and S. Nouvion, University of Texas, Houston, TX

Matching judicial supervision to clients' risk status in drug court

    D.B. Marlowe, D.S. Festinger, P.A. Lee, D.S. DeMatteo, N.S. Patapis, N.K. Mastro, K.M. Benasutti, and M.C. Johle, University of Pennsylvania, Philadelphia, PA

Validity of the adolescent SASSI in a juvenile correctional setting

    L.A.R. Stein, R. Lebeau-Craven, R. Martin, S.M. Colby, N.P. Barnett, C. Golembeske, and J.V. Penn, Brown University and Rhode Island Hospital, Providence, and Rhode Island Training School, Cranston, RI

Criminality, substance use, and perceived social support among female offenders

    M. Staton, J.M. Webster, C.G. Leukefeld, and J. Duvall, University of Kentucky, Lexington, KY

Correlates of recidivism for women parolees from prison-based treatment in California

    N.P. Messina, W.M. Burdon, and M.L. Prendergast, UCLA Integrated Substance Abuse Programs, Los Angeles, CA

Smokers are dopers: Smoking and drug use among female prisoners

K.L. Cropsey, G.C. Villalobos, C.L. St.Clair, and M.L. Stitzer, Virginia Commonwealth University, Richmond, VA; Johns Hopkins University, Baltimore, MD

High interest in smoking cessation treatments among incarcerated females

    G. Villalobos, C. St.Clair, and K. Cropsey, Virginia Commonwealth University, Richmond, VA

Almost half of incarcerated women smokers are nicotine-dependent

    C.L. St.Clair, G.C. Villalobos, and K.L. Cropsey, Virginia Commonwealth University, Richmond, VA

Hepatitis C prison-based peer education: Learning from the "guys in blue"

    C. Munoz-Plaza S. Strauss, J. Astone, D. Des Jarlais, and H. Hagan, National Development and Research Institutes, Inc. and Beth Israel Medical Center, New York, NY

EDUCATION

An interactive Web-based science curriculum uses drug abuse topics to teach high school students biology and chemistry

    R.D. Schwartz-Bloom and M.J. Halpin, Duke University Medical Center and North Carolina School of Science and Math, Durham, NC

Are pharmacists trained to address prescription drug abuse?

    C.A. Gauthier, L. Daughtry, and W.T. Harris, Xavier University of Louisiana, College of Pharmacy, New Orleans, LA

Novice and experienced drug counselors' attitudes on manualized treatment manuals

    L. Simons, H. Houston, and R. Jaccobucci, Widener University, Chester, and Alvernia College, Reading, PA

State counselor requirements: What are their implications for treatment dissemination?

    K. Walker-Smith, M.L.E. Kerwin, K. Yanko, L.A. Benishek, T.M. Christoffel, R.A. Corbin, J.C. Gutierrez, J.M. Wosak, and K.C. Kirby, Treatment Research Institute, Philadelphia, PA

Technology as a dissemination strategy for substance abuse treatment innovation

    C.L. Arfken, E. Agius, M. Dickson, H. Anderson, and A.M. Hegedus, Wayne State University, Detroit, and University of Michigan, Ann Arbor, MI

Beliefs about evidence-based practices in addiction treatment
    H.J. Hagedorn, M.L. Willenbring, M.E. Kenny, and A. Postier, University of Minnesota and Minneapolis
    Veterans Administration Medical Center, Minneapolis, MN

Symposium X -- AGING AND SUBSTANCE ABUSE: WHAT PROBLEMS LIE AHEAD?
Chairs: Timothy P. Condon and Susan R.B. Weiss
Drug abuse in the elderly: Baby boomers and their echo
    Thomas L. Patterson, University of California, San Diego, La Jolla, CA
Using existing national surveys to project future drug use among aging baby boomers
    Wilson Compton, National Institute on Drug Abuse, Bethesda, MD
Use and misuse of alcohol and prescription drugs in elderly populations
    Frederic C. Blow, University of Michigan, Ann Arbor, MI
Comorbidity of late-life addiction and other psychiatric disorders
    David W. Oslin, University of Pennsylvania, Philadelphia, PA
Discussant: Research priorities for study of substance abuse in elderly populations
    Timothy P. Condon, National Institute on Drug Abuse, Bethesda, MD

Oral Communications XII -- GENETIC POLYMORPHISMS
Chairs: MaryJeanne Kreek and Rachel F. Tyndale
Serotonin transporter genotype and acute subjective response to amphetamine
    D.C. Lott, S.J. Kim, E.H. Cook, Jr, and H. de Wit, The University of Chicago, Chicago, IL
Association study of monoamine oxidase A and catechol-O-methyltransferase polymorphisms and club drugs use in the Chinese population
    A. Stadlin, L.N. Wan, B.K.L. Cheung, N. Tam, S. Lui, J.S.K. Lee, and F.Y.K. Leung, Chinese University of Hong Kong and Kwai Chung Hospital, Hong Kong
Decreased metabolic capacity for carisoprodol in heterozygous CYP2C19*1/CYP2C19*2 subjects?
    J.G. Bramness, S. Skurtveit, L. Fauske, M. Grung, A. Molven, J. Mørland, and V.M. Steen, Norwegian Institute of Public Health, Oslo; and Haukeland University Hospital, Bergen, Norway
CYP2A6 genetically slow nicotine inactivators have a reduced risk for smoking and smoke less daily
    R.F. Tyndale, K.A. Schoedel, E.B. Hoffmann, B. Xu, Y. Rao, and E.M. Sellers, University of Toronto and the
Centre for Addiction and Mental Health, Toronto, Canada
Association analysis of polymorphisms of the human TPH2 gene and heavy alcohol use D.A. Nielsen, D. Proudnikov,
K.S. LaForge, A. Ho, B.E. Oosterhuis and M.J. Kreek, The Rockefeller University, New York, NY

Oral Communications XIII -- AND NOW, A FEW WORDS FROM OUR HOSTS: SUBSTANCE ABUSE IN PUERTO RICO
Chairs: William W. Latimer and Rafaela R. Robles
Sexual behaviors and substance use among Puerto Rican adolescents at high and low risk for substance use disorder
    V.E. Febo, R. Herrell, W. Brunetto, K. Merikangas, R. Ramirez, K. Conway, L. Dierker, G. Canino, Medical
    Sciences Campus- UPR, San Juan, PR; Yale University, New Haven, and Wesleyan University, Middletown, CT;
    NIMH and NIDA, Bethesda, MD
Effectiveness of a faith-based treatment for substance abuse: Clinical evaluation in a Puerto Rican sample
    H.B. Hansen, J. Rodriguez, B. Hansen, and T.P. George, Yale University, New Haven, CT
Drugs and sex: A cross-cultural comparison of HIV-risk behaviors among school-based females in the U.S., Puerto Rico, and Mexico
    L.J. Floyd and W. Latimer, Johns Hopkins University, Baltimore, MD
Risk-taking behavior in children and its association with cocaine use later in life
    C.F. Rios-Bedoya, C.L. Storr, and J.C. Anthony, Ponce School of Medicine, Ponce, PR; Johns Hopkins
    University Bloomberg School of Public Health, Baltimore, MD; Michigan State University, East Lansing, MI
Patterns of drug initiation and use among young injection drug users in Puerto Rico: A qualitative study of drug history narratives
    H.A. Finlinson, H.M. Colón, R.R. Robles and M. Soto, Center for Addiction Studies, Universidad Central del
    Caribe, Bayamón, Puerto Rico

Oral Communications XIV -- ADOLESCENT ANIMALS
Chairs: Yossef Itzhak and Jenny L. Wiley
Periadolescent chronic treatment with the cannabinoid agonist CP 55,940, and morphine self-administration behavior in adult male and female rats
    M. Biscaia, B. Fernández, S. Marín, E.M. Marco, M. Rubio, C. Guaza, C. García-Lecumberri, M.P. Viveros and E. Ambrosio, UNED, UCM, and Instituto Cajal, Madrid, Spain
Cocaine increases stimulated dopamine efflux in dorsal striatum more in periadolescent than adult rats
    Q.D. Walker, R.S. Francis, J. Caster and C.M. Kuhn, Duke U. Medical Center, Durham, NC
Differential role of nNOS in MDMA (ecstasy)- and methamphetamine-induced psychomotor stimulation in adolescent and adult mice
    Y. Itzhak, S.F. Ali, and K.L. Anderson, University of Miami, FL; NCTR, FDA, Jefferson, AR
Memory deficit and reduced anxiety in young adult rats given repeated intermittent MDMA treatment during the periadolescent period
    J.S. Meyer and B.J. Piper, University of Massachusetts, Amherst, MA
Sensitization to the abused inhalant toluene in adolescent rats
    J.L. Wiley, Virginia Commonwealth University, Richmond, VA

Oral Communications XV -- GLUTAMATE—WHAT'S ALL THE EXCITEMENT?
Chairs: Raka Jain and James K. Rowlett
Effects of the NMDA receptor antagonist (ketamine) to the operant decrement produced by naloxone in morphine-treated rats
    Raka Jain, All India Institute of Medical Sciences, New Delhi, India
Alteration of morphine's conditioned effects by the NMDA antagonist, LY235959 in C57B16 J.D. Lane, S. Robertson, K.A. Carrigan, L.A. Dykstra, U. of NC at Chapel Hill, Chapel Hill, NC
The metabotropic glutamate receptor 5 antagonist MPEP blocks reinstatement of drug-seeking triggered by cocaine, but not by stress or cues
    Z.X. Xi, J. Gilbert, A. Campos, C.R. Ashby, Jr., and E.L. Gardner, NIDA Intramural Research Program, NIH, DHHS, Baltimore, MD; St. John's University, Jamaica, NY
Attenuation of cocaine and food self-administration by the mGluR5 antagonist MPEP
    J.K. Rowlett, D.M. Platt and R.D. Spealman, Harvard Medical School, New England Primate Research Center, Southborough, MA
Memantine does not have abuse liability
    S.K. Vosburg, C.L. Hart, M. Haney and R.W. Foltin, Columbia University, New York State Psychiatric Institute, New York, NY

Oral Communications XVI -- HIV/AIDS: FROM SINGLE CELLS TO JAIL CELLS
Chairs: Karen S. Ingersoll and James L. Sorensen
Risk behaviors among substance users in HIV-care clinics
    D. Metzger, C. Im, R. Wickrema, K. Mauzar, I. Frank, W. Zhao, C.P. O'Brien, A. Cnaan, W. Ho and S. Douglas, University of Pennsylvania, FIGHT, and the Children's Hospital of Philadelphia, Philadelphia, PA
Impulsivity as a mediator in the relationship between drug choice and sexual risk behavior among heroin and crack/cocaine users
    M.A. Bornovalova, S.B. Daughters, J.J. Curtin and C.W. Lejuez, University of Maryland, College Park, MD; University of Wisconsin, Madison, WI
Found guilty? Psychosocial and HIV risk behaviors in pregnant drug-dependent women with and without criminal justice system involvement
    J. Draper, S. Douglass, D. Langhorst, L. Keyser-Marcus, D. Miles, H. Jones and D. Svikis, Virginia Commonwealth University, Richmond, VA; Johns Hopkins University School of Medicine, Baltimore, MD
Substance use during physical and sexual assault in HIV-infected persons
    C.H. Chuang, J.M. Liebschutz, D.M. Cheng, A. Raj and J.H. Samet, Boston University School of Medicine and Boston University School of Public Health, Boston, MA
Safety, efficacy, and tolerability of nelfinavir containing antiretroviral therapy for patients on methadone maintenance co-infected with HIV and hepatitis C viruses
    S. Kritz, L. Brown, M. Chu, C. Madray, R. King, and K. Young, Addiction Research and Treatment Corporation, Brooklyn, NY

Voucher reinforcement trial to improve methadone treatment for injection drug users with HIV infection
>   J.L. Sorensen, N. Haug, K. Delucchi, V. Gruber, J. Tulsky and S.M. Hall, University of California, San Francisco, CA

An RCT of nicotine patch plus motivational interviewing for HIV+ smokers
>   K.S. Ingersoll, K.L. Cropsey, C. St. Clair, C. J. Walker, N. VandeLinde, J. Cohen, and C. van Zyl, Virginia Commonwealth University, Richmond, VA

ASPD blunts the neuroprotective effects of antiviral treatment in HIV/AIDS
>   L.O. Bauer and J.D. Shanley, University of Connecticut School of Medicine, Farmington, CT

Barriers to treatment of hepatitis C in HIV-infected patients with a history of alcohol problems D.P. Nunes, R. Saitz,
>   H. Libman, J. Vidaver, D.M. Cheng, and J.H. Samet, Boston Medical Center and Beth Israel Deaconess Medical Center, Boston, and DM Stat Inc., Medford, MA

Diet cannot explain the lower weight of drug abusers with HIV
>   J.E. Forrester, K.L. Tucker, and S.L.Gorbach, Tufts University School of Medicine and The Human Nutrition Research Center on Aging, Boston, MA

Late-Breaking Research News -- Chair: Scott E. Lukas

GRANT-WRITING WORKSHOP -- Chair: Suman A. Rao

Welcoming Remarks -- **Timothy P. Condon and Suman A. Rao**

Workshop -- 10TH ANNUAL CONTINGENCY MANAGEMENT WORKING GROUP
Chair: Stacey Sigmon

Workshop -- THE QUEST FOR NON-ABUSEABLE OPIOID ANALGESICS: PAST ATTEMPTS, PAST SUCCESSES AND FUTURE POSSIBILITIES
Chair: Charles Grudzinskas

Workshop -- NOVEL TECHNIQUES AND TECHNOLOGIES IN CHEMISTRY AND PHARMACOLOGY
Chair: Andrew Coop

Workshop -- CAREER DEVELOPMENT: A PERSPECTIVE FROM JUNIOR AND SENIOR RESEARCHERS
Chairs: Teri Levitin, Mark R. Green, and Mark Swieter

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WEDNESDAY, JUNE 16, 2004
POSTER SESSION III

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THEORETICAL/COMMENTARY

Appetitive reinforcement in nonhuman primates: Revisiting the necessity and implementation of feeding restriction for behavioral studies
>   A.J. Kirsten, S.A. Davis, S.N. VonHuben, C.C. Lay, S.N. Katner, and M.A. Taffe, The Scripps Research Institute, La Jolla, CA

Cluster analysis as a method for interpreting drug discrimination data
>   L.P. Carter, C.P. France, W. Koek, University of Texas Health Science Center, San Antonio, TX

Survey and exploratory evaluation of outcome measures used in efficacy studies of treatments for cocaine abuse
>   E. Somoza, P. Somoza, D. Lewis, S. Li, A. Elkashef, F. Vocci, and T. Winhusen, University of Cincinnati College of Medicine and VAMC, Cincinnati, OH; NIDA, Bethesda, MD

Reducing the gap: Research to practice to systems change by collaboration
>   C. Chapman, G. Britt, N. Snead, J. Loving, and T. Mullins, Virginia Commonwealth University, Mid-Atlantic Addiction Technology Transfer Center, and Chesterfield Community Services Board, Richmond, VA

Preparing the new addiction workforce: Pre-service instruction on the science of addiction 5
>   A.H. Skinstad, N.A. Roget, P.K. Horvatich, S. Storti, and W.L. Woods, University of Iowa, Iowa City, IA; University of Nevada, Reno, Nevada; Virginia Commonwealth University, Richmond, VA; Brown University, Providence, RI

Inconsistencies in self-reports of substance abuse and risk behaviors
    N. Schreiber and K. Esposito, University of Miami, Center for Family Studies, Miami, FL
An evaluation of STD/HIV policies within publicly funded drug treatment programs in Los Angeles County
    J. Steinberg, D. Browne, and S. Shoptaw, Los Angeles County STD Program, Los Angeles County Drug and
    Alcohol Program and UCLA Integrated Substance Abuse Programs, Los Angeles, CA
*A comparison of national minimum data collections on service utilization from alcohol and other drug treatment
services*
    P.A. Lawrinson, B. Rush, and J. Copeland, National Drug and Alcohol Research Centre, University of New South
    Wales, Sydney, Australia; Centre for Addiction and Mental Health, Toronto, Canada
Scalable mathematical models for substance use: From social networks to the whole populations
    G.V. Bobashev, W. Zule, W.M. Wechsberg, A.V. Borschev, and A.E. Filippov, RTI International, Research
    Triangle Park, NC
Tryptamine- and piperazine-based substances as novel hallucinogenic drugs of abuse
    S.R. Tella, B. Hayes, and C.A. Sannerud, Drug Enforcement Administration, Washington, DC

DRUG INTERACTIONS

CART 55-102 reduces the locomotor-activating effects of cocaine: An isobolographic analysis
    J.N. Jaworski, H.L. Kimmel, D.A. Mitrano, R.J. Tallarida, and M.J. Kuhar, Yerkes Primate Center of Emory
    University, Atlanta, GA
*Interactions of cocaine and positive GABA-A modulators on repeated-acquisition and performance of response
sequences in rats*
    M. Sayah, L.R. Gerak, J.M. Moerschbaecher, and P.J. Winsauer, LSU Health Sciences Center, New Orleans, LA
*RTI 336, a 3-phenyltropane analog that binds to the dopamine transporter, alters cocaine self-administration and
activity differentially in Lewis vs. F344 rats*
    T.A. Kosten, X.Y. Zhang and F.I. Carroll, Yale University School of Medicine, New Haven, CT; Research
    Triangle Institute, Research Triangle Park, NC
*Fluoxetine enhances the effectiveness of a dopamine transporter inhibitor (RTI-336) to reduce
cocaine self-administration in rhesus monkeys*
    L.L. Howell, F.I. Carroll and A.M. Maguire, Yerkes National Primate Research Center, Emory
University, Atlanta, GA; Research Triangle Institute, Research Triangle Park, NC
*Pharmacological and behavioral characterization of the effects of the competitive NMDA receptor antagonist,
LY235959, on cocaine self-administration in rats*
    R.M. Allen, T.L. Suchey, C.V. Everett, and W.C. Lockhart, University of Colorado, Denver, CO
*Behavioral effects of N-benzylpiperazine and 1-(3-trifluoromethylphenyl)piperazine administered alone and in
combination*
    G.L. Becker and C.P. France, The University of Texas Health Science Center, San Antonio, TX
Effect of MD-354 on clonidine-induced spinal and supraspinal antinociception
    M. Dukat, A. Wesolowska and S. Young, School of Pharmacy, Virginia Commonwealth University, Richmond,
    VA
Progesterone treatment in methadone-stabilized cocaine users
    M. Sofuoglu, G. González, K. Gonsai, J. Poling, A. Oliveto, and T.R. Kosten, Yale University, New Haven, and
    VA Healthcare System, West Haven, CT
*Methadone-maintained patients prefer a methadone/benzodiazepine combination to either drug
alone*
    R. Spiga, R.S. Maxwell, and G. Kehner, Temple University, Philadelphia, PA
Naltrexone in treatment of amphetamines, cannabis and benzodiazepines (poly-drug use)
    G. O'Neil, G. Hulse, D. Arnold-Reed, C. Chan, P. O'Neil, V. Chiera, B. Sunderland, and Y. Liu, A.M.P.R.F.,
    University of Western Australia, Go Medical, Clinpath, and Curtin University, Perth, Australia
Patterns of opiate and cocaine co-use in Canada
    F. Leri, J. Stewart, S. Brissette, S. Brochu, J. Bruneau, N. El-Guebaly, B. Fischer, L. Noël, R. Jürgen, M. Tyndall,
    and C.T. Wild, University of Guelph, Concordia University, CH University Montréal, University Montréal,
    Foothills Hospital, University Toronto CAMH, INSP Québec, BC, Center of Excellence HIV/AIDS, University
    Alberta, Canada

INHALANTS, SEDATIVE-HYPNOTICS

Role of dopamine receptors on the abused solvent toluene-induced hyperlocomotion in mice
, M. Sato, and K. Wada, National Institute of Mental Health, National Center of Neurology and Psychiatry, Chiba, Japan

Dose-dependent impairment of watermaze reversal learning following maternal toluene abuse
J.C. Batis, M.H. Mohammadi, R.F. Ban, J.H. Hannigan, and S.E. Bowen, Wayne State University, Detroit, MI

Effects of acute and repeated exposure to toluene on schedule-controlled behavior in male Swiss Webster mice
S.E. Bowen and E. F. Muhammad, Wayne State University, Detroit, MI

Test of a screening procedure for identifying positive responders to inhalant drugs: Nitrous oxide
D.J. Walker and A.M. Syvertsen, The University of Chicago, Chicago, IL

Behavioral effects of the functionally selective GABA-A receptor agonist SL651498 in monkeys
S.C. Licata, D.M. Platt, and J.K. Rowlett, Harvard Medical School, New England Primate Research Center, Southborough, MA

Acute effects of alprazolam on risky decision-making in human subjects 28
S.D. Lane, D.R. Cherek, O.V. Tcheremissine, L.M. Lieving, and S. Nouvion, University of Texas Health Science Center, Houston, TX

Use of tranquilizers: Who is becoming dependent? 29
G. Mazzotti, M.S. O'Brien and J.C. Anthony, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD; Michigan State University College of Human Medicine, East Lansing, MI

Evolution of flunitrazepam consumption and misuse in the OPPIDUM Program from 2000 to 2002
C. Saillard, J. Micallef, C. Messina-Gourlot, X. Thirion, and CEIP Network, Centre for Evaluation and Information on Pharmacodependance, Marseille, France

Laboratory and questionnaire measures of, and acute effects of alprazolam on, proactive and reactive aggression
S. Nouvion, D.R. Cherek, S.D. Lane, O.V. Tcheremissine and L.M. Lieving, University of Texas Health Science Center, Houston, TX

GABA-A/alpha1 receptor involvement in the hyperphagic effect of benzodiazepines in squirrel monkeys
A.N. Duke, D.M. Platt, J.M. Cook, W. Yin, and J.K. Rowlett, Harvard Medical School, New England Primate Research Center, Southborough, MA; NSB, University of Massachusetts, Amherst, MA; University of Wisconsin, Milwaukee, WI

NICOTINE: ANIMAL STUDIES

Nicotine as a treatment in Parkinson's Disease through regulation of BDNF and dopamine D3 receptor expressions
B. Le Foll and P. Sokoloff, INSERM, Paris, France

Assessment of the effects of chronic nicotine on B2-nicotinic acetylcholine receptors in nonhuman primate using [I-123]5-IA-85830 and SPECT
K.P. Cosgrove, S. Ellis, M. Al-Tikriti, P. Jatlow, M.R. Picciotto, R.M. Baldwin and J.K. Staley, Yale University School of Medicine and VA Connecticut Healthcare System, West Haven CT

Nicotine-boron: A novel potent antagonist at alpha6beta2 and alpha4beta2* nicotinic receptors in rat striatum*
S.P. Sumithran, P.A. Crooks, J. Zhu, G. Zheng, R.L. Papke, and L.P. Dwoskin, College of Pharmacy, University of Kentucky, Lexington, KY; College of Medicine, University of Florida, Gainesville, FL

Effects of nicotine administration on rat brain neurotensin systems
M.E. Alburges and G.R. Hanson, University of Utah, Salt Lake City, UT

Environmental enrichment differentially alters nicotine-induced enhancement of dopamine clearance in rat nucleus accumbens shell and core
J. Zhu, M.T. Bardo, and L.P. Dwoskin, College of Pharmacy, University of Kentucky, Lexington, KY

A new method for GC/MS quantification of nornicotine in rat brain and blood after acute subcutaneous pretreatment with nornicotine enantiomers
X. Wei, D.J. Stairs, N. Neugebauer, M. Bardo, L.P. Dwoskin, and P.A. Crooks, Yaupon Therapeutics, Inc., University of Kentucky, and College of Pharmacy, University of Kentucky, Lexington, KY

Enantiomeric effects of nornicotine on nicotine self-administration and sucrose-maintained responding in rats
D.J. Stairs, N.M. Neugebauer, X. Wei, P.A. Crooks, L.P. Dwoskin, and M.T. Bardo, College of Pharmacy, University of Kentucky and Yaupon Therapeutics, Lexington, KY

Prazosin, an a1 adrenoreceptor antagonist, alters the expression of locomotor sensitization and drug-induced reinstatement of cocaine self-administration

X.Y. Zhang and T.A. Kosten, Yale University School of Medicine, New Haven, CT

Behavioral sensitization is dependent on circumstances surrounding psychostimulant administration

P.B. Yang, A.C. Swann, and N. Dafny, University of Texas-Medical School, Houston, TX

Development of cross-sensitization with psychostimulants depends on environmental cues

A.C. Swann, P.B. Yang, and N. Dafny, University of Texas-Medical School, Houston, TX

Cocaine self-administration in TRß transgenic mice before and after methylphenidate chronic treatment

R. Galici, N.E. Ercil, W.B. Siesser, S.-Y. Cheng, and M.P. McDonald, University Medical Center, Nashville, TN; National Cancer Institute, NIH, Bethesda, MD

The CANTAB Intradimensional/Extradimensional Attentional Shift procedure in rhesus monkeys: A method for acute drug challenge

C.C. Lay, R.D. Schneider, A.J. Kirsten, S.A. Davis, S.N. VonHuben, S.N. Katner, and M.A. Taffe, The Scripps Research Institute, La Jolla, CA

Comparison of [3H]RX821002 binding to alpha-2 adrenoceptors in non-human primate and rodent brain

T.J.R. Beveridge, H.R. Smith, M.A. Nader, and L.J. Porrino, Wake Forest University School of Medicine, Winston-Salem, NC

Effects of methylphenidate on cognitive performance in rhesus monkeys

S.A. Davis, S.N. VonHuben, A.J. Kirsten, C.C. Lay, S.N. Katner, and M.A. Taffe, The Scripps Research Institute, La Jolla, CA

Cocaine and anxiety: Role of the delta opioid system

S.A. Perrine, J.A. Schroeder, K.J. Guardiario, and E.M. Unterwald, Temple University School of Medicine, Philadelphia, PA

Comparison of the binding profile of (+)- and (-)-chloroephedrine with S(+)- methamphetamine

W.H. Soine and B.L. Roth, School of Pharmacy, Virginia Commonwealth University, Richmond, VA, and Case Western Reserve University Medical School, Cleveland, OH

IMAGING

Improved localization of fMRI activation in the basal forebrain at high field using match warped anatomic images

B.B. Frederick, M.L. Rohan, I. Elman, S.E. Lukas, and P.F. Renshaw, McLean Hospital, Harvard Medical School, Belmont, MA

Severity of neuropsychological impairment in cocaine addiction: Association with metabolism in the brain reward circuit

A.C. Leskovjan, R.Z. Goldstein, A.L. Hoff, R. Hitzemann, F. Bashan, S.S. Khalsa, G.J. Wang, J.S. Fowler, and N.D. Volkow, Brookhaven National Laboratory, Upton, NY; University of California, Davis, CA; Oregon Health Sciences University, Portland, OR; Wright Institute, Berkeley, CA; University of Iowa, Iowa City, IA

Cocaine craving correlates with psychostimulant-induced dopamine release and dopamine transporters

D.F. Wong, H. Kuwabara, W. Ye, A. Kumar, Y. Zhou, M. Alexander, J. Brasic, M. Thomas, M. Maris, D. Schretlen, E. London, and D. Jasinski, Johns Hopkins University, Baltimore, MD; University of California, Los Angeles, CA

Brain connectivity by cortico-striato-thalamic looping in a drug-craving paradigm: A comparison of PET and fMRI perfusion techniques

J. Listerud, N. Sciortino, R. Ehrman, A.R. Childress, and C.P. O'Brien, University of Pennsylvania, Philadelphia, PA

Sex difference in plasma nitric oxide end product levels in cocaine dependence

M.J. Kaufman, C.C. Streeter, T.L. Barros, O. Sarid-Segal, H. Tian, E.D. Rouse, K.K. Baumgarner, C.A. Archambault, P.F. Renshaw, and D.A. Ciraulo, Brain Imaging Center, McLean Hospital, Belmont, and Boston University School of Medicine, Boston, MA

Sex differences in brain activation during stress in cocaine-dependent individuals – preliminary results from an fMRI study

C.-S. Li, T.R. Kosten, and R. Sinha, Yale University School of Medicine, New Haven, CT

Stroop impaired in cocaine-dependent subjects

C.C. Streeter, G. Tzilos, O. Sarid-Segal, B. Remus, M. Silveri, C.A. Archambault, E.D. Rouse, K.K. Baumgarner, H. Tian, L.E. Nassar, S.A. Gruber, P.F. Renshaw, D.A. Ciraulo, and D.A.Yurgelun-Todd, Boston University School of Medicine, Boston, and McLean Hospital Brain Imaging Center, Belmont, MA

GABA levels in reserpine-treated cocaine-dependent subjects

O. Sarid-Segal, C.C. Streeter, Y. Ke, E.D. Rouse, H.J. Cabral, M. Afshar, C.A. Archambault, K.K. Baumgarner, H. Tian, L.E. Nassar, B. Remus, P.F. Renshaw, and D.A. Ciraulo, Boston University School of Medicine, Boston and McLean Hospital Brain Imaging Center, Belmont, MA

White matter differences within regions of interest: Implications for substance abuse

S.A. Gruber, M.M. Silveri, P.J. Pimentel, M.L. Rohan, and D.A. Yurgelun-Todd, McLean Hospital/Harvard Medical School, Belmont, MA

Increased white matter hyperintensities in chronic detoxified intravenous methamphetamine users

Y.E. Yoo, H.K. Lee, K.H. Chang, Y.H. Sung, I.C. Song, I.K. Lyoo and P.F. Renshaw, Seoul National University Hospital, Seoul, Korea; McLean Hospital Brain Imaging Center, Belmont, MA

Effects of chronic high-dose methamphetamine in long-term abstinent methamphetamine abusers on striatal dopamine assessed with PET

F.A. Frey, C.R. Schuster, C.E. Johanson, L. Lundahl, P. Keenan, N. Lockhart, R.A. Koeppe, and M.R. Kilbourn, University of Michigan, Ann Arbor and Wayne State University, Detroit, MI

Decreased frontal glucose metabolism correlates with impaired executive functions in methamphetamine users: A flurodeoxyglucose PET and neuropsychological study

S.J. Kim, J. Hwang, H.Y. Lee, S.K. Yune, Y.H. Sung, H.K. Kang, D.S. Lee, P.F. Renshaw, and I.K. Lyoo, Seoul National University Hospital, Seoul, Korea; McLean Hospital Brain Imaging Center, Belmont, MA

Decreased anterior cingulate activity in intravenous methamphetamine users: A single photon emission computed tomography and neuropsychologic test study

Hwang, H.Y. Lee, S.K. Yune, D.S. Lee, P.F. Renshaw, and I.K. Lyoo, Seoul National University Hospital, Seoul, Korea; McLean Hospital Brain Imaging Center, Belmont, MA

Decreased frontal lobe gray matter densities in chronic detoxified methamphetamine user: Voxel- based-morphometry study

A.I. Chung, H.K. Kang, J.Y. Kwon, J. Hwang, S.K. Yune, K.H. Chang, I.K. Lyoo, and P.F. Renshaw, Seoul National University Hospital, Seoul, Korea; McLean Hospital Brain
Imaging Center, Belmont, MA

A 3T proton magnetic resonance spectroscopy study in chronic detoxified intravenous human methamphetamine users

Y.H. Sung, S.K. Yune, K.J. Lee, J. Hwang, I.C. Song, I.K. Lyoo, P.F. Renshaw, Seoul National University Hospital, Seoul, Korea; McLean Hospital Brain Imaging Center, Belmont, MA

Curvature and shape patterns of the corpus callosum in chronic detoxified intravenous methamphetamine users: A Skeletal Shape Analysis

J.S. Oh, I.C. Song, K.S. Park, J.Y. Kwon, J.W. Hwang, P.F. Renshaw, and I.K. Lyoo, Seoul National University, Korea; McLean Brain Imaging Center, Belmont, MA

[I-123] beta-CIT SPECT imaging of dopamine transporters in heroin addicts

L.A. Bizeta, T. Kosten, M. Mouratidis, K. Gonsai, R.M. Baldwin, J.P. Seibyl, J.K. Staley, Yale University School of Medicine and VA Connecticut Healthcare System, West Haven, CT

Gender differences in brain activity during heroin-related cues in opiate-dependent subjects: A perfusion functional magnetic resonance imaging study

D.D. Langleben, S. Busch, N. Sciortino, J. Detre, J. Wang, J. Listerud, C.P. O'Brien, and A.R. Childress, University of Pennsylvania and Philadelphia VA Medical Center, Philadelphia, PA

GENDER

Gender-specific associations between types of childhood maltreatment and drug use variables in cocaine-dependent individuals

S.M. Hyman, M. Garcia, and R. Sinha, Yale University School of Medicine, New Haven, CT

Substance abuse and mental health issues among abused women

M. Yu, T. Edmond, Washington University and Comorbidity Addiction Center, St. Louis, MO

Gender differences in the course of antisocial behavior among injection drug users

S.K. Mikulich-Gilbertson, S. Salomonsen-Sautel, and R.E. Booth, University of Colorado School of Medicine, Denver, CO

Gender and the Assessment of Liability and Exposure to Substance use and Antisocial behavior

A.R. Miller and T.A. Ridenour, Pennsylvania State University, University Park, PA

Gender differences in ecstasy abuse and dependence criteria and diagnoses

S. McCrary, S. Bradford, and L.B. Cottler, Washington University School of Medicine, St. Louis, MO

The intersection of problem gambling, depression, suicidality, and violence among out-of-treatment female substance users

    R.M. Cunningham-Williams, A. Ben Abdallah, C.C. Meeks, and L.B. Cottler, Washington   University School of Medicine, St. Louis, MO

Gender differences, overt and relational victimization, and urban adolescent drug use

    T.N. Sullivan, W. Kliewer, and A.D. Farrell, Virginia Commonwealth University, Richmond, VA

Gender differences in specific cocaine-related abstinence symptoms as measured by the Cocaine Selective Severity Assessment

    K. Kemp, H.C. Fox, and R. Sinha, Yale University School of Medicine, New Haven, CT

Distress tolerance and borderline symptom severity in female inner-city drug users

    N.J. Wolf, C.W. Lejuez, S.B. Daughters, D. Kosson, and T.R. Lynch, University of Maryland, College Park, MD; Finch University/Chicago Medical School, Chicago, IL; Duke University Medical Center, Durham, NC

Gender differences among injecting drug users in Sydney, Australia, 1996-2003

    A. Roxburgh, C. Breen, and L. Degenhardt, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia

A profile of cocaine and amphetamine users in Los Angeles County

    D.A. Crevecoeur and R. Rawson, University of California, Los Angeles, CA

Gender-specific effects of social relationships on crack use among out-of-treatment users

    K.S. Riehman, W.M. Wechsberg, W. Zule, W.K. Lam, G. Bobashev and B. Levine, RTI International, Research Triangle Park, NC

Specialized versus standard chemical dependency treatment for women with children: Attending to heterogeneity in a retrospective multisite study

    R.G. Orwin, W.B. Kissin, R.E. Claus, C.E. Grella, and T. Williams, Westat, Rockville, MD; University of California, Los Angeles, CA

Gender differences in baseline characteristics of stimulant abusers enrolled in methadone vs. outpatient psychosocial treatment

    M.L. Copersino, J.M. Peirce, N.M. Petry, G.E. Bigelow, and M.L. Stitzer, Johns Hopkins University School of Medicine, Baltimore, MD; University of Connecticut, Storrs, CT

An investigation of gender differences using the TCU Client Problem Profile index

    G.A. Rowan-Szal, G.W. Joe, J.M. Greener, K.O. Courtney, and D.D. Simpson, Institute of Behavioral Research, Texas Christian University, Fort Worth, TX

Changes in perceived employment barriers for women and men as a function of drug use

    J.M. Webster, M. Staton, and C.G. Leukefeld, University of Kentucky Center on Drug and Alcohol Research, Lexington, KY

SPIRITUALITY

Differential predictors of maintaining hope across African and Latino-American clients in a narcotics treatment program

    E. Wong and D. Longshore, University of California and Integrated Substance Abuse Programs, Los Angeles, CA

Religious and spiritual beliefs and practices of treatment-seeking opioid abusers: Unappreciated needs and unexplored strengths

    E.R. Disney, M. Kidorf, K. Kindbom, and R.K. Brooner, Johns Hopkins University School of Medicine, Baltimore, MD

Psychometric properties of the religion and spirituality in recovery instrument

    D.W. Watson, D. Longshore, T. Sim, J. Annon, and G. Connors, UCLA Integrated Substance Abuse Programs and Friends Research Institute, Los Angeles, CA

The protective effect of religion in adolescent females' use of illicit drugs

    W.J. Calvert, A.C. Heath and K.K. Bucholz, Washington University School of Medicine, St. Louis, MO

Spiritual growth and recovery from alcoholism

    R. Sterling, S. Weinstein, J. Murphy, S. Gordon, B. Meier, P. Hill, and E. Gottheil, Thomas Jefferson University, Philadelphia, and Caron Foundation, Wernersville, PA; Biola University, La Mirada, CA; University of Washington, Seattle, WA

COMORBIDITY I

PRISM-IV: Reliable diagnosis in alcohol and drug abusers
S. Samet, E. Nunes, J. Meydan, K. Matseoane, and D. Hasin, Columbia University, and New York State Psychiatric Institute, New York, NY

Testing hypotheses regarding causes of comorbidity: Examining the underlying deficits of comorbid disorders
S.H. Rhee, J.K. Hewitt, R.P. Corley, E.G. Willcutt, and B. Pennington, University of Colorado, Boulder, and University of Denver, Denver, CO

Subtypes of illicit drug users: Evidence for a self-medication subtype?
M.T. Lynskey, K.K. Bucholz, E.C. Nelson, P.A.F. Madden, A.A. Todorov, J.D. Grant, N.G. Martin, and A.C. Heath, Washington University, St. Louis, MO

Suspected causal association between cocaine use and occurrence of panic attack
G.F. Alvarado, C.L. Storr, and J.C. Anthony, Faculty of Public Health UPCH, Lima, Peru; Michigan State University, East Lansing MI; Johns Hopkins University, Baltimore, MD

A comparison of psychiatric and demographic characteristics of female and male treatment-seeking, methamphetamine-dependent individuals
J.E. Chudzynski, P. Mercado, E. Moynier, and J.M. Roll, FRI, Inc., Los Angeles, CA

DSM-IV diagnoses of people seeking admission to clinical trials for methamphetamine treatment
T. Freese, R. Rawson, V.J. Pearce, A. Elkashef, E. Smith, and other MCTG Investigator authors, UCLA Integrated Substance Abuse Programs, Los Angeles, CA and National Institute on Drug Abuse, Bethesda, MD

Psychiatric comorbidity in ecstasy users: A one-year follow-up controlled study
R. de-la-Torre, J.M. Gines, F. Fonseca, S. Poudevida, R. Martin-Santos, S. Abanades, M. Farre, and M. Torrens, Institut Municipal d'Investigació Mèdica, Universitat Pompeu Fabra, Universitat Autónoma de Barcelona, and IAPS-Hospital del Mar, Barcelona, Spain

Changes in psychiatric symptomatology among long-term cocaine users
D. Herbeck, Y. Hser, J. Fan, E. Stark, and A. Paredes, UCLA Integrated Substance Abuse Programs, Los Angeles, CA

Comparative analyses of integrated versus parallel treatment of individuals with co-occurring psychiatric and substance abuse disorders
L.F. Mangrum, R. Spence and M. Lopez, University of Texas Center for Social Work Research and the Texas Department of Mental Health and Mental Retardation, Austin, TX

Psychiatric comorbidity and methadone maintenance treatment effectiveness
M.M. Torrens, M. Astals, L. Díaz, A. Domingo-Salvany, and R. Martín-Santos, IAPS-Hospital del Mar and Universitat Autónoma de Barcelona, Barcelona, Spain

Retention in aftercare among dually diagnosed patients following integrated and standard inpatient treatment
H. Dermatis, M. Galanter, C. Rahman-Dujarric, N. Brady, K. Ramaglia, D. LaGressa, and M. Trujillo, New York University and New York University Medical Center, New York, NY

Effectiveness of therapist training on Motivationally Based Integrated Treatment for mentally ill substance-abusing patients
E.P. Schoener, M.J. Henderson, S.J. Ondersma, and C.L. Madeja, Wayne State University, Detroit, MI

Involvement in intensive outpatient dual diagnoses treatment is related to reduced expensive hospital service utilization
F. LaBoy, A. Kampov-Polevoy, B. Higgins, and M. Scimeca, Bronx Veterans Affairs Medical Center, Bronx, and Mt. Sinai Medical Center, New York, NY

Improving care for co-occurring disorders in outpatient substance abuse treatment
S.B. Hunter, K. Watkins, S. Wenzel, S. Paddock, P. Ebener, W. Tu, B. Griffin, and J. Gilmore, Rand Drug Policy Research Center, Santa Monica, CA

Effect of pre-treatment drug use and psychiatric comorbidity on drug treatment outcome
J.M. Peirce, M.S. Kidorf, and R.K. Brooner, Johns Hopkins University School of Medicine, Baltimore, MD

Clinicians' attitudes towards dually diagnosed patients' recovery affects 12-step referral practices
C.L. Villano, A. Rosenblum, S. Magura, A. Laudet, C. Fong, T. Betzler, H. Vogel, and E. Knight, National Development & Research Institutes, Inc., New York, and Albert Einstein College of Medicine, Bronx, NY; ValueOptions Health Care Services, Colorado Springs, CO

Menthol adolescent smokers: Implications for tobacco dependence and cessation treatment
 C.C. Collins, F.H. Franken, and E.T. Moolchan, DHHS, NIH/NIDA Intramural Research Program, Baltimore, MD

Impact of alcohol use on adolescent smoking cessation
 M. Jaszyna-Gasior, J.R. Schroeder, M.L. Robinson, J.M. Berarducci, F.H. Franken, and E.T. Moolchan, DHHS, NIH/NIDA Intramural Research Program, Baltimore, MD

Externalizing disorders among teen smokers requesting treatment: Ethnic differences
 M.J. Frazier, J.M. Berarducci, C.C. Collins, and E.T. Moolchan, DHHS, NIH/NIDA Intramural Research Program, Baltimore, MD

Social construction of dependency and addiction by blunts users:Ethnographic reports
 E. Dunlap, S. Sifaneck, B. Johnson, and A. Golub, National Development and Research Institutes, Inc, New York, NY

Violence exposure and drug involvement among Mexican middle school students
 L.E. Ramos-Lira, F.A. Wagner, and C. Gonzalez-Forteza, Instituto Nacional de Psiquiatria "Ramon de la Fuente", Mexico City, Mexico; Morgan State University, Baltimore, MD

The influence of main sex partner's drug use on the African American adolescent girls' drug use
 P.A. Matson, H.D. Chilcoat, and J.M. Ellen, Johns Hopkins Bloomberg School of Public Health and Johns Hopkins School of Medicine, Baltimore, MD

A comparison of substance abuse treatment issues and outcomes for rural, semi-rural, and urban teens
 B. Murphy, S. Stevens, K. McKnight, S. Godley, and P. Shane, University of Arizona, Tucson, AZ; Chestnut Health Systems, Bloomington, IL; Pacific Research Institute, San Francisco, CA

Relationship of engagement in continuing care with variables related to initial outpatient treatment episode
 S.H. Godley, R.R. Funk, and M.D. Godley, Chestnut Health Systems, Bloomington, IL

Engaging and retaining adolescents in continuing care: How hard are we willing to work for it?
 M.D. Godley, S.H. Godley, M.L. Dennis, R.R. Funk, and L.L. Passetti, Chestnut Health Systems, Bloomington, IL

Subtypes of treatment response among adolescent substance abusers: An application of general growth mixture modeling
 C.E. Henderson, G.A. Dakof, C.L. Rowe, P. Greenbaum, and H.A. Liddle, University of Miami School of Medicine, Miami, and University of South Florida, Tampa, FL

Estimating the causal effect of time in treatment using propensity scores
 G. Ridgeway, D. McCaffrey, and A.R. Morral, Drug Policy Research Center, RAND, Santa Monica, CA, Arlington, VA, and Pittsburgh, PA

The development of Start SMART: Students Making Advertisements to Reduce Tobacco
 S. Zack, J. Weil, S. Nemes, J. Haviland, J. Hoffman, and E. Moolchan, Danya International, Inc., Silver Spring, and DHHS/NIH/NIDA Intramural Research Program, Baltimore, MD

The relationship between risk-taking propensity and adolescent smoking status
 W.M. Aklin, E.T. Moolchan, M.A. Bornovalova, and C.W. Lejuez, University of Maryland, College Park and NIDA Intramural Research Program, Baltimore, MD

Predictors of alcohol abuse/dependence symptoms in American Indian youth
 A. Stiffman and M. Yu, Washington University and Comorbidity Addiction Center, St. Louis, MO

HEALTH SERVICES

Substance abuse treatment is associated with lower health-care costs in substance-abusing Medicaid managed-care enrollees
 K.B. Stoller, R.K. Brooner, C.M. Demarest, L.J. Dunbar, E. Ferrugia, M.M. Riley, E.C. Strain, and C.W. Schmidt, Johns Hopkins University School of Medicine and Johns Hopkins HealthCare, Baltimore, MD

Addiction treatment utilization: Does housing status matter?
 S.G. Kertesz, M. Larson, D.M. Cheng, R. Saitz, and J.H. Samet, University of Alabama, Birmingham, AL; New England Research Institutes, Watertown, and Boston University, Boston, MA

Dynamic effects among adolescents' treatment needs, beliefs, and utilization
 A.R. Morral, T. Schell, and M. Orlando, Drug Policy Research Center, RAND, Arlington, VA and Santa Monica, CA

Comprehensive service delivery in substance abuse treatment: Are client needs being met?
 P.M. Roman, L.J. Ducharme, J.A. Johnson, and H.K. Knudsen, University of Georgia, Athens, GA

The utility of biochemical screening in an urban emergency department
K. McQueen, V. Waters, D. Alexander, M. Mooney, K. Liscum, and S. Basinger, Baylor College of Medicine, University of Houston Graduate School of Social Work, and University of Texas, Houston, TX

Barriers to program fidelity and treatment service delivery in a non-profit, outpatient drug treatment program in Cape Town, South Africa
B. Myers and C.D.H. Parry, Alcohol and Drug Abuse Research Group, Medical Research Council, Cape Town, South Africa

Primary medical care can improve drug and alcohol severity
R. Saitz, N.J. Horton, M.J. Larson, M. Winter, and J.H. Samet, Boston University Medical Center, Boston, Smith College, Northampton, New England Research Institutes, Watertown, MA

Substance abuse treatment program involvement in clinical trials: To what extent are treatment programs research savvy?
H.K. Knudsen, J.A. Johnson, L.J. Ducharme, and P.M. Roman, University of Georgia, Athens, GA

Professionalization of the TC workforce: Implications for quality of care
J.A. Johnson, L.J. Ducharme, H.K. Knudsen, and P.M. Roman, University of Georgia, Athens, GA

Addressing workforce issues: Factors affecting a comprehensive infrastructure
P. Horvatich, N.A. Roget, A. Skinstad, and S. Storti, Virginia Commonwealth University, Richmond, VA; University of Nevada, Reno, NV; University of Iowa, Iowa City, IA; Brown University, Providence, RI

Using lower-cost contingency management to improve work performance and increase employee satisfaction among substance abuse treatment program staff
K. Tracy, P. McAuliffe, and L. Mosel, New York University School of Medicine, New York, NY; CT Renaissance Inc., Norwalk, CT

Naltrexone in private substance abuse treatment centers: A categorical typology of adopters
C.B. Oser, J.A. Johnson, and P.M. Roman, University of Georgia, Athens, GA

Symposium XI -- SIGMA RECEPTORS: EVOLUTION OF AN ENIGMA TO A THERAPEUTIC TARGET FOR DRUGS OF ABUSE
Chairs: Rae R. Matsumoto and Tsung Ping Su
Overview: History, pharmacology and molecular biology of sigma receptors
Wayne D. Bowen, NIDDK/NIH, Bethesda, MD

Sigma receptors: From promiscuous ligands to subtype-selective agonists and antagonists
Andrew Coop, University of Maryland, Baltimore, MD

Antagonism of sigma receptors attenuates cocaine-induced behaviors and gene expression
Rae R. Matsumoto, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Cocaine regulation of dopamine systems via sigma receptors
Linda Werling, George Washington University Medical Center, Washington, DC

Restructuring neurons towards an addictive state: Roles of sigma-1 receptors
Tsung Ping Su, Intramural Research Program/NIDA/NIH, Baltimore, MD

Oral Communications XVII -- USE AND ABUSE *IN UTERO*
Chairs: Claire D. Coles and Loretta P. Finnegan
In utero marijuana exposure effects on the mRNA expression of striatal opioid neuropeptides, prodynorphin and proenkephalin, in the human fetal brain
X. Wang, D. Dow-Edwards, V. Anderson, and Y.L. Hurd, Karolinska Institute, Stockholm, Sweden; State University of New York and Downstate Medical Center, Brooklyn, NY

Mother-child interactions at ages 3 and 5 years: Impact of maternal cocaine use during pregnancy
E.S. Bandstra, C.E. Morrow, V.H. Accornero, R. Sljussar, A.L. Johnson, L. Xue, and J.C. Anthony, Johns Hopkins University, Baltimore, MD; Michigan State University, East Lansing, MI

Prenatal cocaine exposure: 8-year-olds' arousal to social and cognitive challenges
C.D. Coles, J.A. Kable, M.E. Lynch, and K.A. Platzman, Emory University School of Medicine, Atlanta, GA

Risk-taking and delayed discounting in prenatally cocaine-exposed 13-year-olds
M.R. MacDougall, R.N. Ehrman, C.W. Lejuez, H. Hurt, A. Weissman, J.T. Vietri, and A.R. Childress, University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia, and University of Pennsylvania, Philadelphia, PA; University of Maryland, College Park, MD

A randomized controlled study of buprenorphine and methadone in pregnant opioid-dependent patients: Their effect on the neonatal abstinence syndrome
> H. Jones, R. Johnson, D. Jasinski, K. O'Grady, C. Chisholm, R. Choo, M. Crocetti, R. Dudas, C. Harrow, M. Huestis, L. Jansson, M. Lantz, B. Lester, and L. Milio, Johns Hopkins University and NIDA Intramural Research Program, Baltimore, and University of Maryland, College Park, MD; Brown University, Providence, RI

A prospective study of 259 pregnant women treated with either buprenorphine or methadone through delivery, and neonatal parameters of their 260 children
> L. Gourarier, C. Lejeune, S. Aubisson, L. Simmat-Durant, E. Peyret, Centre Monte Cristo Hôpital Européen Georges Pompidou Paris and Groupe d'étude "Grossesse et Addictions", Paris, France

Double-dummy, double-blind comparison of buprenorphine and methadone in pregnant opioid-dependent women
> A. Primorac, R. Ortner, R. Jagsch, K. Rohrmeister, M. Langer and G. Fischer, Medical University Vienna and University of Vienna, Vienna, Austria

Characterizing nicotine withdrawal and craving in pregnant cigarette smokers
> S.H. Heil and S.T. Higgins, University of Vermont, Burlington, VT

Comparing the construct and predictive validity of the ASI and GAIN measures of change after treatment for pregnant and postpartum women
> R. Funk, M.L. Dennis, and S. Godley, Chestnut Health Systems, Bloomington, IL

Relationship between maternal substance use and depression in pregnant women
> K. Reid-Quinones, D. Svikis and J. Draper, Virginia Commonwealth University, Richmond, VA

Oral Communications XVIII -- EPIDEMIOLOGY—THAT'S WHAT COUNTS!
Chairs: Kathleen K. Bucholz and Robin A. Pollini

Gender differences in HIV risk among Caribbean drug users
> H.L. Surratt and J.A. Inciardi, University of Delaware, Coral Gables, FL

Reported drug use among subjects being recruited for an intervention study
> C.B. McCoy, L.R. Metsch, Y. Jeanty and A.J. Coltes, University of Miami, Miami, FL

Epidemiology of ecstasy use in the USA and its relationship with other drug use, abuse/dependence and disruptive behaviors
> S.S. Martins, G. Mazzzotti and H.D. Chilcoat, Johns Hopkins School of Public Health, Baltimore, MD

Prevalence and correlates of psychiatric disorder among a community sample of young adult MDMA/ecstasy users in Ohio
> R.S. Falck, R.G. Carlson, J. Wang and H.A. Siegal, Center for Interventions, Treatment and Addictions Research, Wright State University School of Medicine, Dayton, OH

Epidemiology and receptivity to treatment of college students using and abusing ephedra and related drugs for weight management
> K. Beitz, A. Drews, A. Pearson, J. Lillis and W.C. Follette, University of Nevada, Reno, NV

Characteristics of non-fatal overdose among injection drug users
> R.A. Pollini, L. McCall, D. Vlahov, and S.A. Strathdee for the ALIVE Study, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Connectedness is associated with depression among female substance abusers
> C.E. Mennes, C.C. Meeks, C. Ostella, A. Ben Abdallah, and L.B. Cottler, Washington University School of Medicine, St. Louis, MO

Behavioral problems and the occurrence of tobacco, cannabis, and coca paste smoking in Chile: Evidence based on multivariate response models for school survey data
> L.H. Caris, C.B. Anthony, and J.C. Anthony, University of Chile, Chile; Johns Hopkins University, Baltimore, MD; Michigan State University, East Lansing, MI

Who buys it, who grows it and who gets it for free? Marijuana procurement patterns in the US population
> R. Ramchand and H.D. Chilcoat, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Predictors of new cases of cannabis dependence in a high-risk family study
> K.K. Bucholz, L.J. Bierut, M.A. Schuckit, and V.M. Hesselbrock, Washington University School of Medicine, St. Louis, MO; University of California, San Diego, CA; University of Connecticut Health Center, Farmington, CT

Symposium XII -- DRUGS OF ABUSE AND HIV EXPRESSION
Chairs: Thomas J. Rogers and Phillip K. Peterson
k-Opioid receptor ligand/cocaine interactions and HIV-1 expression
    Phillip K. Peterson, University of Minnesota, Minneapolis, MN
Morphine, substance P, and HIV
    Wen-Zhe Ho, Children's Hospital of Philadelphia, Philadelphia, PA
Opiates and HIV neuropathogenesis: A central role of astroglia in drug-HIV interactions
    Kurt Hauser, University of Kentucky Medical Center, Lexington, KY
Drugs of abuse and HIV encephalopathy: Role of DC-SIGN and IDO
    Madhavan Nair, State University New York, Buffalo, Buffalo General Hospital, Buffalo, NY
Opioids and cocaine: Multiple mechanisms responsible for modulation of HIV-1 replication
    Thomas J. Rogers, Temple University School of Medicine, Philadelphia, PA

Future Federal Funding of Drug Abuse Research -- Chair: Wallace Pickworth

Symposium XIII -- THE ROLE OF BASAL SIGNALING IN DRUG ADDICTION AND PHYSICAL DEPENDENCE
Chairs: Edward Bilsky and Ellen Walker
Mechanisms underlying inverse agonism at opioid receptors: Role of multiple receptor conformations and multiple signaling pathways
    Wolfgang Sadee, Ohio State University, Columbus, OH
Developing alternatives to naloxone and naltrexone for the treatment of opioid addiction and chronic pain: In vivo characterization of 6beta-naltrexol and 6beta-naltrexamide
    Edward Bilsky, University of New England, Biddeford, ME
Links between behavioral signs of opioid abstinence and inverse agonist activity
    Alice Young, Wayne State University, Detroit, MI
Behavioral pharmacology of serotonin inverse agonists
    Ellen Walker, Temple University School of Pharmacy, Philadelphia, PA
Discussant: Implication of basal signaling on the pharmacology of abused drugs: Thoughts from the perspective of receptor theory
    S. Steven Negus, Harvard University, Mclean Hospital, Harvard Medical School, Belmont, MA

Oral Communications XIX -- UNCONVENTIONAL TREATMENTS FOR DRUG AND ALCOHOL ABUSE
Chairs: Joshua A. Lile and David M. Penetar
A double-blind, placebo-controlled trial of naltrexone and fluoxetine for heroin addiction treatment in Russia
    E. Krupitsky, E. Zvartau, E. Verbitskaya, and G. Woody, Pavlov Medical University, St. Petersburg, Russia; University of Pennsylvania and VA Medical Center, Philadelphia, PA
Mood, withdrawal, and physiological responses among racemic-methadone maintenance patients in relation to relative (S)- versus (R)-methadone exposure
T.B. Mitchell, K.R. Dyer, D. Newcombe, A. Salter, A.A. Somogyi, F. Bochner and J.M. White, University of Adelaide, Adelaide, SA, and School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia
Integrating buprenorphine-naloxone tablet treatment for short-term withdrawal from opioids into a residential integrated addiction and mental health service
    G. Brigham, J. Harrer, T. Winhusen, A. Pelt and L. Amass, Maryhaven, Columbus, and University of Cincinnati, College of Medicine and VA Medical Center, Cincinnati, OH; and Friends Research Institute, Inc., Los Angeles, CA
Bee-sting therapy is an alternative method in the heroin abuse complex treatment
    D.K. Tachkuliyeva, Oguz-Khan, Ashgabat, Turkmenistan
Isoflavone administration reduces alcohol intake in heavy drinkers
    D. Penetar, L. Vicens, J. Berko, A. Looby, D. Lee, and S.E. Lukas, McLean Hospital/Harvard Medical School, Belmont, MA

Combining naltrexone and memantine to block the rewarding effects of alcohol: An experimental pilot study in human subjects
M. Warnecke, G. Koller, C. Mayer, J.H. Krystal and C.G. Schuetz, Friedrich Wilhelms University, Bonn, and Ludwig Maximilian University, Munich, Germany; Yale University

Isoflavone treatment reduces alcohol drinking in heavy drinkers: A double-blind, placebo-controlled clinical trial
S.E. Lukas, T. Geaghan, M. Tracy, D. Lee and D. Penetar, McLean Hospital/Harvard Medical School, Belmont, MA

Supervised disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence: A randomized controlled study
E. Laaksonen, H. Alho, and M. Salaspuro, National Public Health Institute and University of Helsinki, Helsinki, Finland

Efficacy of the nicotine lozenge in relieving cue-provoked cravings
M.J. Durcan, C.A. Lemmonds, J. De'Ath, D. Targett, H. Marsh, R. Chan and T. Ong, GlaxoSmithKline, Carshalton, UK

The atypical antipsychotic aripiprazole attenuates the effects of oral d-amphetamine in humans
J.A. Lile, W.W. Stoops, L.R. Hays and C.R. Rush, University of Kentucky, Lexington, KY

Oral Communications XX -- THIS IS YOUR BRAIN ON COCAINE
Chairs: Nina C. DiPietro and Deborah C. Mash

Induction of c-Fos immunoreactivity in the orbitofrontal and cingulate cortices during yohimbine-induced reinstatement of methamphetamine-seeking in rats
J.D. Shepard, D. Chuang, Y. Shaham and M. Morales, Intramural Research Program, NIDA/NIH/DHHS, Baltimore, MD

Norepinephrine transporter regulation in cocaine abusers
D.C. Mash, Q. Ouyang, Y. Qin, J. Pablo, University of Miami School of Medicine, Miami, FL

Acute withdrawal from chronic "binge" cocaine in the rat leads to differential responses of HPA and amygdalar stress systems after opioid antagonist challenge
J. Bendor, Y. Zhou, V.P. Yuferov, A. Ho, M.J. Kreek, The Rockefeller University, New York, NY

Catecholamine response to methamphetamine is related to glucocorticoid levels but not to pleasurable subjective response
D.S. Harris, J.E. Mendelson, O.M. Wolkowitz, V.I. Reus and R.T. Jones, University of California, San Francisco, CA

Medial prefrontal cortex regulation of cocaine-seeking and cocaine-taking behavior: Involvement during maintenance and reinstatement testing in rats
N.C. DiPietro, F.A. Ugalde, H.B. Eichenbaum, K.M. Kantak, Boston University, Boston, MA

A critical role of amygdala ERK/MAP kinase signal pathway in incubation of cocaine seeking in rats
L. Lu, J. Dempsey, B.T. Hope, and Y. Shaham, NIH/NIDA Intramural Research Program, DHHS, Baltimore, MD

Cocaine-induced G1 arrest in a central nervous system progenitor cell line is associated with changes in cyclin A2 and c-myc expression
C.-T. Lee, J. Chen, K.G. Becker, H.M. Geller and W.J. Freed, NIH/NIDA Intramural Research Program, NIA, DHHS, Baltimore and NHLBI, Bethesda, MD

The neurobiology of anger in cocaine addiction: Role of the lateral orbitofrontal gyrus
R.Z. Goldstein, L.A. Cottone, N. Alia-Klein, A.C. Leskovjan, J.S. Fowler, G.J. Wang, R.C. Gur, R. Hitzemann and N.D. Volkow, Brookhaven National Laboratory, Upton, NY; University of Pennsylvania, Philadelphia, PA; Oregon Health Sciences University, Portland, OR

Prefrontal lobe NAA concentration increased after treatment of cocaine abuse
D.P. Olson, C.C. Streeter, Y. Ke, L.E. Nassar, O. Sarid-Segal, S.A. Gruber, D.A. Yurgelun-Todd, S.E. Lukas, D.A. Ciraulo, and P.F. Renshaw, McLean Hospital, Belmont, Harvard Medical School and Boston University School of Medicine, Boston, MA

Rapid phasic BOLD signal changes during human cocaine self-administration
R.C. Risinger, S.L. Amen, B.J. Salmeron, T.J. Ross, R.G. Hoffmann, A.S. Bloom, S.-J. Li and E.A. Stein, Medical College of Wisconsin, Milwaukee, WI; NIDA, Baltimore, MD

Symposium XIV -- MONKEY MODELS REVEAL DRUG ABUSE EFFECTS ON AIDS PROGRESSION
Chairs: Robert Donahoe and Charles Sharp
Methamphetamine alters the course of SIV-induced disease in rhesus monkeys
    Howard Fox, Scripps Research Institute, La Jolla, CA
Effects of morphine on rapid disease course in the macaque model of AIDS
    Anil Kumar, Ponce School of Medicine, Ponce, PR
Confirmation that opiates modulate AIDS progression in a monkey model
    Robert Donahoe, Emory University School of Medicine, Atlanta, GA

Symposium XV -- SCHIZOPHRENIA AND NICOTINE: NEUROBIOLOGICAL MECHANISMS AND THEIR TREATMENT IMPLICATIONS
Chairs: Gary B. Kaplan and Jennifer W. Tidey
Role of mesolimbic dopaminergic systems in nicotine dependence and schizophrenia
    Gary B. Kaplan, Brown Medical School/VA Medical Center, Providence, RI
Sensitivity of schizophrenic smokers to nicotine abstinence and replacement
    Jennifer W. Tidey, Brown University Medical School/Center for Alcohol and Addiction Studies, Providence, RI
Targeted pharmacotherapy for nicotine dependence in schizophrenia: Dopaminergic mechanism
    Tony P. George, Yale University School of Medicine, New Haven, CT

THURSDAY, JUNE 17, 2004
POSTER SESSION IV

COMORBIDITY II
The Tao of TAU
    L.B. Cottler, A. Ben Abdallah, R. Cunningham-Williams, M. Brown, C.C. Meeks, R. Funk, M. Dennis, and E. Spitznagel, Washington University School of Medicine, St. Louis, MO; Chestnut Health Systems, Bloomington, IL
Contracting and behavioral activation therapy: Preliminary efficacy in opioid-dependent patients with persistent depressive symptomatology
    M.C. Chawarski, M.V. Pantalon, and R.S. Schottenfeld, Yale University School of Medicine and the APT Foundation Inc., New Haven, CT
The role of depressive symptoms in predicting drug abstinence status in outpatient substance abuse treatment
    R. Dodge, J. Sindelar, and R. Sinha, Yale University School of Medicine, New Haven, CT
Drug use, depression, and hypogonadism in a community-based cohort (SHINE Study)
    E.T. Golub, E. Pilibosian, J. Cofrancesco Jr., S.A. Strathdee, and A. Dobs, Johns Hopkins University, Schools of Public Health and Medicine, Baltimore, MD
Temperament characteristics moderate response to sertraline in depressed opiate-dependent methadone patients
    W. Raby, K.M. Carpenter, and E.V. Nunes, New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons, New York, NY
The effect of desipramine and environmental context on treatment of depressed cocaine abusers
    A.C. Brooks, K.M. Carpenter, and E.V. Nunes, Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute, New York, NY
Distinguishing between substance-induced and independent depression in cocaine-dependent patients
    A. Leventhal, K. DeLaune, M. Mooney, and J.M. Schmitz, Substance Abuse Research Center, University of Texas, Houston, TX
Marijuana smokers: Treatment seekers show more depressive symptoms than non-treatment seekers
    J.J. Mariani, M. Haney, C. Hart, S. Vosburg, D.M. McDowell, and F.R. Levin, Columbia University and New York State Psychiatric Institute, New York, NY
Characterizing chronic marijuana abuse among depressed alcoholics
    I.M. Salloum, J.R. Cornelius, L. Kirisci, and A. Douaihy, University of Pittsburgh School of Medicine, Pittsburgh, PA
Delay discounting in nicotine-dependent individuals with major depressive disorder
    K.M. Gatchalian, R. Yi, W.K. Bickel, M.W. Johnson, and F. Baker, University of Vermont, Burlington, VT

Behavioral therapy for depression in drug dependence: Preliminary results of a randomized clinical trial

K.M. Carpenter, J. Smith, E. Aharonovich, and E.V. Nunes, New York State Psychiatric Institute and Columbia University College of Physicians and Surgeons, New York, NY

The additive effects of the comorbidity of depression on health and work among treatment-seeking substance abusers

A. Ben Abdallah, C.C. Meeks, C. Woodstock Striley, and L.B. Cottler, Washington University School of Medicine, St. Louis, MO

The intersection of depression and aggression

M. Brown, A. Ben Abdallah, and L.B. Cottler, Washington University School of Medicine, St. Louis, MO

A prospective study of the relationship between cannabis use and psychotic symptoms and relapse in early psychosis

L. Hides, S. Dawe, R.M. Young, and D. Kavanagh, Griffith University, Queensland University of Technology, and University of Queensland, Brisbane, Australia

Cannabis interacts with specific psychotic symptoms to increase severity of violent behavior in individuals with psychotic disorders

N. Alia-Klein, T. O'Rourke, R.Z. Goldstein, L. Cottone, and N.D. Volkow, Brookhaven National Laboratory, Upton, and Kings County Hospital Center, Brooklyn, NY

Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: Involvement of nicotinic receptor mechanisms

K.A. Sacco, A. Termine, A.A. Seyal, M.M. Dudas, J.C. Vessicchio, S. Krishnan-Sarin, P.I. Jatlow, B.E. Wexler, and T.P. George, Yale University School of Medicine, New Haven, CT

Neurocognitive sex differences in bipolar disorder with stimulant dependence

V.A. Nejtek, L.A. Chen, S. Mahbobian, E.J. Nestler, and A.J. Rush, The University of Texas Southwestern Medical Center, Dallas, TX

SEX DIFFERENCES/NEUROENDOCRINE EFFECTS

Sex differences in the modulation of cocaine and amphetamine-regulated transcript expression in the arcuate and paraventricular nuclei of the rat

B. Balkan, O. Gozen, G. Yararbas, E. Koylu, M.J. Kuhar, and S. Pogun, Ege University, Izmir, Turkey; Emory University, Yerkes Regional Primate Center, Atlanta, GA

D1 and D2 receptor activation, mRNA, and binding levels are differentially affected by acute cocaine administration in male and female rats

E.D. Festa, S. Jenab, J. Weiner, T. Niyomchai, S.J. Russo, L.M. Kemen, A. Nazarian, H.B.K. Wu, and V. Quinones-Jenab, Hunter College, City University of New York, New York, NY

Significant association between neurobiological and cognitive responses to stress and cocaine relapse

R. Sinha, M. Talih, R.M. Malison, G. Anderson, and M.J. Kreek, Yale University School of Medicine, New Haven, CT; Rockefeller University, New York, NY

Chronic amphetamine enhancements in locomotion, impairments in visual memory and changes in synaptic protein in female rats are differentially altered by chronic stress

V.N. Luine, V. Bisagno, C.A. Grillo, G.G. Piroli, P. Giraldo, and B.S. McEwen, Hunter College of City University of New York and Rockefeller University, New York, NY

A distinct neurochemical profile for WKY rats at baseline and in response to acute stress: Implications for altered reward in animal models of anxiety and depression

J.J. Mahoney, III, E. Pedrosa, and R. De La Garza, II, Albert Einstein College of Medicine, Bronx, NY

Genomic regions controlling rat corticosterone levels

M.N. Potenza, E.S. Brodkin, B. Joe, X. Luo, E.F. Remmers, R.L. Wilder, E.J. Nestler, and J. Gelernter, Yale University, New Haven, CT

Gender differences in response to stress after prenatal cocaine exposure

S.T. Cunningham, Z.O. Waldon, L.F. Shaw and M.T. Bardo, University of Massachusetts, Boston, MA

Gender differences in response to cues in cocaine dependence

A.L. McRae, K.T. Brady, H. Upadhyaya, M.E. Saladin, E.M. Ferrell, and M.A. Timmerman, Medical University of South Carolina, Charleston, SC

Comparison of the effects of cortisol and cocaine administration on plasma prolactin and growth hormone levels in individuals with cocaine dependence

I. Elman and S.E. Lukas, McLean Hospital, Belmont, MA

Time-course of changes in hippocampal mossy fiber long-term potentiation during chronic morphine treatment
    N.A. Beregovoy, N.S. Sorokina, and M.V. Starostina, Institute of Molecular Biology and Biophysics, Russian
    Academy of Medical Sciences, Novosibirsk, Russia
Antiproliferative effects of subnanomolar concentrations of [D-Ala2,D-Leu5]enkephalin in a CNS progenitor cell line
AF5: A non-opioid action
    S.-Y. Tsai, C.-T. Lee, W.J. Freed, H.M. Geller, T. Hayashi, and T.-P. Su, DHHS, NIH/NIDA Intramural Research
    Program, Baltimore, and NHLBI, Bethesda, MD
Standard delta receptor binding Ki values do not always predict functional Ki values as determined using the
[35S]GTP-gamma-S binding assay
    A.G. Budzynski, C.M. Dersch, S. Ananthan, and R.B. Rothman, NIH/NIDA Intramural Research Program,
    Baltimore, MD; Southern Research Institute, Birmingham, AL
Intrathecal injection of muscarinic receptors and GDNF antisense oligonucleotides inhibits the increase of c-Fos
expression in locus coeruleus of morphine-withdrawal rats
    H. Liu, W. Zhou, S. Tang, and G. Yang, Ningbo Addiction Research and Treatment Center, Ningbo, China
The serine/threonine protein kinase Akt is differentially regulated in the nucleus accumbens by acute and repeated
morphine administration in rats
    D.L. Muller and E.M. Unterwald, Temple University School of Medicine, Philadelphia, PA
Chronic morphine-induced changes in mu opioid receptors and G proteins in cells expressing the cloned mu opioid
receptor
    D. Zimmerman, H. Xu, X. Wang, and R.B. Rothman, NIH/NIDA Intramural Research Program, Baltimore, MD
Intracerebroventricular administration of anti-endothelin IgG selectively upregulates ET-A and
kappa opioid receptors
    X. Wang, H. Xu, M. Morales, and R.B. Rothman, NIH/NIDA Intramural Research Program, Baltimore, MD
Reversal of morphine tolerance in mice with PKC pseudosubstrate peptide inhibitors
    F.L. Smith, P.A. Smith and W.L. Dewey, Virginia Commonwealth University Medical Center, Richmond, VA
Effects of chronic morphine administration on PKA kinetic activity in mouse brain
    G.D. Dalton, F.L. Smith, and W.L. Dewey, Virginia Commonwealth University Medical Center, Richmond, VA
Differential modification of discriminative stimulus and directly observable effects of withdrawal
by a dopamine receptor agonist in LAAM-treated rhesus monkeys
    C.P. France and L.R. McMahon, University of Texas Health Science Center, San Antonio, TX
Ability of 6-beta-naltrexol to antagonize behavioral effects of morphine and precipitate abstinence
    E.F. Muhammad and A.M. Young, Wayne State University, Detroit, MI
Icilin induces hyperthermia by a nitric oxide mechanism
    Z. Ding, A. Cowan, J.L. Werkheiser, T. Gomez, and S.M. Rawls, Temple University Schools of Pharmacy and
    Medicine, Philadelphia, PA

CLUB DRUGS
Serotonergic drugs as transient reinforcers in rhesus monkeys
    W.E. Fantegrossi, J.H. Woods, and G. Winger, University of Michigan, Ann Arbor, MI
Who is becoming dependent on hallucinogens shortly after initiation of use
    A.L. Stone and J.C. Anthony, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD;
    Michigan State University, East Lansing, MI
Binding characteristics of [3H]NCS-382 and [3H]GABA in succinate-semialdehyde-dehydrogenase-deficient mouse
brain
    M.K. Ticku, A. Frazer, A.K. Mehta, G.G. Gould, K.M. Gibson, and M. Gupta, University of Texas Health
    Science Center, San Antonio, TX; Oregon Health and Science University, Portland, OR
Blockade of the behavioral effects of gamma-hydroxybutyrate by GHB and GABA-B receptor antagonists
    A.K. Goodwin, W. Froestl, K.M. Gibson, T. Burlingame, E.E.W. Jansen, C. Jakobs, and E.M. Weerts, Johns
    Hopkins University, Baltimore, MD; Novartis Pharma, Basel, Switzerland; Oregon Health Science University,
    Portland, OR; Clin. Chem.,VU University Medical Center, Amsterdam, Holland
Gamma-hydroxybutyrate as a cardiovascular stimulant: Role of GABA-B and GHB receptors
    A. Hicks, D. Kapusta, and K. Varner, Louisiana State University Health Sciences Center, New Orleans, LA
Cardiovascular responses elicited by repeated, intermittent administration of gamma-hydroxybutyrate
    K. Varner, A. Hicks, and J. Arsenault, Louisiana State University Health Sciences Center, New Orleans, LA

Rate-decreasing effects of and cardiovascular responses elicited by 1,4-butanediol administered alone and in combination with ethanol in rats

L.R. Gerak, A.R. Hicks, P.J. Winsauer, and K.J. Varner, Louisiana State University Health Sciences Center, New Orleans, LA

GHB and metabolites in rat post-mortem tissues

D. Richard, P. Courty, T.W. Faict, B. Ling, A. Eschalier, and F. Coudoré, Laboratoire de Pharmacologie-Toxicologie, CMP B, Institut Régional de Médecine Légale, CHU G. Montpied

Relevance of CYP2D6 polymorphisms in MDMA disposition in humans

M. Farre, R. de-la-Torre, B. O'Mathuna, P.N. Roset, N. Pizarro, M. Segura, M. Torrens, J. Ortuño, M.A. Pujadas, and J. Cami, Institut Municipal d'Investigació Mèdica, Universitat Autónoma de Barcelona, Universitat Pompeu Fabra, and IAPS-Hospital del Mar, Barcelona, Spain

Effects of amphetamine-type drugs on "free" serotonin concentrations in blood from conscious rats: An ex vivo microdialysis investigation

M.C. Nunez, M.H. Baumann, and R.B. Rothman, NIDA Intramural Research Program, Baltimore, MD

Evidence that serotonin and dopamine are involved in distinct aspects of the locomotor activation produced by MDMA (ecstasy) in rats

M.H. Baumann, R.D. Clark, and R.B. Rothman, NIDA Intramural Research Program, Baltimore, MD

Persistent enhancement of (+)-MDMA-induced hyperactivity despite recovery of 5-HT2CR sensitivity following repeated 5-HT2CR agonist administration

M.J. Bubar and K.A. Cunningham, University of Texas Medical Branch, Galveston, TX

Is ecstasy (MDMA) neurotoxicity dictated by selective transport?

C.D. Verrico, G.M. Miller, and B.K. Madras, Harvard Medical School, New England Primate Research Center, Southborough, MA

MDMA (ecstasy) exposure results in impulsivity and is accompanied by long-term increases in 5-HT2A receptor mRNA in frontal cortex of rats

R. De La Garza, II, E. Pedrosa, L.K. Granmayeh, G.F. Moeller, and P.B. Silverman, Albert Einstein College of Medicine, Bronx, NY; University of Texas Health Sciences Center, Houston, TX

Effects of MDMA (ecstasy) on MAP kinases and NOS signaling in rat brain

W.D. Wessinger and S.V. Kiosseva, University of Arkansas for Medical Sciences, College of Medicine, Little Rock, AR

Releaser data as a surrogate for studying the requirements for translocation: The creation of a 3D-QSAR model for 5-HT release

B.E. Blough, K.M. Page, S.W. Mascarella, J.S. Partilla, A. Budzynski, and R.B. Rothman, Research Triangle Institute International, Research Triangle Park, NC; and NIDA Intramural Research Program, Baltimore, MD

3,4-methylenedioxymethamphetamine disrupts behavioral thermoregulation in rats

R.J. Irvine, E.J. Jaehne, J.E. Phillips, and L. Rofe, University of Adelaide, Adelaide, Australia

Acute effect of MDMA and morphine on body temperature in rats

K. Benamar, R.J. Tallarida, E.B. Geller, and M.W. Adler, Temple University School of Medicine, Philadelphia, PA

Role of the serotonin 2A receptor (5-HT2AR) in the hyperlocomotive and hyperthermic effects of (+)-3,4-methylenedioxymethamphetamine

D.V. Herin and K.A. Cunningham, University of Texas Medical Branch, Galveston, TX

Effects of MDMA administration on scopolamine-induced disruptions in rats responding under a multiple schedule of repeated acquisition and performance

P.J. Winsauer, M. Sayah, J.R. Porter, C.B. Corll, J.M. Moerschbaecher, M.S. Delatte, and S.B. Stroble, Louisiana State University Health Sciences Center, New Orleans, LA

MDMA (ecstasy) serves as a robust positive reinforcer in a rat runway procedure

G. Wakonigg, K. Sturm, A. Saria, and G. Zernig, University of Innsbruck, Innsbruck, Austria

Medication or ecstasy? The importance of the logo

A. Daveluy, G. Miremont-Salamé, I. Jeantaud, A.C. Rahis, J.M. Delile, J.P. Gachie, and F. Haramburu, Université Victor Segalen, Bordeaux, France

Poly-substance abuse patterns among young MDMA/ecstasy users: A latent class analysis

R.G. Carlson, J. Wang, R.S. Falck, and H.A. Siegal, Wright State University School of Medicine, Dayton, OH

Profiling problem behaviors among young, female ecstasy users of low income

H.Z. Wu, C. Holzer, J. Grady, and A. Berenson, The University of Texas Medical Branch, Galveston, TX

Psychotropic medication use in designer drug users
     L. Karam, G. Miremont-Salamé, A.C. Rahis, M. Tournier, J.M. Delile, J.P. Gachie, and F. Haramburu, Université Victor Segalen, Bordeaux, France
Biomarkers of club drug neurotoxicity
     M.W. Warren, S. Janssen, R.L. Hayes, K.W.W. Wang, and M.S. Gold, University of Florida, Gainesville, FL
Striatal dopamine release during a motorbike-riding computer game in novelty seekers and recreational "ecstasy" users in SPECT
     A.M. Weinstein, M. Greemland, H. Lerman, and E. Even-Sapir, Sourasky Medical Center, Tel Aviv, Israel
The effects of fluoxetine on response to MDMA, mCPP and d-amphetamine in humans
     M. Tancer and C.E. Johanson, Wayne State University, Detroit, MI
The influence of "withdrawal" on estimating ecstasy dependence: A mixed-method approach
     L. Hoffer, S. McCrary, S. Bradford, and L.B. Cottler, Washington University School of Medicine, St. Louis, MO
The association of personality traits with club drug use in Chinese youth
     L.N. Wan, B.K.L. Cheung, F.Y.K. Leung, N. Tam, S. Lui, J.S.K. Lee, and A. Stadlin, Chinese University of Hong Kong and Kwai Chung Hospital, Hong Kong

DRUG ABUSE IN ADOLESCENTS: BEHAVIORAL STUDIES
Exaggerated behavioral response to cocaine in adolescent rats following binge pattern treatment
     J. Caster, Q. Walker, and C.M. Kuhn, Duke University Medical Center, Durham, NC
Response to cocaine after methylphenidate pre-treatment: Gender and age effects in locomotion and stereotyped behaviors
     A. Torres-Reveron, S.M. Melnick, and D.L. Dow-Edwards, State University of New York Downstate, Brooklyn, NY
Treatment with nicotine during adolescence but not adulthood produces long-term increases incocaine self-administration
     S. Izenwasser, R. Montano, and S.L. Collins, University of Miami School of Medicine, Miami, FL
Adolescent rats are less susceptible to nicotine withdrawal signs relative to their adult counterparts
     L.E. O'Dell, A.W. Bruijnzeel, A. Markou, and G.F. Koob, The Scripps Research Institute, La Jolla, CA
Tobacco-craving reductions during treatment for nicotine dependence in adolescent smokers
     S.J. Heishman, R.C. Taylor, M.L. Robinson, and E.T. Moolchan, NIH/NIDA Intramural Research Program, DHHS, Baltimore, MD
Contingency management for treating the cigarette smoking of adolescents: A pilot study
     J.M. Roll and J.E. Chudzynski, FRI, Inc., Los Angeles, CA
Relationship between white matter volume and cognitive performance during adolescence: Effects of age and risk for drug use
     M.M. Silveri, G.K. Tzilos, and D.A. Yurgelun-Todd, McLean Hospital and Harvard Medical School, Belmont, MA
Development of an affect-congruent Go-NoGo task to screen for functional brain deficits in inner-city adolescents at risk for drug dependence
     M. Goldman, R.N. Ehrman, M.R. MacDougall, A.S. Weissman, J.T. Vietri, H. Hurt, C.P. O'Brien, and A.R. Childress, University of Pennsylvania School of Medicine, University of Pennsylvania, and Children's Hospital of Philadelphia, Philadelphia, PA
Antecedents of drug abuse and dependence: A longitudinal study
     K.E. Fothergill and M. Ensminger, Johns Hopkins University School of Public Health, Baltimore, MD
Abuse types, psychopathology, and physical health in adolescent onset substance use disorder and normal control young women: A longitudinal study
     A. Mezzich, K. Pajer, B.S. Day, and M. Swaney, University of Pittsburgh, Pittsburgh, PA; Ohio State University, Columbus, OH
Childhood ADHD, comorbidity and risk for late-adolescent drug abuse
     K.C. Winters, G.J. August, and G.R. Realmuto, University of Minnesota, Minneapolis, MN

Smoking rates and history of adolescents diagnosed early in life with attention deficit hyperactivity disorder
F.H. Franken, I. Berlin, J.M. Berarducci, and E.T. Moolchan, DHHS, NIH/NIDA Intramural Research Program, Baltimore, MD

Substance abuse in juvenile bipolar disorder
T.E. Wilens, A. Kwon, J. Ditterline, P. Forkner, H. Moore, M. Morris, J. Wozniak, and J. Biederman, Massachusetts General Hospital, Boston, MA

BEHAVIOR: ANIMAL AND HUMAN

Behavioral economic analysis of drug reinforcement using Multiple Choice Procedure data
M.K. Greenwald, Wayne State University School of Medicine, Detroit, MI

Unit price as a determinant of remifentanil choice in rhesus monkeys
C.M. Galuska, G. Winger, J.H. Woods, and S.R. Hursh, University of Michigan Medical School and Science Applications International Corporation, Ann Arbor, MI

The role of the reinforcing effect of substances and motivation for psychoactive substance use and substance choice
M. Fatséas, P. Franques-Reneric, G. Encrenaz, J. Swendsen, J. Tignol, and M. Auriacombe, Université Victor Ségalen, Bordeaux, France

Individual differences in the reinforcing and subjective effects of psychomotor stimulants
S.C. Sigmon and R.R. Griffiths, Johns Hopkins University School of Medicine, Baltimore, MD

The reinforcing effects of methylphenidate: Influence of dose and environmental demands following drug administration
C.R. Rush, W.W. Stoops, J.A. Lile, M.T. Fillmore, and P.E.A. Glaser, University of Kentucky, Lexington, KY

Discriminative-stimulus and self-reported effects of methylphenidate, d-amphetamine, and triazolam in humans
W.W. Stoops, J.A. Lile, P.E.A. Glaser, and C.R. Rush, University of Kentucky, Lexington, KY

Intravenous cocaine discrimination in humans
N. Lockhart, L. Lundahl, H. Schubiner, and C.E. Johanson, Wayne State University, Detroit, MI

Effects of TDIQ in rats and mice trained to discriminate cocaine from saline and in monkeys trained to self-administer cocaine
R. Young, P.M. Beardsley, M. Dukat, and R.A. Glennon, Virginia Commonwealth University, Richmond, VA

Identifying the "switch" to addiction in monkey models of cocaine abuse
M.A. Nader, P.W. Czoty, H. O'Donohue, B.A. Reboussin, S.H. Nader, T. Moore, M. Bounds, and H.D. Gage, Wake Forest University School of Medicine, Winston-Salem, NC

Reinstatement of cocaine-seeking in the presence of an alternative reinforcer in group-housed cynomolgus monkeys
P.W. Czoty, C. McCabe, M.L. Banks, M. Dickens, C.L. Hubbard, and M.A. Nader, Wake Forest University School of Medicine, Winston-Salem, NC

Relationship of the dose to produce reinforcing effect with that of gross behavioral effects in rhesus monkeys
Y. Wakasa, A. Fujiwara, M. Iino, M. Sasaki, and T. Yanagita, Ina Research Inc., Ina-shi, Nagano-ken, Japan

Cocaine's effects on baboons' perception of species-specific affiliative calls differing in vocalizer sex
R.D. Hienz and E.M. Weerts, The Johns Hopkins University School of Medicine, Baltimore, MD

Effects of raclopride and SCH23390 on cognitive performance in rhesus monkeys
S.N. VonHuben, S.A. Davis, A.J. Kirsten, C.C. Lay, S.N. Katner, and M.A. Taffe, The Scripps Research Institute, La Jolla, CA

Persistent cocaine self-administration: Selective disruption in learning dependent on the insular/orbitofrontal cortex in rats
K.M. Kantak, T. Udo, F.A. Ugalde, C. Luzzo, N.C. DiPietro, and H.B. Eichenbaum, Boston University, Boston, MA

Cocaine dependence impaired performance in a new neuropsychological battery sensitive to prefrontal functions (FAB)
S. Nicastri and P.J. Cunha, University of Sao Paulo and Hospital Israelita Albert Einstein, Sao Paulo, Brazil

Neuropsychological impairment of cocaine-dependent subjects
P.J. Cunha and S. Nicastri, University of Sao Paulo and Hospital Israelita Albert Einstein, Sao Paulo, Brazil

Deficits on the Cambridge Decision-Making Task in chronic high-dose methamphetamine abusers following long-term abstinence
T.M. Cederlind, C.D. Aubie, C.E. Johanson, C.R. Schuster, and T.W. Robbins, Wayne State University, Detroit, MI; University of Cambridge, Cambridge, UK

Neurocognitive function in chronic high-dose methamphetamine abusers following long-term abstinence
L. Lundahl, P. Keenan, C.R. Schuster, and C.E. Johanson, Wayne State University, Detroit, MI

Classical and emotional Stroop performance and treatment response
M. Mouratidis, J. Poling, M. Sofuoglu, A. Oliveto, and T. Kosten, Yale University School of Medicine and VA Connecticut Healthcare System, West Haven, CT

Perceived benefits of low-threshold motivational and cognitive-behavioral group counseling for drug users in a soup kitchen setting
D.J. Kayman, A. Rosenblum, C. Gordon, and S. Magura, National Development and Research Institutes, Inc., New York, NY

Logical reasoning in methamphetamine abusers during the first month of abstinence
S.L. Simon, S. Berman, J. Dacey, W. Ling, R. Rawson, and E.D. London, David Geffen School of Medicine, University of California, Los Angeles, CA

The effect of an alternative source of reinforcement on human methamphetamine self-administration
C. Harding, D.Tzortzias, J. Chudzynski, T. Newton, and J. Roll, FRI, Inc. and University of California, Los Angeles, CA

Growth curve analysis of methamphetamine use trajectories from initiation to treatment
M.-L. Brecht, UCLA Integrated Substance Abuse Programs, Los Angeles, CA

POLYDRUGS: TECHNOLOGY ISSUES, TREATMENT

Internet as dealer: Knowledge of the internet as a source of illicit drugs by patients in residentialtreatment for drug dependence
S. Gordon and C. Siatkowski, Caron Foundation, Wernersville, PA

Controlled substances on the internet
R. Forman, University of Pennsylvania, Philadelphia, PA

Assessing substance abuse consumers' perceptions of treatment
J.R. Koch and M. Shawver, Virginia Commonwealth University and Department of Mental Health, Mental Retardation and Substance Abuse Services, Richmond, VA

Combining biometric and psychometric measures of substance use
M.L. Dennis, R. Lennox, C.K. Scott, and R. Funk, Chestnut Health Systems, Chicago and Bloomington, IL; Psychometric Technologies, Hillsborough, NC

Validity of self-reported drug use by the Addiction Severity Index in comparison to urine toxicology, in French-speaking drug users
C. Denis, E. Lavie, M. Fatséas, S. Brisseau, P. Franques-Reneric, and M. Auriacombe, Université Victor Segalen, Bordeaux, France

Acceptability of audio-assisted computer self-interview among substance abusers seeking treatment in Rio de Janeiro, Brazil
A. Simoes, F. Bastos, R. Moreira, L. Beck, C. Lemos, R. Barcelos, C. Bueno, R. Silva, C. Silva, T. Knett, R. Ferreira, E. Campagnuci, and D. Metzger, Office of the State Health Secretary, Oswaldo Cruz Foundation, and Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; University of Pennsylvania, Philadelphia, PA

Chemical submission: Study of case reports
S. Djezzar, F. Questel, H. Gourlain, D. Fompeydie, N. Richard, C. Gatignol, and S. Dally, CEIP Paris, hôpital Hôtel-Dieu, hôpital F. Widal, and Afssaps, Paris, France

Psychosocial outcomes following participation in residential behavioral pharmacology laboratory studies
N.P. Vadhan, C.L. Hart, B. Roe, J. Colley, M. Haney, and R.W. Foltin, Columbia University and The New York State Psychiatric Institute, New York, NY

Actual versus expected placement of substance-use-disorder clients into appropriate level of treatment after assessment
S. Stevens and R. Spence, Texas Commission on Alcohol and Drug Abuse and University of Texas, Austin, TX

Assessing drug use severity among drug users in treatment
D. Klempova and Y.I. Hser, University of California Integrated Substance Abuse Programs, Los Angeles. CA

A psychometric evaluation of the Beck Depression Inventory-II among drug-dependent patients
K. Dyer, A. Marsh, and S. LaVincente, University of Western Australia, Curtin University, and Next Stop, Perth. Western Australia, University of Adelaide, Adelaide, South Australia, Australia

Oral fluid vs. urine for drug abuse screening
K. Verebey and M. Patel, Ammon Analytical Laboratory, Linden, NJ

Using multiple methods to develop a comprehensive drug treatment service system
>A. Ritter, L. Berends, K. Bowen, N. Clark, S. Clemens, M. Devaney, J. Richards, and R. Tiffen, Turning Point Alcohol and Drug Centre, Melbourne, Australia

Self-reinforcement as a predictor of retention of candidates for treatment
>C. Gottlieb, E. Aharonovich, A. Brooks, and C. Nuygen, Columbia University College of Physicians and Surgeons and New York State Psychiatric Institute, New York, NY

Duration of most recent abstinence attempt and prospective treatment drop-out as a function of distress tolerance in residential treatment-seeking inner-city drug users
>S.B. Daughters, R.A. Brown, D.R. Strong, C.W. Kahler, M.A. Bornovalova, N.J. Wolf, G. Hernandez, B. Simmons, K. Dreaper, and C.W. Lejuez, University of Maryland, College Park, MD; Brown Medical School and Butler Hospital, Brown University Center for Alcohol and Addiction Studies, Providence, RI

Pilot trial of effectiveness of mindfulness meditation for substance abuse patients
>A. Alterman, J. Koppenhaver, E. Mulholland, L. Ladden, and M. Baime, University of Pennsylvania, Philadelphia, PA

Association between addiction beliefs and readiness to change in newly admitted outpatient treatment clients
>V. Stanick and A. Laudet, National Development and Research Institutes, Inc., New York, NY

Recovery management check-ups to shorten the cycle of relapse, treatment re-entry, and recovery
>C.K. Scott, M.L. Dennis, and M.A. Foss, Chestnut Health Systems, Chicago and Bloomington, IL

Correlates of 12-step affiliation in a community sample of former substance users
>A.B. Laudet and W.L. White, National Development and Research Institutes, Inc., New York, NY; Chestnut Health Systems, Bloomington, IL

Motivational change in contingency management for substance use
>D.M. Ledgerwood and N.M. Petry, The School of Medicine and The Human Nutrition Research Center on Aging at Tufts University, Boston, MA

Sacramento County dependency drug court: Year-one findings
>S.M. Boles, N.K. Young, T. Moore, and S. DiPirro-Beard, Children and Family Futures, Irvine, and Sacramento County Alcohol and Drug Services Division, Sacramento, CA

PROGRAM DESCRIPTION

2004 update of NIDA methamphetamine clinical trials
>E.V. Smith, A. Elkashef, R. Rawson, V.J. Pearce, W. Ling, F. Vocci, J. Campbell, W. Haning, J. Mawhinney, M. McCann, D. Weis, B. Johnson, and T. Newton, DHHS/NIH/NIDA, Bethesda, MD; UCLA Methamphetamine Clinical Trial Group and University of California, Los Angeles, CA; University of Texas, San Antonio, TX

Developing a hepatitis A and B vaccination program within an outpatient opioid-treatment program
>P. McLaughlin, Hartford Dispensary, Hartford, CT

Characteristics of patients admitted to a newly established methadone-treatment program
>J.T. Carroll and D.S. Metzger, NorthEast Treatment Centers and University of Pennsylvania, Philadelphia, PA

Maintaining a high standard of care for publicly funded methadone patients in the face of severe budget cuts: A contingency management approach
>G. Rhodes, K. Harris, and C. Schuster, Wayne State University, Detroit, MI

Methadone medical maintenance: Physician-pharmacy model
>A. Beeder, E.A. Wells, E. Curet, K. Alexander, R. Millman, H. Joseph, and L. Borg, Weill Cornell Medical College and The Rockefeller University, New York, NY

Maximizing the validity of interviewer-collected self-report data: A quality assurance model in action with the GAIN
>J.C. Titus, M.K. White, and M.L. Dennis, Chestnut Health Systems, Bloomington, IL

Introducing evidence-based practices in addiction settings using organization development methods
>M. Amodeo, M.A. Ellis, and J.H. Samet, Boston University School of Social Work, and Boston University Medical Center, Boston, MA

Experience with the addiction severity index in France. A descriptive report of training and adaptation to tobacco and non-substance-addictive behaviors
>M. Auriacombe, C. Denis, E. Lavie, M. Fatseas, P. Franques-Reneric, J.-P. Daoulouede, and J. Tignol, Université Victor Segalen, Bordeaux, France

Pilot program for intensive outpatient treatment of severe and chronic dually diagnosed veterans shows initial successes

B. Higgins, L. Travaglini, F. LaBoy, and M. Scimeca, Bronx Veterans Affairs Medical Center and MIRECC, Bronx, and Mt. Sinai Medical Center, New York, NY

Using a white paper to engage stakeholders—improving services for patients affected by alcohol, tobacco, and drugs in a publicly funded healthcare system

V. Waters, K. McQueen, and S. Basinger, Baylor College of Medicine and University of Texas Health Science Center, Houston, TX

A substance abuse prevention program for youth in the workplace

J. Weil, N. Linder, A. Johannson, S. Libretto, S. Nemes, and E. Moolchan, Danya International, Inc., Silver Spring, and DHHS/NIH/NIDA Intramural Research Program, Baltimore, MD

Empowering African American communities to fight drug abuse: Spreading the word

K.R. Harewood, C.T. Domino, D.G. Bellamy, A.B. Stephens, and A.C. Howlett, North Carolina Central University, Durham, NC

Drugged driving: A phenomenon often overlooked?

E. Øiestad, P.V. Syversen, M. Krogh, A.S. Christophersen, and J.G. Mørland, Norwegian Institute of Public Health, Oslo, Norway

LITERATURE REVIEW

The active ingredients of technology transfer: Activities and strategies that promote the adoption of evidence-based practices

N.A. Roget, P. K. Horvatich, A.H. Skinstad, and S. Storti, University of Nevada, Reno, NV; Virginia Commonwealth University, Richmond, VA; University of Iowa, Iowa City, IA

Key findings of a comprehensive review of psychological interventions for opiate-dependent clients on maintenance pharmacotherapies

N. Lee and A. Ritter, Turning Point Alcohol and Drug Centre, Melbourne, Australia

Management of chronic pain in substance abusers

I. Maany, University of Pennsylvania, Philadelphia, PA

Assessment of adolescent drug use: A comparison of approaches

W. Kliewer, D.S. Svikis, and C. Wagner, Virginia Commonwealth University, Richmond, VA

Oral Communications XXI -- TRAUMA, STRESS, AND DURESS
Chairs: Scott F. Coffey and Aimee L. McRae

Stress unveils a latent behavioral-conditioned response and gene expression changes in the prefrontal cortex of rats exposed to cues associated with low doses of nicotine

C.A. Schiltz, A.E. Kelley, and C.F. Landry, University of Wisconsin, Madison, WI

Alcohol dependence and PTSD: Subjective and biological stress reactivity

S.E. Back, K.T. Brady, A.L. McRae, C.R. Randall, and R. Anton, Medical University of South Carolina, Charleston, SC

Subject retention and reduced cue-elicited alcohol craving following trauma-focused prolonged exposure for alcoholics with PTSD

S.F. Coffey, P.R. Stasiewicz, P.M. Hughes, and M.L. Brimo, University at Buffalo, State University of New York, Buffalo, NY

Trauma-specific factors and stress responding in comorbid PTSD and substance use disorder E. SantaAna, M. Saladin, E.G. Spratt, M.A. Timmerman, K.T. Brady, A. McRae and A.E. Waldrop, Medical University of South Carolina, Charleston, SC

Trauma history and PTSD among youths in treatment for alcohol and other substance use disorders

J.M. Hawke, J. Ford, R. Haberek, and Y. Kaminer, The National Development and Research Institutes, Inc., New York, NY, and the University of Connecticut Health Center, Farmington, CT

Traumatic events related to cocaine dependence: Family and community factors

S.E. Afful, J.R. Kleinheider, L. Cottler, A. Stiffman and L.J. Bierut, Washington University School of Medicine, Saint Louis, MO

Factors related to PTSD symptomatology in cocaine-dependent homeless

K.M. Lester, J. Milby, M.J. Freedman, R. Vuchinich and J.E. Schumacher, The University of Alabama, Birmingham, AL

Traumatic event exposure and psychiatric outcomes
 E.C. Nelson, A.C. Heath, P.A.F. Madden, M.T. Lynskey, A.L. Glowinski, K.K. Bucholz, Washington University School of Medicine, St. Louis, MO

Expectancies of substance use effects on trauma symptomatology in individuals with substance dependence and ongoing distress from traumatic events
 A. Marsh, C. Hayes, and K. Dyer, Curtin University, School of Pharmacology, University of WA, Next Step Drug and Alcohol Services, Perth, Western Australia, Australia

Characteristics of women with sexual abuse histories at follow-up for methadone treatment
 K.O. Courtney, N.G. Bartholomew, G.A. Rowan-Szal, and D.D. Simpson, Texas Christian University, Fort Worth, TX

Oral Communications XXII -- OPIATES AND OPERANTS
Chairs: S. Stevens Negus and Anthony L. Riley

Pharmacological modulation of choice between heroin and food in rhesus monkeys: Effects of naloxone, buprenorphine and methadone
 S. Negus, McLean Hospital-Harvard Medical School, Belmont, MA

Cue-induced resumption of heroin-seeking in rats after abstinence: An alternative model of craving and relapse to drug abuse
 W. Zhou, F. Zhang, S. Tang, H. Liu, J. Gu and G. Yang, Ningbo Addiction Research and Treatment Center, Ningbo, China

Reinforcing and discriminative stimulus effects of heroin and oxycodone in rats
 J.L. Newman, C.D. Cook, L.S. Harris and P.M. Beardsley, Virginia Commonwealth University, Richmond, VA

The effects of cross-fostering on morphine-induced conditioned taste aversions, in Fischer and Lewis rats
 M.A. Gomez-Serrano, J.R. Glowa, and A.L Riley, American University, Washington, DC; Pfizer Global Research and Development, Groton, CT

The impact of morphine preexposure on its rewarding and aversive properties
 G.R. Simpson and A.L. Riley, University of Miami, Coral Gables, FL; American University, Washington, DC

The influence of morphine training dose on the persistence of CPP during repeated pairing and testing, extinction and reinstatement
 M. Evola, S.E. Bowen and A.M. Young, Wayne State University, Detroit, MI

Effects of stress modulation on morphine-induced conditioned place preferences in the F344, LEW and Sprague-Dawley rat strains
 I. Grakalic, C.W. Schindler, K.C. Rice, and A.L. Riley, NIH/NIDA Intramural Research Program, Baltimore and NIH/NIDDKD, Bethesda, MD; American University, Washington, DC

Discrimination of a possible antagonist-precipitated withdrawal cue from an acute state of opiate dependence in rats
 N.T. Jones, E.F. Muhammad and A.M. Young, Wayne State University, Detroit, MI

Morphine-3-glucuronide has opposite effects on morphine and morphine 6-glucuronide-induced locomotor activity
 M. Handal, Å. Ripel, T. Aasmundstad, S. Skurtveit and J.G. Mørland, Norwegian Institute of Public Health, Oslo, Norway

Psychomotor sensitization due to morphine-6-glucuronide, a morphine metabolite
 J.G. Mørland, M. Handal, Ø. Grotlie, Å. Ripel and S. Skurtveit, Norwegian Institute of Public Health, Oslo, Norway

Oral Communications XXIII -- RISKY BUSINESS AMONG ADOLESCENTS: PREVENTION AND TREATMENT
Chairs: Michelle K. White and Murat Yucell

Early intervention for teen substance abuse: A randomized controlled trial of Multidimensional Family Therapy with young adolescents referred for drug treatment
 C.L. Rowe, H.A. Liddle, G.A. Dakof, and C. Henderson, University of Miami, Miami, FL

Say yes first: Adolescent alcohol/drug prevention follow-up results
 K. Zavela, V. Battistich, and B.J. Dean, University of Northern Colorado and Island Grove Treatment Center, Greeley, CO; University of Missouri, St. Louis, MO

Barriers to care: Adolescent treatment for SUD in public and private centers
 C.L. Dempsey, P.D. Riggs, H.K. Knudsen, and P.M. Roman, University of Colorado School of Medicine, Denver, CO; University of Georgia, Athens, GA

Predicting residential placement, relapse and recidivism among adolescents with the GAIN
   M. White, M.L. Dennis, and R. Funk, Chestnut Health Systems, Bloomington, IL
The risk of early drug use on youth violent offending
   Y.F. Chan, H.D. Chilcoat, C.L. Storr and J.C. Anthony, Johns Hopkins Bloomberg School of Public Health,
   Baltimore, MD; Michigan State University College of Human Medicine, East Lansing, MI
Medication-sensitive behavioral dyscontrol in children at risk for adolescent substance abuse
   S.J. Donovan, E.V. Nunes, J.W. Stewart, New York State Psychiatric Institute, New York, NY
Association of clinical assessments of treatment response with change in serotonin receptors and diurnal salivary
   cortisol in substance-dependent, depressed adolescents
   M. Lohman, P.D. Riggs, M. Laudenslager, and S.K. Mikulich-Gilbertson, University of Colorado School of Medicine,
   Denver, CO
Genetic and environmental interactions for tobacco, alcohol and illicit drug use in adolescent female twins
   D.R. Miles, J.L. Silberg, R.W. Pickens, and L.J. Eaves, Virginia Commonwealth University, Richmond, VA
Structural brain correlates of age of first alcohol and cannabis use: A magnetic resonance
imaging study in healthy males
   M. Yücel, A.L. Condello, D.I. Lubman, S.J. Wood, W.J. Brewer, D. Velakoulis, M.T. Wong and C. Pantelis,
   ORYGEN Research, University of Melbourne, and Mental Health Research Institute, Melbourne, Australia
The effects of adolescent drug use on adult role functioning: A longitudinal study examining gender differences
   K.M. Green and M. Ensminger, Johns Hopkins University School of Public Health, Baltimore, MD

Oral Communications XXIV -- WHAT'S NEW IN DRUGS OF ABUSE
Chairs: Alison Oliveto and Elise M. Weerts
BD1063, a sigma receptor antagonist, attenuates both 3, 4-methylene-dioxymethamphetamine and DOI-induced
locomotor stimulation
   D.L. Gilmore, and R.R. Matsumoto, University of Oklahoma Health Sciences Center, Oklahoma City, OK
Behavioral effects of gamma-hydroxybutyrate in humans
   A. Oliveto, J. Poling, R. Pruzinsky, K. Gonsai, T.R. Kosten, and B.A. Martell, Yale University, New Haven, and
   VA Connecticut Healthcare System, West Haven, CT
Evaluation of physical-dependence potential of gamma-hydroxybutyrate
   E.M. Weerts, A.K. Goodwin and R.R. Griffiths, Johns Hopkins University School of Medicine, Baltimore, MD
Oral dose ranging with ketamine, a prototypic NMDA antagonist
   M.K. Romach, E.M. Sellers, H.L. Kaplan, L.C. Fernandes, J. Oldenhof and S. McDonald, Ventana Clinical
   Research Corp. and University of Toronto, Toronto, Canada; Forest Research Institute, Jersey City, NJ
Pharmacological characterization of the novel kappa opioid agonist Salvinorin A in the mouse K.M. Kugle, L.J.
   Valdes, J.H. Woods, J.R. Traynor and W.E. Fantegrossi, The University of Michigan, Ann Arbor, MI

Oral Communications XXV -- ABUSE.COM
Chairs: Carol J. Boyd and John W. Hopper
Introduction
   J.W. Hopper, McLean Hospital and Harvard Medical School, Belmont, MA
Use of salvia divinorum, an unscheduled hallucinogenic plant: A Web-based survey of 500 users
   M.J. Baggott, E. Erowid, F. Erowid and J.E. Mendelson, California Pacific Medical Center Research Institute, San
   Francisco, CA
Anabolic-androgenic steroid users: Results of a Web-based survey
   J. Langenbucher, T. Hildebrandt, S. Carr, S. Roth, S. Park, Rutgers University, Piscataway, NJ
Gender differences in the temporal relationship between prescribed anti-depressants and prior drug and alcohol use
   C.J. Boyd, S.E. McCabe and C.J. Teter, University of Michigan, Ann Arbor, MI
Patient perceptions of addiction
   J. Guary, E.H. Adams, J.D. Haddox, and S.H. Schnoll, Harris Interactive, Rochester, NY, Purdue Pharma L.P.,
   Stamford, CT

Symposium XVI -- TN COMMUNITY-BASED TREATMENT EVALUATION: RESULTS OF WAVE 1 STUDIES
Chairs: Betty Tai and Maxine Stitzer
Buprenorphine detox in community treatment clinics
    Walter Ling, University of California, Los Angeles, CA
Motivational interviewing for enhanced treatment engagement in community treatment clinics
    Sam Ball, Yale University School of Medicine, West Haven, CT
Motivational incentives: Effects on retention and drug use in community treatment clinics
    Maxine Stitzer, Johns Hopkins University School of Medicine, Baltimore, MD
NIDA's Clinical Trials Network: Progress and prospects
    Betty Tai, National Institute on Drug Abuse, Bethesda, MD
Discussant
Warren Bickel, University of Vermont, Burlington, VT

Oral Communications XXVI -- DOUBLE EXPOSURE: DRUG INTERACTIONS
Chairs: Gregory D. Busse and Mark A. Smith
Cerebral blood-flow velocity in cocaine and marijuana abusers: A comparison between cigarettesmokers and non-smokers
    K. Tate, R.I. Herning, W. Better and J.L. Cadet, NIH/NIDA Intramural Research Program, Baltimore, MD
Differences in cerebral metabolism but not cognitive performance due to marijuana use by methamphetamine abusers
    B.T. Voytek, S. Berman, S.L. Simon, W. Ling, and E.D. London, David Geffen School of Medicine, UCLA, Los Angeles, CA
Spaced preexposure to alcohol does not reverse the attenuating effects of alcohol on cocaine place conditioning
    G.D. Busse, E.T. Lawrence and A.L. Riley, American University, Washington, DC
Increased reinforcing efficacy of heroin and cocaine after certain heroin self-administration histories
    S.J. Ward, M. Stridh-Ellgren, D. Morgan, D.C.S. Roberts, Wake Forest University School of Medicine, Winston-Salem, NC; The Karolinksa Institute, Stockholm, Sweden
Cross-sensitization between opioids and cocaine
    M.A. Smith and J.L. Greene, Davidson College, Davidson, NC

Oral Communications XXVII -- NICO-TEEN
Chairs: Eric T. Moolchan and Himanshu P. Upadhyaya
Assessment of nicotine dependence in adolescents
    C. Thurstone, P.D. Riggs, S.K. Mikulich-Gilbertson, University of Colorado Health Sciences Center, Denver, CO
Neuroendocrine response to dopaminergic agents in adolescents with nicotine dependence
    K.T. Brady, H.P. Upadhyaya, and W. Wang, Medical University of South Carolina, Charleston, SC
Adolescent female smokers: Gender-specific-prevalence, risk and protective factors
    P.S. Meszaros, J.R. Koch and A. Huebner, Virginia Polytechnic Institute and State University, Blacksburg, and Virginia Commonwealth University, Richmond, VA
Examining gender differences in the relation between dieting and smoking behaviors among adolescents
    M.M. Maldonado-Molina, L.M. Collins and T.A. Ridenour, Pennsylvania State University, University Park, PA
Does marijuana use impact reduction of adolescent tobacco use?
    E.T. Moolchan, D.H. Epstein, F.H. Franken, M.L. Robinson, S.J. Heishman, and M. Jaszyna-Gasior, DHHS, NIH/NIDA Intramural Research Program, Baltimore, MD

Symposium XVII -- EMPIRICAL EVALUATION OF ETHICAL ISSUES IN CLINICAL DRUG ABUSE RESEARCH
Chairs: David S. Festinger and David A. Gorelick
The ethics of incentives in drug abuse treatment research
    David S. Festinger, Treatment Research Institute, Philadelphia, PA
Empirical data on addictive risk of participation in substance abuse research studies
    David A. Gorelick, Intramural Research Program/NIDA/NIH/DHHS, Baltimore, MD

The informed consent comprehension interview: Assessing the core elements of informed consent
    Ralph Spiga, Temple University School of Medicine, Philadelphia, PA

Symposium XVIII -- DRUG ABUSE AND SUICIDAL BEHAVIOR: CAUSATION, COMORBIDITY, OR COMMON ETIOLOGY
Chairs: James D. Wines, Jr. and Rumi K. Price
Epidemiologic and genetic research on suicide and suicidality
    Rumi K. Price and Anne L. Glowinski, Washington University, St. Louis, MO
The phenomenology of drug-related suicide attempts
    James D. Wines, Jr., McLean Hospital/Harvard Medical School, Belmont, MA
Discussant
    Wilson M. Compton, National Institute on Drug Abuse, Bethesda, MD

Oral Communications XXVIII
PAINSTAKING RESEARCH IN HUMANS
Chairs: J. David Haddox and Walter Ling
Moderate to severe physical pain and associated characteristics in persons seeking treatment for substance use disorders in four treatment modalities
    J.S. Potter, K. Prather, I.B. Janis, R.D. Weiss, McLean Hospital, Harvard Medical School, Belmont, MA
Persistent pain promotes return to substance use after detoxification
    M.J. Larson, M. Paasche-Orlow, R. Saitz, D.M. Cheng, C. Lloyd-Travaglini and J.H. Samet, New England Research Institutes, Watertown, and Boston Univ. School of Med., Boston, MA
Opioid-dependent patients are cross-tolerant to the antinociceptive effects of s(+) ketamine, ketorolac or tramadol and high-dose morphine
    P.A. Athanasos, C.S. Smith, J.L. Hay, J.M. White, A.A. Somogyi, F. Bochner, and W. Ling, Univ. of Adelaide, and Royal Adelaide Hosp., Adelaide, Australia; Univ. of CA, Los Angeles, CA
Self-reported efficacy and adherence associated with modified-release opioids
    E.H. Adams, S. Shaikh, J.D. Haddox and S.H. Schnoll, Harris Interactive, Rochester, NY; Purdue Pharma L.P., Stamford, CT
Physicians' perceptions on pain control and addiction
    J.D. Haddox, E.H. Adams, J. Guary and S.H. Schnoll, Purdue Pharma L.P., Stamford, CT, and Harris Interactive, Rochester, NY

Nora D. Volkow, M.D., Director

National Institute of Drug Abuse, Bethesda, MD

This year NIDA celebrates 30 years of progress in drug abuse research with scientific advances that have revolutionized our understanding of abuse and addiction. Important discoveries about genetics, neurotransmitters and neuropeptides, intracellular pathways, neural circuits, and behavior have provided convincing evidence that addiction is as complex a disease as cancer, diabetes, or heart disease. All are marked by a degree of heritability and biological vulnerability that can interact with external events and unhealthy behaviors, leading to disease. Together with insights about appropriate receptor function and reward circuitry, advances in molecular and imaging technologies have revealed that drug addiction alters neurobiology as well as behavior, but that research-based approaches can prevent addiction from occurring or effectively treat it once it develops.

NIDA continues to strive to be responsive to the future needs of the field, and to take advantage evolving scientific opportunities. Our comprehensive research programs comprise four priority areas: prevention research, treatment, training, and HIV/AIDS and other medical conditions. Notably, several new and expanded initiatives have begun. Recommendations of the HIV/AIDS Workgroup concerning organization, portfolio and collaboration across NIDA are being implemented. NIDA looks forward to increasing HIV/AIDS expertise in all of its Divisions and in the Clinical Trials Network, and to more effectively integrate HIV/AIDS research and prevention strategies into drug abuse and addiction studies. A new NIDA Division has been created. The Division of Clinical Neuroscience, Development and Behavioral Treatment was formed to better integrate clinical neurobiology with human development and behavioral therapies, as well as to take advantage of advances in imaging to better understand the neurobiological underpinnings of drug abuse and addiction.

Brain imaging research is providing important insights that have significantly increased our knowledge and changed our thinking about drug addiction and brain development. It is now known that gray matter continues to develop throughout at least age 20 [1,2]. Dramatic changes occur in brain structure and function throughout the transition from childhood to adulthood. The prefrontal cortex and other areas of the brain critical to memory, impulse control, and decision-making undergo extreme changes during the transitional years between childhood and adulthood [3], helping to explain the propensity of adolescents to engage in risk-taking behavior and thrill-seeking. These changes occur at a time in life when there is an increased reliance on these brain regions in behavioral control [4]. New technologies have led to the understanding that addiction is a developmental disorder that begins in adolescence, and sometimes as early as childhood.

NIDA will encourage more research on the developing brain and the effects of drugs of abuse on the brain across the lifespan. Studies are revealing that there are age-specific responses to drugs of abuse. For example, animals exposed to nicotine during the period of development corresponding to peri-adolescence [5] differed from those exposed post-adolescence in the amount of nicotine they self-administered as adults. Indeed, the transcript levels of various nicotinic acetylcholine receptor subunits in the ventral midbrain differed in animals treated during peri-adolescence from those treated in the post-adolescent period. The progression of young people from experimentation (or first use) into illicit drug use is also more precipitous than that of adults [5-7]. Adolescence may be a critical developmental period in which drugs of abuse have distinct effects that facilitate dependence later in life. Understanding how the normal brain changes, the different responses to drugs of abuse throughout varying developmental stages, and the role of social environment and other factors in decision-making and risk-taking will help us advance targeted interventions that prevent the initiation of drug abuse and its escalation to addiction.

Epidemiological data has shown that individuals, and particularly adolescents with mental disease are at much higher risk for developing substance addiction [8-11]. NIDA is encouraging research into the comorbidity of drug addiction and mental illness, as well as ways in which an individual's genes can interact with the environment to enhance, diminish, or cancel vulnerability. NIDA and NIMH have established priorities for genetic research to identify gene variations that increase vulnerability to mood and drug abuse disorders or their comorbidity, and to clarify how environmental factors can modulate gene expression and influence the development and course of either

disorder separately or their comorbidity. This will allow us to gain a basic understanding of the neurobiology of both diseases, in addition to providing insight into genetic, cultural and social risk and protective factors. Such information will ultimately guide the development of appropriate prevention and early intervention strategies.

We are encouraged at the large response to several recently published requests for applications (RFAs) for prevention research in children and adolescents, treatment interventions, and HIV/HCV. Additionally, an RFA on translational research and program announcements (PAs) on collaborative clinical trials in drug abuse and epidemiology of drug abuse have been issued. NIDA is pleased to participate with other NIH institutes in five PAs and five RFAs. These initiatives will focus on genetics, comorbidity, HIV/AIDS, and services (partnering with SAMHSA).

To bring effective new medications and behavioral treatments to practitioners, NIDA is focusing on identifying new treatment targets and piloting new treatment strategies. A wide variety compounds with differing mechanisms of action have shown promising results in the institute's research programs. Some pharmaceuticals, such as topiramate (Topamax), a GABA agonist, already have FDA approval for use in other medical conditions, and seem to have efficacy as therapies for addiction to cocaine. The FDA-approved anti-seizure medication gabapentin (Neurontin), modulates the action of glutamic acid decarboxylase (GAD, the GABA synthetic enzyme), and is under investigation for effectiveness in treating cocaine addiction. Baclofen (Lioresal; an antiepileptic $GABA_B$ receptor agonist), disulfiram (Antabuse; unknown mechanism for cocaine addiction), Modafinil (unknown mechanism) and Antalarmin (inhibitor of corticotropin releasing factor) are all in various stages of investigation as treatments for addiction to cocaine (see [12] for review).

Treatments for marijuana dependence are being actively investigated by NIDA researchers. Five major conclusions and recommendations resulted from the consultant's meeting for the RFA "Medications Development for Cannabis-Related Disorder" (RFA-DA-04-014):

- The epidemiology for cannabis used disorder is well defined, with a lifetime prevalence of 9%
- Agonist and antagonist medications may be the most promising as therapeutic strategies
- Improvements are needed in physician and counselor training and in incentivizing pharmaceutical companies to become involved in medications development for cannabis use disorder
- Medications currently approved for other uses should be studied at varying doses and schedules for treatment of cannabis use disorder
- Clinical trial designs need improvement

Marijuana is still the most used illegal drug in this country, and treatments for cannabis use disorder are urgently needed.

All drugs of abuse act in the brain by altering normal biological processes. These changes, in turn, cause alterations in behavior and thinking. The concept of increased dopamine (DA) in mesolimbic brain regions as the basis of the reinforcing effects of drugs has been central to drug abuse research for many years, and has been the most reproducible finding in drug dependence and addiction. Recent imaging studies have implicated additional brain regions in reward processes, particularly the frontal cortex (for review, see [13]). DA is involved in the regulation and motivation of behaviors that are indispensable for survival, saliency and pleasure[14]. Food, essential to survival, increases dopamine, which in turn motivates and drives us to learn that it is salient and to engage in behaviors that result in obtaining food. Drugs of abuse also increase dopamine, but at a greater magnitude and duration than natural reinforcers. The ability of drugs to directly increase dopamine in the nucleus accumbens is considered to be crucial for their reinforcing effects, and is associated with drug reward and drug seeking [15].

Research has identified differences between the brains of those at risk for addiction and individuals that are not at risk. Individual biology is extremely important—genetics can make an individual more vulnerable or alternatively more resilient to the effects of drugs. The cognitive impairment associated with chronic drug abuse is increasingly being recognized, assisted by recent brain imaging studies. Genetic studies have been useful in identifying inherited traits that are strongly linked to substance abuse and its risk factors and in suggesting neurobiological and behavioral connections. Drug intoxication disrupts brain regions involved in normal processes of motivation, reward and inhibitory control such that poor decision-making and risky behavior become the norm. Further exposure to drugs or to environmental cues linked to drugs results in a conditioned response that often precipitates relapse in former drug users. Past developmental history, such as conduct problems during childhood and adolescence, can also make

some individuals more vulnerable, and environmental factors —particularly stress—play an extremely important role in facilitating addiction[16,17]

Current research is aimed at developing medications that reverse brain changes resulting from chronic drug exposure. NIDA also plans to foster investigations on behavioral interventions that take advantage of new imaging tools to monitor plastic changes linked with treatment interventions and their subsequent effects on addiction. Other therapeutic approaches will seek to interfere with the expression of conditioned responses. It is critical that the many exciting discoveries that are being made in the laboratory are translated for use in the community. Likewise, it is important that basic research be guided by community needs.

NIDA will continue to encourage our bench and bedside researchers to communicate and collaborate. We will also continue working with agencies like the Substance Abuse and Mental Health Services Administration (SAMHSA) that have responsibility for implementing treatment and prevention programs in communities. Recruitment, training, and support of more clinicians and researchers will be essential components of our treatment priorities. NIDA remains committed to blending research and practice through its national drug abuse treatment Clinical Trials Network (CTN) and its Criminal Justice Drug Abuse Treatment Studies (CJ-DATS). We will also continue to work with agencies such as the Department of Justice, the Food and Drug Administration, the Office of National Drug Control Policy, and others to ensure that our research is responsive to public need. Such collaborations will also expedite the translation of research findings into relevant clinical and community practice.

Minority populations are disproportionately affected by the consequences of drug abuse and addiction, including HIV/AIDS. Behavioral and cultural issues likely play roles in the overrepresentation of minorities in these areas, but the involvement of biological factors related to infectivity or susceptibility cannot be ruled out. Interventions that target prevention and treatment in drug addiction will help curtail the growth of the HIV/AIDS epidemic. This will require a better understanding of how drug intoxication affects behaviors that may put a person at risk for HIV infection. These issues will be addressed, in part by coordinating strategies with the NIDA Office of Special Populations, by inclusion of HIV prevention where possible into existing cohort studies, and by expanding HIV-specific research in areas such as pharmacogenetics, imaging, natural history, and adherence into existing cohort studies and networks.

The nervous system, comprised of over 3 trillion cells, has a critical role in the functioning of all organ systems. Diseases of the nervous system, including drug addiction, account for six of the top ten causes of death, and affect one in three Americans. These diseases have a major impact on academic performance, workplace productivity, social functioning and quality of life. Many disorders of the nervous system are characterized by behavioral manifestations that are difficult to quantify, and which change as a function of the interactions between biological and environmental variables. Drugs can produce brain toxicity either by their deleterious effects on blood flow, or through a direct toxic effect on neurons.

Drugs are distributed throughout the entire body, and as a result, they contribute to morbidity and mortality in a wide variety of diseases. Nicotine, for example, is a major contributor to lung cancer, but it is also recognized that smokers have a much higher probability of developing cancers in many other areas of the body. Drug use is now the major risk factor identified in new cases of AIDS, hepatitis C, and tuberculosis in the United States, and a growing number of cases of these infectious diseases are now reported among the partners of intravenous drug users. Abused drugs also contribute to cancer, cardiopulmonary diseases, mental illness, and new data is showing that they may contribute to obesity. Imaging studies will continue to be extremely important for increasing our understanding of the mechanisms by which abused substances contribute to various diseases and outcomes.

It is important for NIDA to be able to respond to emerging issues in drug addiction. The epidemic of prescription drug abuse is particularly troubling. The problem is made evident by the 10.5% of 12th graders who have tried Vicodin and the increasing number of emergency room admissions citing the use of opiates/analgesics as reasons for admission. Immediate goals in this area are:

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- A better understanding of the epidemiology and characteristics of this type of drug abuse in order to begin to appropriately target intervention
- Development of approaches for better evaluation and detection of addiction in people being treated with opiates/analgesics for pain
- Developing appropriate treatment strategies in conjunction with improved techniques for management of chronic pain
- To understand the factors that make an individual more susceptible to prescription drug abuse in order to design effective early interventions
- Assessing the best tactics to counteract the illegal availability of prescription drugs on the internet

Our ability to improve the effectiveness of drug use prevention strategies and treatment interventions depends on understanding the underlying neurobiology of addiction as well as the biological, genetic, social, psychological, and environmental factors that predispose individuals to drug addiction. Integration of research at the various levels of analysis, from gene to protein to cell is extremely important to facilitate the translation of findings from the bench to patients, and ultimately into communities. NIDA plans partnerships with other neuroscience institutes of the NIH to take advantage of the wide infrastructure of each. The formation of multidisciplinary teams will help generate results that will benefit the public, the entire neuroscience community, and facilitate the dissemination of information to those that need it.

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INTRODUCTION OF THE 2004 NATHAN B. EDDY AWARD RECIPIENT

K. C. Rice

NIH/NIDDK, Bethesda, MD

It is a great privilege for me to introduce James H. Woods as the 2004 Nathan B. Eddy Award winner. This award is given to the very best of scientists among us who have had an extraordinary impact on the sciences associated with drug abuse, and it is widely recognized as the most prestigious award in drug abuse research. He has been a major contributor to the CPDD for many years. Jim is the only behavioral pharmacologist who has been recognized by the Institute of Scientific Information (ISI) as a "highly cited researcher." His c.v. lists more than 400 papers and his work has been cited more than 4100 times since 1980 according to a recent ISI Science Citation Index search. He is the recipient of the 2001 CPDD Mentorship Award and the Solvay Duphar Award of the American Psychological Society. Jim has lectured and consulted widely, and has served on numerous editorial boards, government committees, study sections and independent groups nationally and internationally. Currently, he holds joint appointments as Professor in the Department of Pharmacology of the University of Michigan Medical School and in the Department of Psychology of the University of Michigan.

Let me, briefly, describe Jim's background, dissimilar in so many ways from what most would consider a normal path for a budding scientist. His grew up in Kentucky and southern Ohio, as the only child of devoted parents. He was also surrounded by adoring grandparents, aunts, uncles, and cousins, with his loyal dog, King, at his side.

His academic record in school was not spectacular, but school was an opportunity to be with friends, and make arrangements for baseball or football games. Jim's high school Dean of Students annoyed him so much by telling him he was not college material that he applied to and was accepted by Ohio University.

Jim's first stroke of major good fortune occurred when he took a psychology course in his junior year at college. The teacher was a young instructor named Gilbert Johns, and Dr. Johns opened Jim's eyes to the glories and possibilities of the experimental analysis of behavior. He was converted. He resigned his prospective commission in the Air Force and rejected the opportunity for a professional football career. After graduation from Ohio University in 1959, with a B.S. degree, he looked for an opening in a psychology graduate program and was accepted into the University of Virginia (UVA) Ph.D. program and went to Charlottesville with much determination and anticipation.

UVA was perfect for Jim. The students taught each other in concentrated seminar classes. Experimental analysis of behavior was not a strong point of the program, although a fellow student, Don Thompson, was also very interested in this area, and the two young men taught each other the fundamentals of this aspect of psychology. It is worthy of note that Bill Morse had gotten a Master's degree from this program several years earlier, before he went on to Harvard to work with B. F. Skinner of Skinner Box fame. Not a bad track record for a graduate program that emphasized neither operant behavior nor drugs.

Jim's research required many late hours running rats in the lab, which was fundamentally very boring for him but after writing his thesis he received his Ph.D. in 1968. A friend from Ohio University was doing graduate study at the University of Michigan, and Jim asked him to see if there might be employment opportunities there. After a little scouting around, his friend happened on the second stroke of major good fortune for Jim. Dr. Charles R. Schuster, a new assistant professor in the Pharmacology Department, was looking for a research associate. Dr. Schuster was a psychologist who was using operant behavior to evaluate the reinforcing effects of drugs of abuse in rhesus monkeys. It sounded like a marvelous opportunity, and Jim left for Ann Arbor in 1964. As most of you all know, he has been there ever since.

Although I will leave it to Jim to tell you the rest of the story, I would like to mention the first time I ever saw Jim. This was at my first CPDD meeting in 1975, and he was presenting what appeared to me as an almost endless series of very similar graphs. Having been trained only in chemistry, I didn't then appreciate the significance of the single dose suppression data he was describing but my impression was "this guy sure knows what he is doing". Needless to say this has been reinforced countless times in the last 29 years. Jim's original interest at Michigan was opioid

drugs, and his curiosity about them has made him a world expert in their behavioral effects. This curiosity took him from expertise in mu to expertise in kappa to expertise in delta. He and his scientific colleagues have described and developed methods for the classification of opioids in rhesus monkeys that are universally recognized as extremely useful in opioid research. But it has taken him beyond opioids as well. When a new opportunity presents itself – a physician-chemist has made a catalytic antibody directed against cocaine, can he test it in rats? A graduate student has taken an interest in stress hormones; can he direct a thesis on this topic? A chemist is making selective dopamine antagonists and needs a good *in vivo* assay; can he identify one and use it? --Jim will take up a new area of behavioral pharmacology and literally bury himself in the literature until he understands it and can work intelligently in the area.

So there are lots of nice things different people could say about Jim Woods. His students would say he is an excellent mentor. His sailing companions report that he drives a mean sailboat every chance he gets. His grandchildren get a big kick out of him, and he them, and he is a good and loyal friend.

It is, now, my great pleasure to introduce my friend and colleague, Jim Woods, the 2004 Nathan B. Eddy awardee.

MONKEYS, MICHIGAN, ME, AND MU

James H. Woods

University of Michigan, Ann Arbor, MI
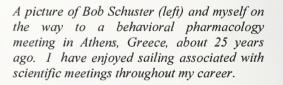
A presentation to the College on Problems of Drug Dependence on occasion of receiving the Nathan B. Eddy Award

It is a great pleasure to receive the Nathan B. Eddy Award. Some of my science heroes and heroines have been honored previously. I am humbled to be considered among them. The science story that I would like to tell you about has to do, primarily, with what my colleagues and I have learned and are learning about the behavioral pharmacology of opioids in animals, mostly rhesus monkeys, as indicated by my title. I will deviate here and there to inject some human pharmacology, some speculations, and some late breaking news. In other words, the talk is a bit of a grab bag that I hope will be both enlightening and entertaining. I first must consider some of the Michigan part of my title, a bit of both reminiscence and history.

History

I studied experimental psychology as a graduate student at the University of Virginia, and my first real job was in Charles Schuster's laboratory at Ann Arbor in the Department of Pharmacology in the Medical School. I was so excited to start work that I arrived in Michigan from Charlottesville, Virginia, the day after I finished my Ph.D. thesis experiments. I had convinced Bob Schuster that I was interested in his research and needed work, and he was happy to offer me a research assistantship. (It is nice to have this occasion to acknowledge Bob's gracious support over the course of my career.)

A picture of Bob Schuster (left) and myself on the way to a behavioral pharmacology meeting in Athens, Greece, about 25 years ago. I have enjoyed sailing associated with scientific meetings throughout my career.

He had just joined the Department and was building a new laboratory. It was a family effort; his comedian brother-in-law was making equipment for him in his spare time. Other people of eventual note were arriving with me at the same place at the same time, 40 years ago, come this fall. Steve Goldberg and Julian Villarreal were starting their graduate student careers in Pharmacology; Steve Holtzman, Maxine Stitzer, and Gail Winger started in Pharmacology or Psychology the following year. Many of them were supported by an NIMH training grant that was instrumental for me as well.

The Chair of the Department of Pharmacology was Maurice Seevers, a world renown narcotic pharmacologist and physician, and the first Eddy Awardee. He and a number of members of the Department, including Tomoji

Yanagita, were studying narcotics (Domino, 2004). Dr. Yanagita's experiments, done with Gerry Deneau and Dr. Seevers, were especially interesting because they were using narcotics and many other drugs of abuse as reinforcers in rhesus monkeys (Deneau *et al.*, 1969). Bob had been hired because of his and Travis Thompson's ground-breaking and behaviorally sophisticated research at Maryland with narcotic self-administration in rhesus monkeys (Thompson and Schuster, 1964). It was this type of research that drew me to approach Bob for a position. The very bright-young-Mexican physician, Julian Villarreal, was using some of the behavioral equipment in the Schuster lab to characterize some cholinergic drugs, and Julian and I became very good friends. John Falk was just a flight of stairs away doing behavioral research on adjunctive behavior in the Department of Pathology, an interesting set of juxtapositions. I had a rich pharmacological and behavioral environment within which to learn; it was fun. I didn't have to travel to Mecca, I lived there.

Graduate students, in addition to those mentioned above, came in good number and high quality, the lab grew, and things just kept getting better and better. A grant administrator from NIMH visited, asked if I was doing any teaching of the psychology graduate students in the laboratory, and I said that I was doing a bit. A couple days thereafter I got a call from the Chair of Psychology, and he said that he would like to offer an adjunct appointment in their Department. I have always believed that I had a good governmental agent, and over the years, this appointment has been a very nice opportunity for me to help train some excellent students of behavior.

Shortly thereafter, Bob went to the University of Chicago at the call of Jerry Jaffe and Danny Friedman, and my direct boss then became the Chair of Pharmacology, Dr. Seevers. He soon suggested that I take over a research grant of his, a grant with the modest title of *The Psychopharmacology of Drug Dependence*. I assured him that I was too young and inexperienced, and he said, do it anyway, so I did. When I had successfully renewed his grant, Dr. Seevers said that I should be an Assistant Professor. It was that simple in those days. That starter grant continued for over 20 years. You see, I told you I was in Mecca.

Julian Villarreal, me, and Maurice Seevers
pretending to read some cumulative records.

There is much fun to be had with the various nuances of receptor theory's application to the understanding of opioid behavioral actions. As I was being taught some opioid theory by my colleagues, new opioids that were the inventions of medicinal chemists from all over the world were being studied by Julian Villarreal in an adjacent lab as part of the abuse liability program initiated and controlled by Nathan B. Eddy. Dr. Seevers had recognized Julian's perceptiveness and scientific skill. He made him an Assistant Professor and gave him a very large colony of physically dependent rhesus monkeys. Julian and I agreed on the overlap of Ann Arbor and Mecca.

Julian took up the challenge of understanding opioid actions in normal and morphine dependent rhesus monkeys. He worked out methods of studying opioids that allowed the classification of opioid agonists and antagonists, and, importantly, opioids with limited efficacy (Villarreal, 1973). Julian developed some ideas about the concept of opioid dependence that are as novel today as they were when he first invented them (Villarreal et al., 1985; Cruz et al., 1996). In addition, he and his students described the pharmacology of some unusual opioids that William Martin came to call kappa opioids (Martin et al., 1976). In fact, Julian's information was very important for both Martin's, and subsequently, Kosterlitz's group (Hutchinson et al., 1975) to accept the existence of kappa opioid receptors. A very important fact was that, although the actions of kappa agonists could be reversed by opioid antagonists, these agonists failed to suppress selective signs of morphine withdrawal in rhesus monkeys, and themselves induced a state of dependence distinct from those produced by morphine (Gmerek and Woods, 1986). These findings remain important conceptually and historically. The discovery and characterization of novel opioid effects of compounds were exciting science to me then, and, they continue to be.

In a couple of years after receiving his doctorate and tenure a year later, Julian left Ann Arbor for Mexico and patriarchy, and after a short period, I took over his laboratory, another grant, and the responsibility of evaluating narcotic abuse liability for the, then, Committee on Problems of Drug Dependence. In this capacity I started a friendship with Arthur Jacobson and Kenner Rice that continues today. Arthur served as Biological Coordinator of narcotic abuse liability assessment through the Committee. Kenner, Arthur's boss at the Medicinal Chemistry laboratory of the NIDDK, is appreciated for his mastery of the medicinal chemistry of opioids. I thank them both for their long-term support.

Mu opioid receptor pharmacology with comparison to kappa

With the acuity of hindsight, one can see the evidence accumulating over more than 50 years that opioids work through receptors. Much of that evidence is provided by really good behavioral pharmacology: e.g., the behavioral effects of opioids occur with very small doses -- the smallest of any effect produced by the drugs -- and these behavioral effects can be antagonized by selective surmountable opioid antagonists in an orderly manner. Although this is indirect evidence by today's standards, this information was sufficient to establish receptor mediation then and remains sufficient today.

The discovery of opioid receptor binding sites and endogenous substances that share pharmacological properties with morphine came later. I remember vividly being told about how receptors were "finally" discovered when binding sites were described for the first time. To me and some of my colleagues, this was an interesting finding, but somewhat of a slight to the role that behavioral pharmacology had played in earlier establishing the existence of the opioid receptor. Another "initial discovery" of an opioid receptor was made when the first opioid receptor was cloned, although this advance was rather awkwardly delayed due to the lack of opioid molecular biologists. Nevertheless, as I have come to recognize throughout my career, every central nervous system research area is enriched by the development of new techniques and by the intellectual rigor and thought necessary to establish the relation of new to old findings. New techniques occasionally force conceptual issues. These "rediscoveries" of basic pharmacological principles probably reflect the reverent regard given the receptor concept in pharmacology; all who contribute in one way or another, want to claim their contribution's importance. Well, at least only a true skeptic would raise a general question of the reality of and the usefulness of receptors and the theory associated with them in these days. All interested parties will, I hope, continue to argue about what constitutes sufficient evidence at all levels of description for application of the concepts and associated theory. (See Kenakin, 2004, for an historical account of receptor theory over a similar period of description to that which I will sketch for behavioral pharmacology of opioid receptors.)

By the late 1970s opioid research was flourishing in Ann Arbor (Stan Watson, Huda Akil, and Bob MacDonald had been added to the faculty) and many other places as well. Three opioid receptors were commanding attention, viz., mu, kappa, and delta opioid receptors, and we took on the task of describing the behavioral pharmacology of these receptors in the monkey in considerable detail. I believed this to be an important contribution because the behavioral effects of centrally acting drugs were not clearly or convincingly related to receptors at that time, so we faced a good basic science problem for behavioral pharmacology. Moreover, in my opinion, the classification of opioid behavioral effect by receptor type would also help enormously with the task of predicting abuse liability of new agents that were continuing to arrive at a high rate. There was also a scientific gain by illustrating how quantitative aspects of receptor theory could be used to make inferences about behavioral pharmacological effect. I also thought that the analysis of opioid actions through multiple receptors could be pacesetting for the analysis of other classes of pharmacological receptors, a prejudice that continues with me.

Though this is a bit of a personal description, I wouldn't want the reader to come to think that this was a singular effort; many laboratories and individuals participated with me directly through the years (Table 1), and it is a pleasure to be able to acknowledge each of them in this small way. Especially, Steve Holtzman, Steve Goldberg, Bob Schuster, and Bill Morse contributed in a variety of ways to my intellectual disposition during that time, and some of these influences have become so imbedded that I have long since assumed ownership.

TABLE 1. Contributors to opioid characterization in various species

M. Aceto	I. Derrick	S. Hursh	H. Mosberg	R. Solomon
A. Alt	D. Downs	S. Husbands	J. Moerschbaecher	C.B. Smith
H. Akil	L. Dykstra	A. Jacobson	N. Naughton	K. Stephens
J. Aspen	P. Emmerson	D. Jewett	S. Negus	M. Takasuna
J. Bagley	J. Folk	C. Johanson	C. Neilan	P. Tepper
A. Bertalmio	C. France	E. Jutkiewicz	M. Nemeth	J. Terner
R. Briscoe	M. Gatch	J. Katz	N. Nieland	M. Torregrossa
D. Broom	L. Gerak	M. Kilbourn	E. Pakarinen	J. Traynor
T. Burke	D. Gmerek	S. Kishioka	K. Palmer	R. Valentino
E. Butelman	S. Goldberg	M.C. Ko	C. Paronis	J. Vivian
S. Calderon	M. Greenwald	W. Koek	P. Portoghese	E. Walker
K. Chang	L. Harris	K. Lee	M. Reilly	S. Watson
M.J. Clark	D. Hein	J. Lewis	A. Remmers	K. Williams
E. Coale	S. Herling	A. Mansour	K.Rice	G. Winger
S. Comer	E. Hoenicke	E. May	R. Rothman	A. Young
A. Coop	E. Hong	I. McFadyen	B. Schuster	J. Yu
B. De Costa	H. Houshyar	R.M. McNutt	M. Seggel	G. Zernig
		F. Medzihradsky	P. Skjoldager	J.K. Zubieta

Let me provide you with some of highlights of the work on the behavioral classification of opioid agonists (Table 2), which will show you the framework that we have used for understanding and classifying new opioid effects. I must say that I consider this work to be one of our most important contributions to opioid pharmacology; the classification continues to be improved and refined to this day and will, I hope, for as long as opioids remain important for therapeutics and the understanding of pharmacology. If history be our guide, it may be quite awhile into the future.

TABLE 2. Classification of agonist effects at the mu, kappa, and delta opioid receptor in the rhesus monkey.

Effects in rhesus monkeys	Classes of Opioid Receptor		
	Mu	Kappa	Delta
Analgesia	+	+	+/-
Antihyperalgesia	+	+	+
Respiratory Depression	+	-	-

Discriminative Effects	+	+	+
Reinforcing Effects	+	-	-
Dependence	+	+	-

(+ indicates the presence of the effect; - indicates an absence of the effect.)

Table 2 provides an overview of the research findings. Morphine given intramuscularly to a monkey produces a reliable thermal analgesic effect at a 0.3-1.0 mg/kg. If one adds a source of inflammation to the painful stimulus, the potency of morphine is increased to a range of doses that is not very different from doses used as analgesics in humans (Negus *et al.*, 1993). Morphine reduces respiration at active analgesic doses; its margin of safety in monkeys appears to be much the same as it is in humans (e.g., Paronis and Woods, 1997). Variation in potency and effect across humans and rhesus monkeys is quite small for all opioids where comparisons are possible. (This is, of course, one of the reasons Dr. Seevers made the choice of incorporating rhesus monkeys into his scheme for abuse liability assessment of opioids. It was a remarkably fortunate choice; he could not have anticipated how effectively the monkey would respond to kappa opioids, for example. One only hopes that his perspicuity persists for other opioid receptor systems.) Indeed, the dose-related respiratory depressant syndrome associated with acute toxicity in humans and monkeys may be handled in much the same way with narcotic antagonists; again, the doses of antagonist necessary are much the same in humans and monkeys (Kishioka *et al.*, 2000; Martin *et al.*, 1968). Kappa agonists induce analgesic and antihyperalgesic effects centrally or peripherally in the monkey (Ko *et al.*, 1998; 1999).

Discriminative stimulus effects

Monkeys can be trained to discriminate and reliably report the enteroceptive effects of morphine and morphine-like compounds. This turns out to be a very informative, receptor-mediated effect. Monkeys and other research animals report that a variety of mu opioid receptor agonists share morphine's enteroceptive effects, but are different enteroceptively from kappa or delta opioid agonists (Hein *et al.*, 1981; Herling and Woods, 1981; Brandt *et al.*, 1999). Under certain conditions, this assay is also helpful in characterizing mu opioid agonists that differ in efficacy. Although the discriminative stimulus effect of centrally acting drugs is quite sensitive, being responsive to fairly low levels of activation of the receptor, training animals to discriminate between large and small doses of a full agonist makes this an appropriate measure for partial agonist activity. A partial agonist may produce responding appropriate for the small but not the large dose of a full agonist (e.g., Koek and Woods, 1989).

Agonists at other receptors produce selective discriminative effects. Hence, monkeys trained to discriminate the enteroceptive effects of either kappa or delta agonists report that morphine is different from either. Animals can also be trained to discriminate withdrawal states from mu or kappa agonists. The agonist is administered daily, and differential responding is trained to administration of saline or a surmountable antagonist (France and Woods, 1989; France, 1995). Under these circumstances, drugs with reduced efficacy and selectivity for these receptors will be reported reliably by the monkey or bird to be enteroceptively similar to abstinence from the agonist. Whether neutral antagonists and inverse agonist have the same effects, and whether acute and chronic dependence produce similar enteroceptive effects are areas of considerable contemporary research interest for the understanding of opioid dependence associated with the different types of receptors.

Reinforcing stimulus effects

In many procedures, morphine is not a particularly strong reinforcer when compared with ultra-short, fast-acting, mu opioid agonists (e.g., alfentanil, remifentanil). Many hundreds of injections of remifentanil will be administered per hour by rodents (Z. Cooper and K. Williams, Unpub. observations) and monkeys (C. Galuska, Unpub. observations), whereas morphine maintains, under optimal conditions, only a few injections. This difficulty with maintaining a lot of reinforced-responding with morphine caused Bob Schuster and me some concern and considerable problems in early studies, though we eventually overcame some of them to show at least that dependence development was not necessary to sustain the reinforcing effect of morphine (Woods and Schuster, 1968). Things got better, and others of us showed that the potency of mu opioid agonists as reinforcers was nevertheless related to their potency to suppress abstinence in dependent monkeys (Young *et al.*, 1981), and, as our prowess in manipulating the reinforcing effect
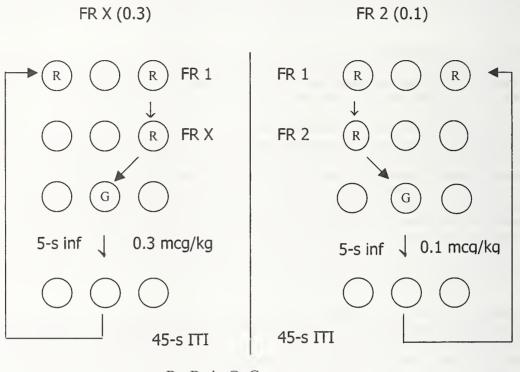
grew, we showed that the potency of surmountable antagonists to prevent the reinforcing effect of mu agonists was the same as their *in vivo* potency to antagonize other mu effects (Bertalmio and Woods, 1989). As I will describe below, we can now ask sophisticated behavioral questions about the reinforcing effects of opioids in monkeys that neither Bob nor I would have anticipated when the two of us started working with opioids as reinforcers in the monkey.

Behavioral pharmacologists need to work both sides of their interdisciplinary street; it is one aspect of the field that is especially interesting. A good example of behavioral explication of opioid action comes from the analysis of opioid reinforcers within the conceptual context of behavioral economics. This context allows us to analyze the importance of fundamental pharmacological variables as they affect reinforcing effectiveness.

My colleagues Gail Winger and Steve Hursh have started to use this procedure by measuring the consumption of opioids when they are delivered as intravenous reinforcers. The price of the opioid commodity was varied by changing the number of responses necessary to obtain each injection of the opioid (fixed ratio value) or the dose administered with each injection. As they and others have shown, drug consumption goes down as its price (response requirement/dose per injection) is increased. Assuming that the relative reinforcing effect of a drug can be defined by the price at which the animal no longer increases the number of responses necessary to defend drug consumption, we have found that the duration of action of opioids appear not to be important as a determinant of reinforcing effectiveness (Ko *et al.*, 2002b), but onset of action and efficacy are important. Other things equal, fast acting drugs are better reinforcers than slower acting drugs (Winger *et al.*, 2002), and demand is greater for fentanyl compared with nalbuphine (Hursh and Winger, 1995; Ko *et al.*, 2002b). In short, we have concluded that opioid demand is a function of mu agonist efficacy and speed of onset.

But, are drugs just like any other commodity, food for example, to the monkey or are they unusual commodities? Perhaps opioids and other drugs of abuse are unusual reinforcers. Chad Galuska has found something of relevance in studies of choice of the ultra-short acting mu agonist remifentanil when it is available at different prices. He found that large doses of remifentanil are chosen over smaller doses even if the larger doses are delivered at considerably higher prices. Let me take the time to show you an example of this effect. The experiment consisted of 60 trials each experimental session. Each trial consisted of a choice between one of two levers, followed by the illumination of the light over the selected lever (Figure 1). Rhesus monkeys could obtain the drug by selecting either lever, but the price (number of responses/dose) could be the same or different on each lever. The response requirement was met on the selected lever, followed by the injection, a short timeout, and the initiation of the next trial. The simple prediction made by behavioral economic theory is that monkeys will chose the cheaper of the alternatives, as defined by responses/dose. Indeed, this happens with nondrug reinforcers for a variety of species, reinforcers, and circumstances (Bickel and Vuchinich, 2000).

Discrete-Trial Procedure: Increasing Cost of Large-Dose Alternative

FR X (0.3)   FR 2 (0.1)

R= Red   G=Green
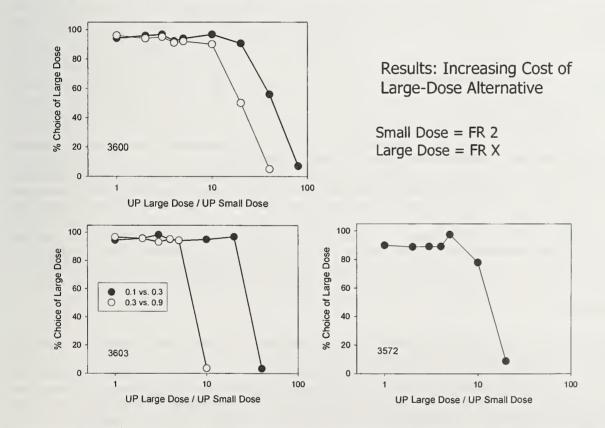
Figure 1. Each of 60 trials proceeds as indicated by the schematic: two keys on each side of the panel are lit, a choice of the right or left key arranges a response requirement and a dose of remifentanil to be delivered immediately following the completion of the response requirement (2 responses on the left key and 0.1 mcg/kg, and on the right key, a number of responses = X followed by a 0.3 mcg/kg injection). Note that when right key responses equal 6, the price of the two alternatives is the same.

When drugs are available in this choice situation, however, Chad has found something different. If remifentanil is available at a small dose (0.1 ug/kg/inj) on one lever and at a 3 times larger dose on the other, their prices are equal when the fixed ratio for the small dose is three times smaller than the fixed ratio for the large dose. At this equal price situation, the monkeys are not indifferent between the two options, but consistently chose the larger dose with the larger ratio value. Surprisingly, even when the price of the larger dose is increased so that it is much higher (30-90 times higher) than the price for the smaller dose, the monkeys continue to choose the larger dose. Another interesting aspect of reinforcing dose and preference is that at higher absolute doses (0.3 vs 0.9 ug/kg/inj), the effect of price on preferences for the larger dose is attenuated (Figure 2).

Results: Increasing Cost of Large-Dose Alternative

Small Dose = FR 2
Large Dose = FR X

Figure 2. The effect of increasing cost of the large dose alternative when the alternative responses deliver either 0.1 ug/kg or 0.3 ug/kg and, subsequently, 0.9 ug/kg or 0.3 ug/kg. Three monkeys (3600, 3603, and 3572) are shown. Note that when the abscissa values are 1, behavioral economic notions of unit price predicts indifference.

These latter findings were unanticipated and they raise many experimental questions. We believe that we have stumbled on an important wedge to start to explore differences in the reinforcing effects of drug and nondrug commodities. Others have data to suggest similar effects with large cocaine doses, which are preferred even when they are delivered after longer delays (Anderson and Woolverton, 2003), and smokers prefer cigarette puffs to other commodities even when they are more expensive economically (Madden *et al.*, 2000). Future studies are planned to determine whether this is the case when non-drug reinforcers are evaluated in a a variety of similar protocols in our laboratory.

In vivo pA2 measures

One of the intellectual delights of working with opioids is the very rich medicinal chemistry that has contributed so strongly to our understanding of their mechanisms. I have been particularly interested in surmountable antagonists that differentiate receptors and their effects so clearly *in vivo*. The best measure of this antagonist effect is the pA2 measure; introduced to pharmacology and championed by Hans Schild. It is expressed in logarithmic units, and the higher the number, the more potent the compound is to antagonize agonist effects. Many have used it to study opioid effects *in vivo* and *in vitro*; we have used the measure to differentiate receptor mediated effects in rhesus monkeys

Table 3: Apparent pA2 values for quadazocine as an antagonist of different effects induced by opioid agonists (modified from Woods *et al.*, 1992).

AGONIST	ANALGESIA	DRUG DISCRIMINATION
Alfentanil	7.6	7.9
Morphine	8.2	7.8
Levorphanol	not available	7.6
Bremazocine	6.1	6.3
U50488	6.4	6.1
Ethylketocyclazocine	6.4	6.4

A set of pA2s for six different opioid agonists are shown in Table 3; three agonists work through the mu receptor to produce both analgesia and discriminative effects in monkeys, whereas the other three agonists work through the kappa receptor to produce analgesic and discriminative effects. These findings are consistent with other behavioral evidence and in vitro evidence for this classification (Woods *et al.*, 1992). The pA2 findings also show that the type of receptor (kappa or mu) is not differentiated by effect; the same pA2s are found with the analgesic effect as with the discriminative effect. Thus, pA2 analysis indicates that the analgesic and discriminative stimulus effects of the mu agonists are likely mediated through a common mu opioid receptor, and the analgesic and discriminative stimulus effects of the kappa opioid agonists appear to be mediated through a different, but common kappa opioid receptor. Other opioid actions can also be classified with a surmountable antagonist using the same logic (e.g., Woods *et al.*, 1992).

Dependence

When I started my work in the evaluation of abuse liability of opioids, the only measure used for abuse liability assessment was that of pharmacological equivalence of a substance to morphine and its ability to produce dependence in monkeys. There were a variety of protocols used to evaluate this equivalence, and the methods were entirely observational and remarkably reliable. All compounds were assessed in blinded procedures in monkeys that were maintained with s.c. morphine given several times per day. Known compounds were routinely assessed for comparison with themselves as historical controls. If compounds had novel characteristics in standard procedures, they were assessed following their own chronic administration to confirm the novel findings. The data indicated that morphine-like dependence was sustained by any substance that had strong agonist effects and that penetrated the central nervous system.

Eventually, we replaced this procedure with a drug discrimination procedure in which morphine- dependent monkeys (3.2 mg/kg morphine each day) were trained to report administration of naltrexone. Thus, the monkeys responded on one response key if they had been given an opioid antagonist and made a different response when the antagonist was not administered. The consequence of responding correctly in either condition was the termination of a stimulus associated with electric shock delivery. Under these training conditions, monkeys reliably reported the administration of different antagonists. If compounds had some efficacy, they failed to induce a "withdrawal" reaction. Only compounds with strong mu opioid receptor agonist activity reversed a "withdrawal" reaction (France and Woods, 1989). Subsequently, it was shown that the potency of antagonists in the earlier procedure in which morphine withdrawal was simply observed was strongly correlated with their potency in producing the

discriminative stimulus of "withdrawal" (France *et al.*, 1990). Furthermore, a pA2 value of quadazocine of 7.5 was found in the antagonist discrimination model of opioid dependence. This value was entirely compatible with earlier findings based on observational studies in the dependent monkey, and with values of pA2 given in Table 3. Thus, the *in vivo* affinity of narcotic antagonists for mu receptors was not changed by morphine dependence.

Delta Opioid Receptors

When we started to characterize compounds that worked through the delta opioid receptor about 15 years ago, we compared the newly developed non-peptidic delta agonists with agonists that are selective for other opioid receptors. These drugs were synthesized at Burroughs-Welcome by Ken Chang and Robert McNutt, and a great deal of our understanding of the behavioral pharmacology of delta opioid receptors has resulted from studies using these drugs. In the monkey, these compounds were effective against inflammatory pain (Butelman *et al.*, 1995) but not against thermal pain (Negus *et al.*, 1994; Brandt *et al.*, 2001a). They suppressed food-reinforced responding, failed to suppress respiration, they had no reinforcing effects (Negus *et al.*, 1994), and they produced distinct discriminative stimulus effects, with no overlap with either mu- or kappa- discriminative stimulus effects (e.g., Comer *et al.*, 1993b; Brandt *et al.*, 1999). In preliminary studies, the compounds are without dependence capacity (Brandt *et al.*, 2001b). In short, these compounds activated the delta receptor and induced a pattern of effects distinctly different from those of other opioid classes.

Sandy Comer found in mice that delta agonists produced a brief, apparently benign convulsion that could be prevented by pretreatment with a selective delta antagonist (Comer *et al.*, 1993a). Delta-induced convulsions occurred in all animals that were thoroughly studied, i.e. mice, rats, and squirrel and rhesus monkeys. We speculated in an early paper that the convulsant activity might portend antidepressant potential (Comer *et al.*, 1993a), and we much later began to study the compounds in a behavioral assay predictive of antidepressant activity, viz., the forced swim assay. The compounds were quite active, being similar to all other major pharmacological categories of antidepressant, e.g., SSRIs, monoamine inhibitors, tricyclics, and electroconvulsive shock in that respect (Jutkiewicz, 2004). They were dissimilar to classic antidepressant drugs in that the delta agonists were active with single doses rather the (sometimes) prolonged, chronic administration required of other drugs. We can summarize the major findings about their actions as follows:

1. If SNC-80 like compounds have significant agonist activity, they will have antidepressant activity in the forced swim assay. Other ways of activating the receptor, e.g., inhibiting enkephalin degradation, will also produce a delta-receptor-mediated effect (Jutkiewicz and Torregrossa, unpublished observations).
2. Although convulsions (and seizures) follow administration of large doses of SNC-80 -like compounds, neither seizures nor convulsions are necessary for antidepressant behavioral effect (e.g., Broom *et al.*, 2002; Jutkiewicz, 2004; Jutkiewicz *et al.*, 2004).
3. Tolerance develops differentially to the behavioral effects of SNC-80-like compounds. It develops more rapidly and to a greater extent to the convulsant and locomotor stimulating effects than to the effects in the forced swim assay (Jutkiewicz *et al.*, in press).
4. These compounds activate the receptor in different areas of the brain where the receptor is prominent, e.g., frontal cortex, caudate putamen, and hippocampus (Jutkiewicz *et al.*, in press).
5. Where the agonist activates the delta receptor, it also activates brain-derived growth factor (Torregrossa *et al.*, 2004) - a trophic factor strongly associated with most antidepressant drugs, regardless of the manner by which they initiate actions in brain, e.g., reuptake of NE or serotonin, or through electrically induced seizures.

We currently hold the position that delta agonists might provide a novel pharmacological mechanism to induce antidepressant action, and it may be associated with rapid effect and may affect a different patient population than the currently available modes of therapy.

ORL-1 Receptor

I have a remaining project to describe to you that captures both Michigan and monkeys at their most hopeful. It comes from the scientific tactic of comparing compounds bearing close resemblance to opioids, a project that would have made Dr. Eddy proud, and some important work from our lab on it has been conducted by Holden Ko. A couple of years ago we described the effects of ORL (opioid receptor like)-1 agonists in a procedure meant to detect

peripheral analgesic effects (Ko *et al.*, 2002a). Since many of you won't know much about this receptor, let me tell you a bit about it. Ten years ago, several laboratories described a receptor that was a close analogue to the three opioid receptors that I have been describing and it shared considerable structural homology with them. Consensus was reached that it was indeed a single entity, a novel opioid-like receptor, and shortly thereafter, two groups reported an endogenous peptide ligand. The characterization of the peptide, OFQN, has been curious; it was found initially that it produced pain in rodents; some indeed proposed that the endogenous peptide be referred to as nociceptin. Consequently, some drug discovery efforts to this day have held to the possibility that antagonists at this receptor site might be novel analgesics. The rodent behavioral pharmacology on analgesic effects of ORL1 receptors can be characterized as confusing; many other drug discovery programs have abandoned an analgesic objective for agonists at this site (Mogil and Pasternak, 2001). We believe this is a mistake; OFQN is a strong thermal analgesic in the monkey when delivered intrathecally. It is comparable to morphine. It has a substantial duration of action of 2-3 hours; Bob Kennedy and colleagues at Michigan have measured its duration in cerebrospinal fluid for us and its time course of analgesic action is consistent with its presence in cerebrospinal fluid. There is only one metabolic product, and it is not active at the ORL1 receptor. At analgesic doses of OFQN, we have not observed any of the classical opioid signs of intoxication, such as sedation or respiratory depression; we have yet however to evaluate very large doses. We have used the surmountable, selective nonpeptidic antagonist, J 113397, to reverse the intrathecal analgesic effect of OFQN; classical opioid antagonists are without effect.

A nonpeptidic ORL1 agonist, Ro 64-6198, has been reported to be inactive in rodent analgesic assays (Dautzenberg *et al.*, 2001), yet in our hands its analgesic effects are similar to OFQN, and we obtained analgesic effects following systemic administration. Again, the ORL1 receptor antagonist prevented the analgesic effect at the same doses that reversed the effects of OFQN; classical opioid antagonists were ineffective. We are further encouraged because Ro 64-6198 fails to maintain self-injection responding when it is substituted for either cocaine or methohexital in rhesus monkeys, experiments conducted in the lab by Bill Fantegrossi and Chad Galuska. We believe that agonists at this receptor may confer significant pain relief in human subjects; we hope to evaluate this as soon as we can do the acute toxicology in monkeys to insure reasonable safety margins. We have a lot of research to do on this set of compounds, but we are very hopeful that they may provide a new pharmacological class of strong analgesics with an, as yet, undetermined set of side effects. Nevertheless, we know enough to predict that they will not be similar to those that we have dealt with the opioids.

Experimental Therapeutics

Now to a slightly different set of themes, more related to experimental therapeutics, a topic close to the interests of the namesake of the Award. I want to discuss two somewhat separate topics; all related to "side effects" of the use of morphine-like drugs. These problems or effects were of considerable scientific interest to both Drs. Eddy and May.

Nathan B. Eddy (left) talking with Everette May at the NIDDK Laboratory of Medicinal Chemistry. Dr. May was also an Eddy Awardee and responsible for hiring Kenner Rice. Drs. Eddy and May were also the first and second Biological Coordinators of narcotic evaluation for the CPDD. Arthur Jacobson was the third, and Andy Coop serves as the contemporary Biological Coordinator.

Constipation is the major side effect of opioids in the treatment of chronic pain. Mu opioid receptors exercise both central and peripheral control of gastric motility in these respective locations, and a mu antagonist that acted selectively in the periphery might be able to attenuate mu agonist-induced constipation. A mu-antagonist whose distribution is restricted by the blood-brain-barrier to the peripheral nervous system was synthesized by Dennis Zimmerman and colleagues (Zimmerman *et al.*, 1994), and has been developed by the Adolor Corporation (Schmidt, 2001). It is being fast tracked for FDA approval by the end of the year. Its generic name is alvimopan (ADL 8-2698) and it may represent an important break through in the well being of patients who are receiving morphine-like narcotics chronically.

A potential breakthrough in treatment of opioid abuse is the recent development of very long-acting forms of narcotic pharmacotherapies. This has been a very long-standing interest of our research and treatment communities. The clinical objective has never been met although it may now be imminent. Sandy Comer and her colleagues (2002) have demonstrated in humans a formulation of naltrexone that is effective in blocking mu opioid effects for nearly a month. This is an encapsulated microsphere preparation by Biotek Inc. It can be injected intramuscularly and has little irritation. Two doses were examined for their capacity to antagonize i.v. heroin in cumulative doses over the course of six weeks. Using visual analogue measures of "good drug effect", the small dose of encapsulated naltrexone produced complete antagonism of 25 mg of heroin for three weeks, followed by a return of the effects of heroin over the next couple of weeks. The larger dose of depot naltrexone was quite effective for 5 weeks. Interestingly, the miotic effects of heroin were less effectively antagonized in these same subjects. Sustained release formulations similar to those used by Comer and colleagues have been made with buprenorphine. The Johns Hopkins group have recently reported some quite pleasing initial findings, suggesting that a single injection of 58 mg may suppress abstinence and protect against a small opioid challenge for 6 weeks (Sobel *et al.*, 2004).

Is six weeks the limit of a long-acting opioid antagonist? Perhaps not. A group from Perth Australia has been using naltrexone in larger doses in an implant containing 10 tablets of encapsulated naltrexone made up in a polymer. The 1.7 gm of naltrexone is released at less than a 0.5% per day; more than one pellet can be used and therapeutic blood levels may be maintained for over a year (Hulse *et al.* 2004). This eliminates the compliance issue that has plagued naltrexone and provides continuous presumed protection for very long periods, surely allowing nonpharmacological rehabilitation to be carried out without significant concern for opioid relapse. Is a year of opioid abstinence enough to accomplish significant rehabilitation? Their clinical data are encouraging that this may result in effective treatment of opioid abuse, and these formulations need desperately to be evaluated in different patient populations and different environments.

These new formulation studies remind me that we should reconsider some ideas put forward by Avram Goldstein nearly 30 years ago at this meeting when he referred to a "steps" program of treatment of opioid abuse (1976). The goal was eventual narcotic abstinence through a series of pharmacological "assists" that initially were inducements to therapy in the form of i.v. morphine, followed by s.c. morphine, then to oral methadone, to the longer-acting oral L-alpha, acetyl methadol (LAAM), then naltrexone three times a week, and eventually, for the very successful patient, supervised abstinence. We may soon have a variety of pharmacotherapies that could be used in a mix and match type of "steps" program for patients interested in narcotic pharmacotherapy. It sounds very appealing to me, and I hope NIDA's clinical trials network is up to the task of finding appropriate means to implement some of these approaches. It could be that we are embarking on a new era in the pharmacotherapy of opioid abuse.

Finally

I would like to take this opportunity to express my appreciation to the Awards Committee of the College and to all the members of the College who have expressed their support for me. I would also like to acknowledge the many students, graduate and postgraduate, and colleagues who have contributed to the enlivening of my opioid world. And of course, I would like to thank the College for supporting financially and professionally the efforts of the Drug Evaluation Committee and the National Institute on Drug Abuse for funding the vast majority of the research described here.

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INTRODUCTION OF THE MARIAN W. FISCHMAN MEMORIAL AWARD

R. W. Foltin

New York State Psychiatric Institute and Columbia University, New York, NY

It gives me great pleasure to introduce Dr. Nancy K. Mello as the recipient of this year's Marian W. Fischman award.

Exactly 10 years ago, Dr. Mello introduced me as the recipient of the Joe Cochin award, and her kind words embarrassed me mightily. Today, I hope to return the favor.

Dr. Mello received her Ph.D. from Pennsylvania State University in 1960. She completed her postdoctoral training at Harvard, where she spent time in B.F. Skinner's laboratory. She left Harvard to work at NIMH from 1967 to 1974. She heeded the call of the ivy and returned to Harvard as Associate Director and then Co-Director of the Alcohol and Drug Abuse Research Center with Dr. Jack Mendelson.

Now for the embarrassing part, Dr. Mello (as of February) had 234 refereed publications, of which she was first author on 85. She has written one book and edited another 9 books. While these numbers are impressive, it is important to note that all this stuff was of high quality. Dr. Mello has published 12 papers in the likes of JAMA and Science, and, what I think must surely be a record, 59 papers in JPET!

A google search using "Nancy K. Mello" yielded 592 items. This blurb from the 2002 McLean Hospital report, announcing that Dr. Mello had received the largest grant ever awarded to McLean Hospital (excuse the quality of the screen-shot picture) caught my eye.

2002 - McLean Hospital Annual Report

Record research grants

Nancy Mello, PhD, co-director of McLean's Alcohol and Drug Abuse Research Center and director of the Behavioral Science Laboratory, was awarded a $6.4-million grant from the National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA). The goal of her five-year investigation is to examine novel pharmacological and biological approaches to the treatment of cocaine and polydrug abuse.

Another, perhaps, more real, indicator of Dr. Mello's success is that you can find some of the books she has edited up for sale on Ebay!

Marian looked up to Nancy as a friend and a role model. Marian told me once that she thought Nancy was the only other female member of Division 28 of the APA when Marian joined. Marian also enjoyed all the fine meals she had at meetings with Jack and Nancy.

Finally, the scientific careers of Nancy and Marian have a lot in common, but to me the most important commonalities are how they both care about their junior scientists, their willingness to spend time with others, and the fact that both can make you laugh.

Nancy can, like Marion could, make people Happy

MARIAN W. FISCHMAN MEMORIAL LECTURE (2004)

EVALUATION OF DRUG ABUSE TREATMENT MEDICATIONS: CONCORDANCE BETWEEN CLINICAL AND PRECLINICAL STUDIES

N.K. Mello

**Alcohol and Drug Abuse Research Center, McLean Hospital and Harvard Medical School
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PREFACE

I am honored to present the third annual Memorial Lecture to commemorate the achievements of the late Marian W. Fischman. Marian was a dedicated and creative scientist and an effective science advocate. She was also an outstanding mentor and very supportive of her trainees and junior collaborators. And Marian was a wonderful colleague and a delightful person to be with. All of us who knew her continue to mourn her loss.

Marian was a pioneer in clinical research on the behavioral and physiological effects of cocaine. Between 1976 and her untimely death in 2001, Marian published an outstanding series of groundbreaking clinical studies of the effects of cocaine. Marian's research was reviewed by Chris Ellyn Johanson in the First Memorial Lecture (Johanson 2003). Briefly, in a series of important papers by Marian and her colleagues, it was shown that cocaine's abuse-related effects can be systematically studied in humans in the clinical laboratory, that these effects of cocaine are dose-dependent, and the subjective effects of cocaine are highly correlated with the drug's plasma concentration and physiological effects. Moreover, cocaine self-administration by humans is amenable to environmental manipulations including schedule of reinforcement, availability of alternative reinforcers and treatment with candidate medications. A few examples of some important papers follow: (Evans *et al.* 1999; Fischman 1984, 1987,1988; Fischman and Foltin 1992; Fischman and Schuster 1980,1981,1982; Fischman *et al.* 1976, 1990; Foltin and Fischman 1991, 1991a, 1992a and b, 1994a and b, 1996, 1997, 1998; Foltin *et al.* 1995; Javaid *et al.* 1978; Johanson and Fischman 1989; Ward *et al.* 1997a and b).

Marian was an active member of the Board of Directors of the College on Problems of Drug Dependence (CPDD) and our terms on the Board overlapped. With the sponsorship of the CPDD, Marian and I worked together to edit two monographs. The first was based on a CPDD-sponsored meeting in 1988, and resulted in a monograph entitled Testing for Abuse Liability of Drugs in Humans (Fischman and Mello 1989). The second monograph, published in 1991, was a review of the abuse liability of stimulants, opioid mixed agonist-antagonist drugs, anxiolytics and sedative hypnotics (Fischman and Mello 1991). It was a great pleasure to work with Marian on these monographs, and we felt that we had accomplished something important for CPDD and for the field.

Both of these CPDD monographs focused on drug abuse liability, and much of the preclinical research of that time was primarily concerned with predicting the abuse liability of novel compounds using drug self-administration and drug discrimination procedures. These behavioral procedures were also used to analyze the pharmacological mechanisms underlying the reinforcing effects of drugs, as well as tolerance and physical dependence. There was considerably less interest in using drug self-administration models to predict the effectiveness of drug abuse treatment medications. Yet, I thought that this was an obvious application of these powerful behavioral procedures, and I organized a symposium on this topic for the 1991 meeting of the CPDD. That symposium was entitled "Behavioral Strategies for the Evaluation of New Pharmacotherapies for Drug Abuse Treatment" (Mello 1992), and papers were presented by Bob Balster, Roger Spealman and Bill Woolverton. Evaluation of potential drug abuse treatment medications continues to be a dominant theme in my research. In the remainder of this paper, I will review and discuss some preclinical and clinical findings from my laboratory.

CHALLENGES IN PRECLINICAL EVALUATION OF CANDIDATE TREATMENT MEDICATIONS

The development and evaluation of new drug abuse treatment medications has been greatly facilitated by the availability of animal models of drug self-administration (Mello 1992; Mello and Negus 1996). Animals will reliably self-administer most drugs that are abused by man, and it is reasonable to expect that medications that decrease drug self-administration should be more effective clinically than medications that do not change or increase drug self-administration. Drug self-administration models can be used to evaluate medications that substitute for or antagonize the effects of abused drugs. These medication evaluation strategies do not depend on any particular conceptualization of the pathogenesis of drug abuse, and the effects of antagonists and agonists on drug self-administration can be interpreted in terms of pharmacological interactions with the target drug of abuse.

Animal drug self-administration models offer a number of methodological advantages for the systematic evaluation of new medications. Unlike clinical trials, compliance with the medication regimen is ensured, and there is no confounding influence of unreported polydrug abuse. The effects of a new treatment medication on an ongoing pattern of drug self-administration can be evaluated quantitatively under controlled experimental conditions. Accurate baseline measures of the daily dose and frequency of drug self-administration can be determined before, during, and after administration of the treatment medication, whereas in clinical studies, the drug abuse history and the usual pattern of drug use are often unknown. It is also possible to monitor medication safety during exposure to the abused drugs, and to detect any adverse side effects that compromise animal health. In addition, uncontrolled social factors such as expectancy or placebo effects and peer pressure cannot complicate the interpretation of data obtained in animal models. Finally, preclinical evaluations are more cost-effective than extensive clinical trials.

Despite these several methodological advantages, assessing the clinical relevance of animal models of drug self-administration is an ongoing challenge. Many of the potential treatment medications that selectively reduce drug self-administration in preclinical studies have not been approved by the FDA for evaluation in man. This limits opportunities for cross validation of medication effectiveness between preclinical studies and clinical trials. The schematic in **Figure 1** shows an ongoing assessment of the concordance between medication evaluations in animal models and human drug abusers. Ideally, preclinical studies can be used to predict the effectiveness of medications in clinical trials, and confirmatory clinical results validate the predictive value and clinical relevance of animal models of drug self-administration. The result would be to accelerate identification of new medications for drug abuse treatment.
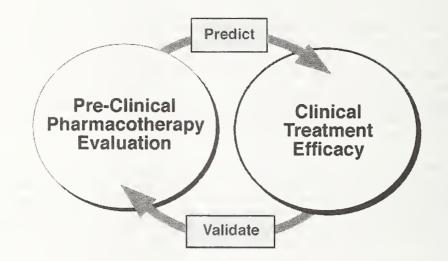
Figure 1

Figure 1: Cross validation of preclinical and clinical models. Validation of the effectiveness of animal models for preclinical evaluation of drug abuse treatment medications requires assessing the degree of concordance between preclinical studies and outpatient clinical studies. Eventually, the preclinical model should enable users to predict the potential effectiveness of new pharmacotherapies. This interactive process of cross-validation and prediction is essential for refinement of the preclinical model of drug self-administration. From Mello NK (1992); Behavioral Strategies for the Evaluation of New Pharmacotherapies for Drug Abuse Treatment. NIDA Research Monograph 119. Washington, DC: Government Printing Office, pp 150-154.

Fortunately, there are some instances in which the concordance between findings from clinical and preclinical evaluations has been clearly documented. The remainder of this review will describe some clinical and preclinical findings from my laboratory that illustrate the potential predictive value of animal models for medication evaluation. Much of my research has focused on the opioid mixed agonist antagonist buprenorphine, and I will describe some relevant findings from those studies. More detailed reviews of our research on buprenorphine have been published elsewhere (Mello and Mendelson 1985, 1992, 1993, 1995; Mendelson and Mello 1992; Mello *et al.* 1993).

BUPRENORPHINE FOR THE TREATMENT OF OPIOID ABUSE AND DEPENDENCE

Background

Buprenorphine was approved by the FDA for the outpatient treatment of opioid abuse in October, 2002. Importantly, buprenorphine can be prescribed by qualified physicians to private patients. The availability of buprenorphine, a safe and long-acting medication, provides another treatment option for physicians and patients (Jones 2004). The odyssey of buprenorphine from early clinical trials in the late 1970's to FDA approval in 2002 was long, and fraught with many obstacles. Our research group played a small part in this journey, and a comprehensive review of the buprenorphine story has been published in a book entitled *"Buprenorphine: Combating Drug Abuse with a Unique Opioid"* (Cowan and Lewis 1995).

Buprenorphine was synthesized by John Lewis at Reckitt and Colman, Inc. (Lewis 1974, 1995; Lewis *et al.* 1983), and he received the Eddy Award from CPDD in recognition of this significant achievement. Buprenorphine is a congener of the potent mu opioid agonist, etorphine and an opioid antagonist, diprenorphine. Because buprenorphine is derived from a combination of these two compounds, it is often referred to as an opioid mixed agonist-antagonist (Schuster and Harris 1985). From a treatment perspective, buprenorphine combines the characteristics of opioid agonist and antagonist pharmacotherapies for opioid addiction and offers some advantages over using either agonists or antagonists alone. Unlike opioid agonists, abrupt discontinuation of buprenorphine treatment usually does not produce severe and protracted withdrawal signs and symptoms (Jasinski *et al.* 1978; Fudala *et al.* 1989). Buprenorphine is also safe, and its antagonist component prevents lethal overdose even at

approximately 10 times the analgesic therapeutic dose (Banks 1979). This reduces the risk for drug overdose deaths, which are often associated with illicit methadone abuse (Kreek 1978), although buprenorphine in combination with benzodiazepines may be fatal (Jones 2004). Finally, the opioid agonist component of buprenorphine appears to be very important for patient acceptance and is the primary advantage of buprenorphine over treatment with the opioid antagonist, naltrexone. The risk for illicit diversion has been reduced by combining buprenorphine with the opioid antagonist naloxone (Jones 2004).

Clinical Studies

The first clinical pharmacology studies of buprenorphine were published in 1978 by Donald Jasinski and co-workers (Jasinski *et al.* 1978). They found that buprenorphine antagonized the physiological and subjective effects of high doses of morphine for up to 29.5 hours (Jasinski *et al.* 1978). Buprenorphine's long duration of action is an important advantage for drug abuse treatment. Don Jasinski and John Lewis made it possible for our group to study the effects of buprenorphine on heroin self-administration in heroin-dependent men (Mello and Mendelson 1980). Our subjects were 10 heroin-dependent men who had used heroin for over 10 years and had failed in conventional treatment programs. After admission to a dedicated clinical research ward and detoxification with methadone, they were given gradually ascending doses of buprenorphine or placebo, administered subcutaneously, over 14 days. Men were then maintained on placebo or 8 mg per day of buprenorphine for 10 days and given an opportunity to work on a simple operant task for points for heroin or money. After the 10-day buprenorphine or placebo treatment, men assigned to buprenorphine treatment were given gradually descending doses over five days and men assigned to placebo treatment were given gradually decreasing doses of methadone to prevent heroin withdrawal signs.

Men could work for either money or for heroin, and it took approximately five minutes to earn one point on a second order FR 300 (FI 1 sec:S) schedule. The operant manipulandum was a garage door opener, and each response was transmitted to computer-controlled circuitry. After 90 minutes of performance on the operant task, subjects could earn $1.50 or a single injection of heroin. Heroin was administered intravenously, and a maximum of three heroin injections was available each day (one injection every eight hours). During the first five days of buprenorphine or placebo treatment, a total of 21 mg of heroin was available each day. During the second five days of buprenorphine or placebo treatment, a total of 40.5 mg of heroin was available each day.

Heroin self-administration data for individual subjects are shown in **Figure 2**. Three men who were maintained on placebo treatment worked at the operant task for all the heroin that was available. In contrast, three men who were maintained on buprenorphine self-administered only one or two heroin injections over the entire 10-day treatment period. It is obvious that buprenorphine treatment dramatically reduced heroin self-administration. We also studied four subjects under both placebo and buprenorphine treatment conditions. Under placebo conditions, each subject took between 90 and 100 percent of the heroin available, whereas during buprenorphine treatment conditions, heroin self-administration was greatly reduced. One subject (number 8) could not tolerate the 8 mg dose of buprenorphine and was maintained on 4 mg per day. This subject took more heroin than the subjects maintained on 8 mg per day. We concluded that buprenorphine significantly reduced heroin self-administration by heroin-dependent men (Mello and Mendelson 1980). Buprenorphine was well tolerated and opioid side effects were mild and transient (Mello *et al.* 1982). A more complete review of these studies has been published (Mello and Mendelson 1995).

Figure 2

Heroin Self-Administration During Buprenorphine or Placebo Treatment
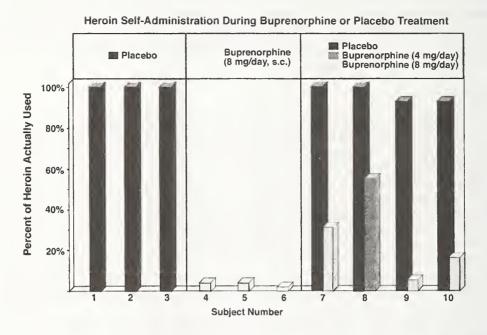
Figure 2. Percentage of available heroin used during 10 days of treatment with buprenorphine or placebo buprenorphine. Three subjects were maintained on placebo-buprenorphine (left columns); three subjects were maintained on buprenorphine (8 mg/day, s.c.) (middle columns), and four subjects were studied under both buprenorphine and placebo-buprenorphine conditions (right columns). Adapted from Mello and Mendelson, Science (1980).
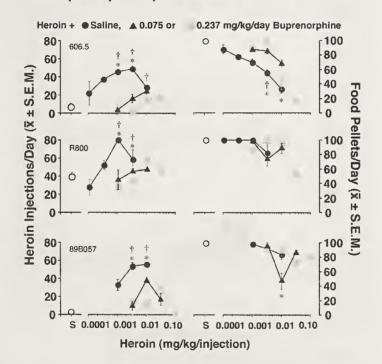
Preclinical Studies

Although we have studied the effects of a number of candidate treatment medications on drug self-administration in rhesus monkeys, many of these have not been approved for clinical use (Mello and Negus 1996, 2000; Negus *et al.* 1999). Buprenorphine offered an opportunity to cross validate findings from clinical studies and preclinical studies in non-human primates. The drug self-administration procedures have been described in detail in our original reports (Mello *et al.* 1990a, 1992) and are briefly summarized here. Monkeys were trained to press a key on an operant response panel to earn food (1 g banana-flavored pellets) on a second order schedule that required 32 or 64 responses for a single reinforcer [FR 2 or FR 4 (VR 16:S)]. The response key was transilluminated with different colors to signal the availability of food, drug or a timeout period when responding had no scheduled consequences. After food-maintained responding was stable, monkeys were surgically implanted with a double lumen i.v. catheter in the jugular vein or the femoral vein under aseptic conditions. The double lumen catheter has the advantage that drugs can be administered through one catheter lumen and the treatment medication can be administered through the second catheter lumen, so it is not necessary to flush the catheter contents into the vein before administering a treatment.

In most of our studies, food availability was followed by cocaine availability and a two-hour timeout period, and four such sessions were run each day. Food sessions always were before drug sessions so that intoxication would not compromise food intake. We study both drug- and food-maintained responding so we can determine if medication effects are selective for drug reinforcement or reflect a general disruption of operant responding (Mello 1992; Mello and Negus 1996). In some studies, a long-acting treatment medication or saline control treatment was administered during a morning timeout period. In other studies, a short-acting treatment medication was administered every 20 minutes. We usually examined the effects of *chronic* medication treatment for seven or 10 days or longer, because this is most analogous to the way medications are administered clinically. Moreover, we have often found that the effects of the treatment medication may change with repeated administration.

BUPRENORPHINE'S EFFECTS ON HEROIN SELF-ADMINISTRATION

On the basis of our clinical studies of buprenorphine's effects on heroin self-administration in heroin-dependent men (Mello and Mendelson 1980), we expected that buprenorphine would also decrease heroin self-administration by rhesus monkeys. **Figure 3** shows one example of cross validation between clinical and preclinical studies of the effects of treatment medications. Heroin self-administration dose-effect curves were determined during saline treatment and during treatment with buprenorphine (0.075 or 0.237 mg/kg/day). Each treatment was studied for 10 days at each of four unit doses of heroin (0.0001-0.10). Each data point shown in Figure 3 is the average of the last three days of 10 days of treatment. It is apparent that buprenorphine (0.075 or 0.237 mg/kg) shifted the heroin dose-effect curve downwards and to the right, and had less effect on food-maintained responding in comparison to saline control treatment (Mello and Negus 1998).

Figure 3

Buprenorphine ▼ Heroin Self-Administration

Heroin + ● Saline, ▲ 0.075 or ■ 0.237 mg/kg/day Buprenorphine

Figure 3. Effects of buprenorphine on heroin and food self-administration in rhesus monkeys. Dose-effect curves for heroin alone (0.0001-0.10 mg/kg/inj) are shown for individual monkeys in the left panel. The mean number of injections per day of heroin during saline treatment (closed circles) or buprenorphine treatment (0.075 mg/kg/day, triangles and 0.237 mg/kg/day, shaded squares) are shown on the left ordinate. Points above S show data from sessions when saline was available for self-administration (open circles). The dose of heroin available for self-administration is shown on the abscissa. In the right panel, food-maintained responding during saline self-administration (open circles) and heroin (0.0001-0.10 mg/kg/inj) self-administration during saline treatment (closed circles) and buprenorphine treatment [0.075 mg/kg/day, triangles and 0.237 mg/kg/day, shaded squares) is shown for individual monkeys. Each data point is the average of the last 3 days of 10 days during saline or buprenorphine treatment ($\bar{x}$ ± S.E.M.). Statistically significant differences between corresponding heroin doses during saline control treatment and buprenorphine treatment are indicated as follows: * 0.075 mg/kg/day buprenorphine different from saline, p<0.05; + = 0.237 mg/kg/day buprenorphine different from saline, p<0.05. Adapted from Mello and Negus, J. Pharmacol. Exp. Ther. (1998).

Buprenorphine's Effects on Cocaine Self-Administration

In the late 1980's, we wondered if buprenorphine would also reduce cocaine self-administration. This notion was based in part on accumulating evidence of interactions between dopaminergic and endogenous opioid systems. Ron Hammer had just reported that cocaine increased opioid receptor density in brain areas associated with drug reinforcement (Hammer 1989). We found that cocaine stimulated release of LH, a gonadotropin hormone regulated in part by endogenous opioid inhibitory control of hypothalamic luteinizing-hormone-releasing-hormone (LHRH) (Mello *et al.* 1990b and c; Mendelson *et al.* 1992). This effect of cocaine was unexpected. It was well established that opioid antagonists stimulated LH release by antagonizing endogenous opioid inhibition of LHRH (Yen *et al.* 1985). There was considerable interest in the co-modulatory interactions between endogenous opioid and dopaminergic systems in brain (Herz and Shippenberg 1988; Koob and Bloom 1988; Watson *et al.* 1988). Nonetheless it was surprising to find that buprenorphine dose-dependently reduced cocaine self-administration by rhesus monkeys. **Figure 4** shows that after only five days of buprenorphine treatment, cocaine injections per day decreased significantly in comparison to 15 days of saline treatment. At a higher dose of buprenorphine, fewer than 10 cocaine injections per day were self administered over 15 days. We published these data in Science in 1989, and this finding has been repeatedly replicated in our laboratory and in a number of other preclinical studies (Mello and Mendelson 1995). As described below, several outpatient clinical studies have also shown that buprenorphine decreases cocaine self-administration (Kosten *et al.* 1989a and b; Gastfriend *et al.* 1993a; Montoya *et al.* 2004).

Figure 4
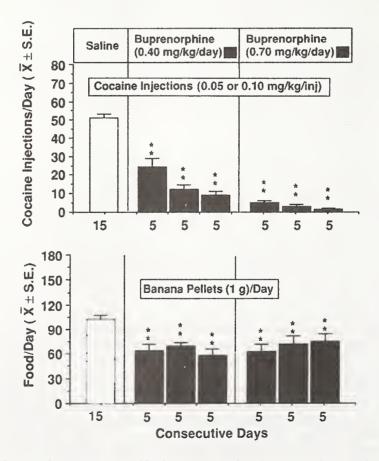
Figure 4. Buprenorphine reduces cocaine self-administration by rhesus monkeys. The effects of single daily infusions of buprenorphine or a saline control solution on cocaine and food self-administration are shown. Saline treatment is shown as an open bar in the left panel and buprenorphine treatment 0.40 mg/kg/day is shown as closed bars in the middle panel and 0.70 mg/kg/day is shown as closed bars in the right panel. The average number of cocaine injections self-administered is shown in the top row. The average number of food pellets self-administered is shown in the second row. The number of days that each treatment condition was in effect is shown on the

abscissa. Each data point is the mean ±SEM for five subjects. The statistical significance of each change from the saline treatment as determined by analysis of variance for repeated measures and Dunnett's tests for multiple comparisons is shown by asterisks (**p< 0.01). Reproduced from Mello et al., Science (1989), with permission of the publishers. Copyright 1989 by the A.A.A.S.

We were interested to learn if buprenorphine's reduction of cocaine self-administration would persist over a long period of time, or if tolerance would develop to buprenorphine's effects on cocaine self-administration (Mello *et al.* 1992). After a 15-day saline treatment baseline period, monkeys were treated with 0.32 mg/kg/day buprenorphine for four months. **Figure 5** shows that cocaine self-administration was reduced throughout the 120 day period. Food-maintained responding was initially reduced but returned to and exceeded baseline levels. During the post-buprenorphine 15 day saline treatment period, cocaine self-administration recovered, although not to pretreatment baseline levels. These findings were encouraging insofar as they suggested that any effect of buprenorphine on cocaine self-administration would persist during a long period of treatment.

Figure 5
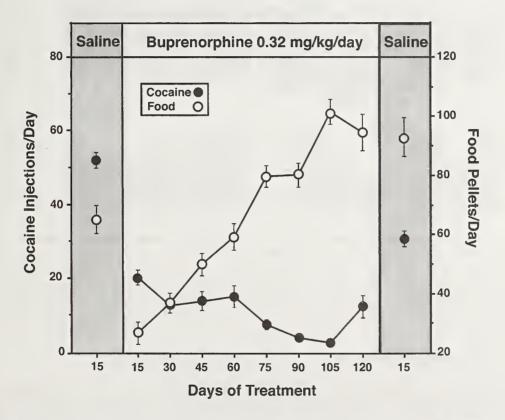
Figure 5. Effects of 3-4 months of daily buprenorphine treatment (0.32 mg/kg/day) on cocaine and food self-administration. Each of the data points for cocaine injections (filled circles) and food pellets (open circles) during the pre-buprenorphine saline control period is the average ±SE of four monkeys over 15 days. The first 100 days of buprenorphine treatment are an average of data from four monkeys and days 101-120 are an average of data from three monkeys. Adapted from Mello et al., J. Pharmacol. Exp. Ther. (1992).

The mechanisms underlying buprenorphine's robust effects on cocaine self-administration are unknown. Because buprenorphine has both mu opioid agonist and antagonist effects, we tried to determine which component was most important for its interactions with cocaine. We administered ascending doses of the long-acting opioid antagonist naltrexone 20 minutes before buprenorphine, and compared the effects of the buprenorphine + naltrexone combination with the effects of buprenorphine alone on cocaine self-administration. In earlier studies, we found that naltrexone alone did not decrease cocaine self-administration by rhesus monkeys (Mello *et al.* 1990a). **Figure 6** shows the percent change in cocaine injections from baseline during treatment with 0.40 mg/kg/day buprenorphine alone and with buprenorphine in combination with four doses of naltrexone. There was a significant naltrexone

dose-dependent decrease in the effectiveness of buprenorphine in reducing cocaine self-administration. We interpreted these data to suggest that the mu opioid agonist component of buprenorphine was essential for its effects on cocaine self-administration in rhesus monkeys (Mello *et al.* 1993c). Subsequently, we learned that low efficacy mu agonists were more effective in reducing cocaine self-administration than high efficacy mu agonists (Negus and Mello 2002).
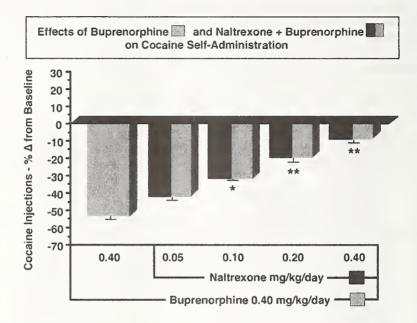
Figure 6

Figure 6. Comparison of the effects of buprenorphine only with buprenorphine-naltrexone combinations on cocaine self-administration. The average number of cocaine injections (mean ±SEM) self-administered are shown as percentage change from the saline treatment baseline before buprenorphine administration. A 10-day period of buprenorphine treatment (0.40 mg/kg/day) is shown at the left as a grey bar. Successive 10-day periods of ascending doses of naltrexone (0.05 – 0.40 mg/kg/day) administered 20 min before buprenorphine (striped and black bars) are shown at the right. Adapted from Mello et al., Neuropsychopharmacology (1993), Macmillan Publishers Ltd.
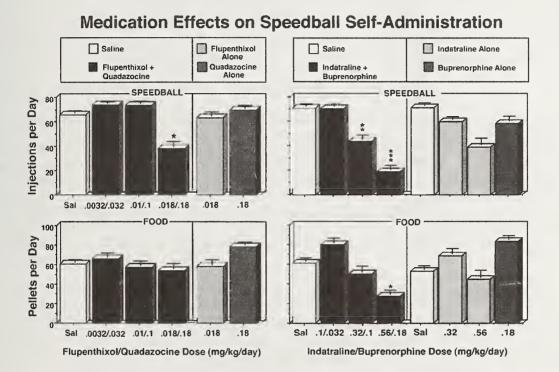
A PRECLINICAL MODEL OF SPEEDBALL SELF-ADMINISTRATION

It is increasingly rare to find persons who use only heroin or only cocaine exclusively. Dual dependence on cocaine and heroin or heroin dependence with occasional cocaine use are common patterns (Condelli *et al.* 1991; Kreek 1991; NIDA 2002). A survey of over 900 heroin-dependent persons found that 63 percent reported using cocaine with heroin in a speedball over a six-month period (Schütz *et al.* 1994). In 1995, we reported the development of a polydrug abuse model in the rhesus monkey (Mello *et al.* 1995). We found that monkeys would avidly self-administer speedballs that consisted of a simultaneous injection of cocaine and heroin in a 3 to 1 dose ratio. We then began to explore various strategies for reducing speedball self-administration. We hypothesized that a combination of medications that targeted both the cocaine and the heroin component of the speedball might be more effective in reducing speedball self-administration than treatment with only one of the same medications alone.

In one study, we examined the effects of treatment with a combination of the dopamine antagonist flupenthixol and the mu antagonist quadazocine (Mello and Negus 1999). We found that those two antagonist drugs in combination reduced speedball self-administration far more effectively than either drug administered alone. These data are shown in the left panel of **Figure 7**. The highest dose of flupenthixol + quadazocine produced a three-fold rightward shift in the speedball dose-effect curve. However, the effects of the flupenthixol + quadazocine combination were transient and associated with sedation (Mello and Negus 1999). In contrast, treatment with a

combination of the monoamine reuptake inhibitor indatraline and buprenorphine produced a sustained downshift in the speedball dose-effect curve that persisted throughout all ten days of treatment (Mello and Negus 2001). The buprenorphine and indatraline combination was also more effective in reducing speedball self-administration than treatment with indatraline alone, or a low dose of buprenorphine alone (0.18 mg/kg). These data are shown in the right panel of Figure 7.

Figure 7

Figure 7: Effects of saline, ascending doses of flupenthixol + quadazocine combinations and flupenthixol or quadazocine alone [left panel] or ascending doses of indatraline + buprenorphine combinations and indatraline or buprenorphine alone on speedball- and food-maintained responding [right panel]. Saline and doses of flupenthixol + quadazocine (mg/kg/day) [left panel] or indatraline + buprenorphine [right panel] are shown on the abscissa. The number of speedball injections per day (row 1) or food pellets per day (row 2) are shown on the left ordinate. Speedballs consisted of a unit dose of cocaine (0.01 mg/kg/inj) and heroin (0.0032 mg/kg/inj) in combination. Speedball- and food-maintained responding during saline treatment are shown as open rectangles, and as black rectangles during treatment with each medication combination. Speedball- and food-maintained responding during treatment with each medication alone are shown as light gray rectangles during treatment with flupenthixol alone [left panel] or indatraline alone [right panel], and as dark gray rectangles during treatment with quadazocine alone [left panel] or buprenorphine alone [right panel]. Each data point represents the average number of injections or food pellets ($\bar{x}$ ± S.E.) during 10 consecutive days of saline or drug treatment in a group of four monkeys [left panel] or three to five monkeys [right panel]. The asterisks indicate a significant change from the saline treatment baseline (*=p<0.05; **=p<0.01; ***=p<0.001). Adapted from Mello and Negus, Neuropsychopharmacology (1999 and 2001), Macmillan Publishers Ltd.

Given that buprenorphine alone significantly reduced both heroin and cocaine self-administration by rhesus monkeys, we anticipated that buprenorphine would also reduce speedball self-administration. Over a dose range of 0.075 to 0.75 mg/kg/day, buprenorphine dose-dependently reduced speedball self-administration. **Figure 8** shows that at a dose of 0.237 mg/kg/day, buprenorphine treatment reduced speedball self-administration and shifted the speedball dose-effect curve one log unit to the right (Mello and Negus 1998). These effects were selective for speedball self-administration, because food-maintained responding were equivalent to or higher during buprenorphine treatment than during saline treatment. It appeared that buprenorphine antagonized the suppressive

effects of speedballs on food-maintained responding. Interestingly, 0.237 mg/kg/day was the lowest buprenorphine dose that reduced cocaine self-administration in our earlier studies (Mello *et al.* 1990a).
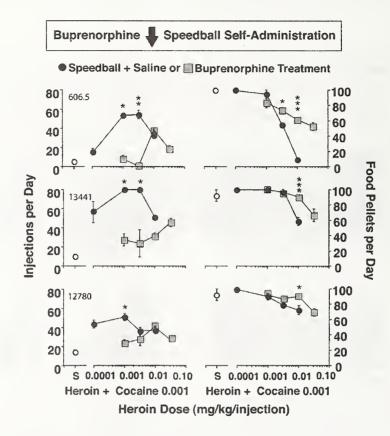
Figure 8

Figure 8: Effects of Buprenorphine (0.237) mg/kg/day on speedball dose-effect curves for individual monkeys. Dose-effect curves for a low dose of cocaine (0.001 mg/kg/inj) in combination with one of four doses of heroin (0.0001-0.032 mg/kg/inj) are shown for individual monkeys (left panel). The unit dose of heroin in combination with cocaine is shown on the abscissa. Points above S show data from saline treatment sessions when saline was the solution available for self-administration (open circles). Self-administration of each heroin + cocaine speedball combination during saline treatment (closed circles) and during buprenorphine treatment (0.237 mg/kg/day) (shaded squares) is shown on the left ordinate as injections per day. Each data point is the average of the last 3 days of 10 days of self-administration of each heroin + cocaine combination for each monkey ($\bar{x}$ ± S.E.M.). Food-maintained responding during saline self-administration (open circles), self-administration of heroin + cocaine combinations during saline treatment (closed circles) and during buprenorphine treatment (0.237 mg/kg/day) (shaded squares) is shown in the right panel. The number of 1g banana-flavored pellets per day earned during each condition is shown on the right ordinate. Statistically significant differences between corresponding speedball doses during saline control treatment and buprenorphine treatment are indicated by asterisks (*=p<0.05; **=p<0.01; ***=p<0.001). From Mello and Negus, J. Pharmacol. Exp. Ther. (1998).

CLINICAL STUDIES OF BUPRENORPHINE FOR TREATMENT OF HEROIN + COCAINE

The effectiveness of buprenorphine in reducing cocaine self-administration by rhesus monkeys led to clinical laboratory studies to determine the safety of buprenorphine in combination with single doses of cocaine, morphine or saline in human drug abusers (Teoh *et al.* 1993). Twenty men who fulfilled DSM-III-R criteria for concurrent cocaine and opioid dependence were admitted to a clinical research ward and treated with single daily doses of 4 or 8 mg sublingual buprenorphine for 21 days. Challenge doses of cocaine (30 mg, i.v.), morphine (10 mg, i.v.) and saline were given before and during buprenorphine treatment. There were no adverse interactions between

buprenorphine and cocaine or morphine on measures of cardiovascular function, respiration or temperature. Moreover, buprenorphine tended to decrease the respiratory depressant effects of morphine. We concluded that buprenorphine should be safe for treatment of persons with dual cocaine and opioid dependence (Teoh *et al.* 1993).

The effects of buprenorphine on speedball self-administration by rhesus monkeys are consistent with clinical reports of the effects of buprenorphine on concurrent heroin and cocaine dependence. In 1993, David Gastfriend in our group published the results of an open trial with buprenorphine (4 or 8 mg s.l.) which showed that both heroin and cocaine self-administration were reduced in 22 men with a ten-year history of drug dependence. Needle use, needle sharing and measures of addiction severity were also reduced over 12 weeks (Gastfriend *et al.* 1993b). In 2004, scientists at the NIDA Intramural Program reported a randomized trial of buprenorphine for the treatment of concurrent opiate and cocaine dependence. They concluded that sublingual buprenorphine at a dose of 16 mg/day was well tolerated and effective in reducing concurrent opiate and cocaine dependence (Montoya *et al.* 2004).

THE ROLE OF AGONIST THERAPIES IN THE TREATMENT OF DRUG ABUSE

There is an ongoing debate concerning the optimal approach to the development of drug abuse treatment medications. It now appears that agonist medications are more effective for drug abuse treatment then antagonist medications. Although antagonists are pharmacologically effective in reducing the effects of an illicit drug, treatment with antagonist medications usually is not acceptable to the client population. The opioid antagonist naltrexone is one compelling case in point. Naltrexone, like buprenorphine, significantly reduced heroin self-administration by heroin dependent men (Mello *et al.* 1981), but naltrexone was not generally accepted by patients for outpatient treatment (Meyer and Mirin 1979; Schecter 1980). Naltrexone has proved most useful for treatment of former opioid-dependent professionals who must remain drug free to maintain their medical license. In contrast, the mu opioid agonist methadone, and more recently, the mixed opioid agonist-antagonist buprenorphine, are well accepted by patients in treatment.

Recent preclinical findings from our laboratory are consistent with the notion that agonist medications can be very effective in reducing cocaine self-administration. We have found that *d*-amphetamine selectively reduces cocaine self-administration in several behavioral procedures (Negus 2003; Negus and Mello 2003a and b). Using the same operant behavioral procedures described earlier for our preclinical studies of buprenorphine, we compared the effects of three doses of *d*-amphetamine with saline treatment in monkeys trained to self-administer cocaine on a second-order schedule [FR 2 (VR 16:S)]. Each treatment condition was in effect for seven days. *d*-Amphetamine was administered once every 20 minutes to ensure a constant dose level. **Figure 9** shows that during saline treatment and low dose *d*-amphetamine treatment (0.01 mg/kg/hr), there was no effect on either cocaine- or food-maintained responding. However, at higher doses of *d*-amphetamine (0.032 and 0.1 mg/kg/hr) there was a significant decrease in cocaine self-administration, and food-maintained responding was less affected (Negus and Mello 2003b).
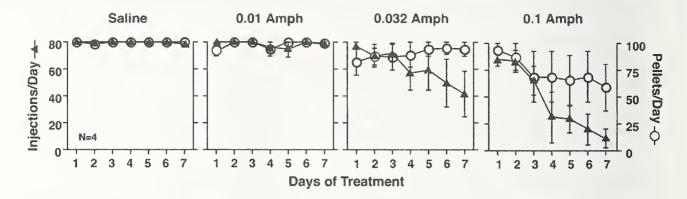
Figure 9

Figure 9: Time course of effects of saline or d-amphetamine (0.01-0.1 mg/kg/hr) on responding for 0.01 mg/kg/injection cocaine and food pellets. Abscissae: Consecutive days of treatment. Left ordinates: Number of cocaine injections (0.01 mg/kg/injection) delivered on each day of treatment (filled triangles, maximum=80). Right ordinates: Number of food pellets delivered on each day of treatment (open circles, maximum=100). Each point shows mean data from four monkeys, and error bars show the SEM. Statistical analysis indicated a significant effect of d-amphetamine dose [F(3,9)=7.93; p=0.0088] and treatment day [F(3,18)=21.96; p<0.0001] on cocaine self-administration and a significant interaction between d-amphetamine dose and treatment day [F(3,54)=4.17; p<0.0001]. A high dose of 0.1 mg/kg/hr d-amphetamine significantly decreased cocaine self-administration relative to saline control (p<0.01, Duncan post hoc test). In contrast, there was not a significant effect of d-amphetamine dose [F(3,9)=2.09; p=0.17] or treatment day [F(3,18)=0.70; p=0.59] on food-maintained responding, although the interaction between d-amphetamine dose and treatment day approached significance [F(3,54)=1.77; p=0.055]. Adapted from Negus and Mello, Drug Alc. Depend. (2003b).

As in our earlier studies of buprenorphine (Mello *et al.* 1992), we were interested to see if the effects of *d*-amphetamine on cocaine self-administration were sustained during long-term chronic treatment. **Figure 10** shows the effects of 28 days of *d*-amphetamine treatment on cocaine- and food-maintained responding by rhesus monkeys. Cocaine self-administration remained significantly reduced throughout the entire period of *d*-amphetamine treatment, whereas food-maintained responding returned to baseline levels within nine days after treatment began. After *d*-amphetamine treatment was discontinued, food-maintained responding remained at baseline levels, and cocaine self-administration gradually increased over seven days. Recovery of cocaine self-administration indicated that the sustained reduction in cocaine self-administration was a *d*-amphetamine effect and not due to uncontrolled variables.

Figure 10

Effects of Chronic d-Amphetamine on Cocaine- (▲) and Food- (○) Maintained Responding
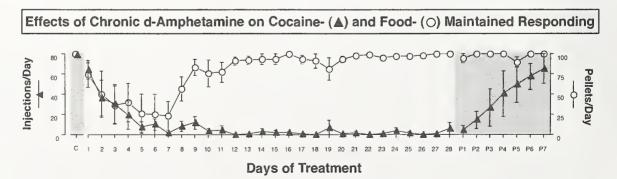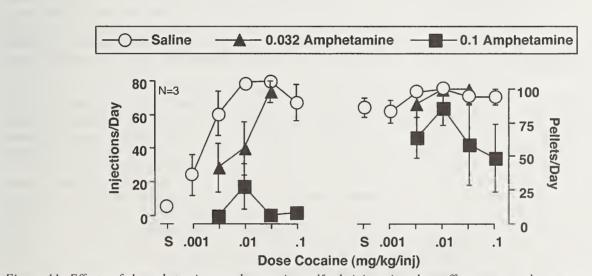
Figure 10. Effects of 28-day treatment with 0.1 mg/kg/hr d-amphetamine on responding for 0.01 mg/kg/injection cocaine and food pellets. Abscissa: Consecutive days of treatment. Left ordinate: Number of cocaine injections (0.01 mg/kg/injection) delivered on each day of treatment (filled triangles, maximum=80). Right ordinate: Number of food pellets delivered on each day of treatment (open circles, maximum=100). Each point shows mean data from four monkeys, and error bars show the SEM. Points in the shaded area on the far left over "C" show average numbers of cocaine injections and food pellets per day when 0.01 mg/kg/injection cocaine was available during saline treatment for 7 days in a separate experiment. Points in the shaded area to the far right over "P1-P7" show post-treatment data collected during the first seven days after d-amphetamine treatment was discontinued. During this time, the same unit dose of cocaine (0.01 mg/kg/injection) was available, and saline was substituted for 0.1 mg/kg/hr d-amphetamine as the treatment. Adapted from Negus and Mello, Drug Alc. Depend. (2003b).

We also determined cocaine dose-effect curves during saline treatment and examined the effects of two doses of *d*-amphetamine on cocaine- and food-maintained responding. As shown in **Figure 11**, 0.032 and 0.1 mg/kg/hr *d*-amphetamine produced dose-dependent and significant rightward and downward shifts in the cocaine self-administration dose-effect curve, with no significant effects on food-maintained responding.

Figure 11

Figure 11. Effects of d-amphetamine on the cocaine self-administration dose-effect curve and concurrent food-maintained responding. Abscissae: Unit dose of cocaine available during daily drug components in mg/kg/injection. Points above S show data collected when saline was the solution available for self-administration. Ordinate (left panel): Mean number of cocaine injections delivered per day during the last three days of each treatment. Ordinate (right panel): Mean number of food pellets (1g) delivered per day during the last three days of each treatment. All points show mean data from three monkeys, and error bars show the SEM. Statistical analysis indicated significant effects on cocaine self-administration of cocaine dose [F(2,4)=10.31; p=0.026] and d-amphetamine dose [F(2,4)=139.8; p=0.0002], but not a significant interaction between cocaine dose and d-amphetamine dose [F(2,8)=1.21; p=0.38]. Both 0.032 and 0.1 mg/kg/hr d-amphetamine produced effects significantly different from saline treatment (p<0.01; Duncan post hoc test). In contrast, there was not a significant effect on food-maintained responding of cocaine dose [F(2,4)=5.37; p=0.074] or d-amphetamine dose [F(2,4)=2.21; p=0.23], and there was not a significant interaction between cocaine dose and d-amphetamine dose [F(2,8)=0.94; p=0.49]. Adapted from Negus and Mello, Drug Alc. Depend. (2003b).

d-Amphetamine's selective reduction of cocaine self-administration by rhesus monkeys is a robust effect, observed when cocaine self-administration was maintained under a progressive ratio schedule (Negus and Mello 2003a), and in a food vs. cocaine choice procedure (Negus 2003) as well as under a second-order schedule (Negus and Mello 2003b). There was no evidence of increases in cocaine-maintained responding during *d*-amphetamine treatment as is sometimes observed during continuous cocaine infusion (Panlilio *et al.* 1998). In that study, when the cocaine infusions began 30 min before the session and the total cocaine treatment dose was approximately twice the amount usually self-administered in a session, only two of seven monkeys decreased cocaine-maintained responding. The other five monkeys increased cocaine self-administration at some cocaine infusion durations (Panlilio *et al.* 1998). When cocaine was administered as a pre-session bolus, followed by a continuous cocaine infusion during the session, cocaine self-administration was decreased at a moderate unit dose but not at a high unit dose (Glowa and Fantegrossi 1997). *d*-Amphetamine is longer acting than cocaine, and administration every 20 min resulted in more consistent effects on cocaine self-administration (Figures 9, 10 and 11) than continuous cocaine infusions in previous studies. Under the conditions of our experiments, *d*-amphetamine, a non-selective monoamine releaser, was similar to GBR-12909, a long-acting dopamine reuptake inhibitor, in its effects on cocaine-maintained responding (Rothman and Glowa 1995).

CONCLUSIONS

Figure 12 summarizes the concordance between clinical and preclinical evaluations of buprenorphine and *d*-amphetamine as drug abuse treatment medications. Buprenorphine consistently reduces cocaine self-administration in both clinical and preclinical studies (Mello and Mendelson 1995). Buprenorphine also reduces heroin self-administration in both clinical and preclinical studies (Mello and Mendelson 1995; Mello and Negus 1998). Finally, when cocaine and heroin are used concurrently, buprenorphine reduces both cocaine and heroin use in clinical studies (Gastfriend *et al.* 1993b; Montoya *et al.* 2004) and speedball self-administration in preclinical studies (Mello and Negus 1998, 2004).

The non-selective monoamine releaser, *d*-amphetamine also shows a promising profile for cocaine abuse treatment. *d*-Amphetamine selectively reduces cocaine self-administration by rhesus monkeys with minimal effects on food-maintained responding (Negus 2003; Negus and Mello 2003a and b). John Grabowski and co-workers systematically examined the effectiveness of *d*-amphetamine for the treatment of cocaine abuse in stimulant abusers and in polydrug abusers (Grabowski *et al.* 2001, 2004a and b). Recently, Grabowski's group reported that the combination of *d*-amphetamine and methadone effectively reduced both cocaine and heroin use in polydrug abusers (Grabowski *et al.* 2004a and b). We are currently studying the effects of treatment with *d*-amphetamine in combination with buprenorphine on speedball self-administration in our non-human primate polydrug abuse model. Data obtained thus far indicate that a combination of *d*-amphetamine + buprenorphine significantly reduced speedball self-administration and shifted the speedball dose effect curve downwards and to the right (Mello and Negus 2004). Of course, we recognize that the introduction of *d*-amphetamine as a cocaine abuse treatment agent may be somewhat problematic, but these data encourage the development of other long-acting monoamine releasers with less abuse liability (see Grabowski *et al.* 2004b; Rothman *et al.* 2004, submitted).

Figure 12

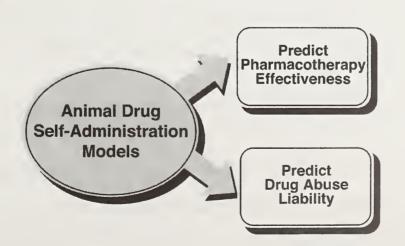**Concordance Between Clinical (■) and Pre-Clinical (□) Evaluations**

Treatment Medication	Cocaine		Heroin		Cocaine + Heroin	
	Clinical	Pre-Clinical	Clinical	Pre-Clinical	Clinical	Pre-Clinical
Buprenorphine	⬇	⬇	⬇	⬇	⬇	⬇
Amphetamine	⬇	⬇	—	—	⬇ + methadone	⬇ + buprenorphine

Figure 12. Concordance between clinical and preclinical evaluations of the effects of buprenorphine and of amphetamine on self-administration of cocaine, heroin and cocaine + heroin speedballs. The treatment medication is shown in the far left column. The effects of each treatment medication on cocaine (second column), heroin (third column) and cocaine + heroin speedballs (fourth column) are shown as downward pointing arrows (indicating decreases in drug self-administration) or as horizontal bars (indicating not studied). Clinical studies are shown as black arrows and preclinical studies are shown as white arrows. In row two, column four, amphetamine was studied with methadone or with buprenorphine.

Figure 13

In summary, there is compelling evidence that preclinical drug self-administration models can predict the effectiveness of pharmacotherapies for drug abuse treatment and there is considerable concordance between the results of clinical treatment trials and preclinical findings (**Figure 12**). Moreover, drug self-administration is a powerful behavioral technique for assessing both medication effectiveness and drug abuse liability. This conclusion is shown graphically in **Figure 13.** Drug self-administration procedures are a productive merger between the operant tradition of behavioral science and pharmacology. The basic procedures have been repeatedly refined and can be used to ask a number of experimental questions that are relevant to medications development (Mello and Negus 1996) as well as to examine the effects of drugs on physiological and neuroendocrine endpoints (Mello and Mendelson 2002). Some of the pioneers in the development of intravenous drug self-administration procedures in non-human primates are members of the CPDD today. Some of the earliest studies were published by Tomoji Yanagita (Yanagita *et al.* 1965; Deneau *et al.* 1969; Yanagita 1973, 1975, 1977), Bob Schuster (Schuster and Thompson 1969; Schuster and Balster 1972; Schuster 1976) and Joe Brady (Brady and Griffiths 1977). Those of us who have followed and built on their original innovations remain very much in their debt. Preclinical evaluation of drug abuse treatment medications is an ongoing challenge, and we continue to refine our models to address the new questions posed in this ever evolving and inherently fascinating field.

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ACKNOWLEDGMENTS

BIOLOGICAL EVALUATION OF OPIOIDS, STIMULANTS, AND DEPRESSANTS. I. AN OVERVIEW OF THE STUDIES PERFORMED BY THE DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2004)

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THE DRUG EVALUATION COMMITTEE

The Drug Evaluation Committee (DEC) evaluates analgesics, stimulants, and depressants for preclinical physical dependence potential as a public health service. DEC works with researchers from academia, industry, and also governmental organizations (FDA, DEA, WHO) to characterize the pharmacological profile of compounds in order to facilitate decisions on matters ranging from medication development to drug scheduling. The duties of the Biological Coordinator of DEC (Dr. A. Coop) involve receiving samples for evaluation and distributing them blind to the relevant pharmacological groups within DEC. All data are collated by the Biological Coordinator, who maintains a confidential database and corresponds with the submitters. The Biological Coordinator also maintains the DEC website (http://www.cpdd.vcu.edu/images/dec.pdf) which contains archived DEC annual reports together with the DEC indices, a list of all compounds evaluated by DEC and reference to their year of publication. The other members of DEC are in the two analgesic testing groups, at Virginia Commonwealth University (VCU, Drs. L. Harris, M. Aceto, P. Beardsley, C. Cook) and the University of Michigan (UM, Drs. J. Woods [DEC Chair], J. Traynor), and three stimulant/depressant testing groups, at the University of Mississippi Medical Center (UMMC, Dr. W. Woolverton), University of Texas Health Science Center at San Antonio (UTHSCSA, Drs. C. France, L. McMahon), and UM (Drs. W. Fantegrossi, J. Woods). Drs. J. Winter (University of Buffalo) and K. Cunningham (University of Texas Medical Branch at Galveston) currently serve as special purpose members, and Drs. T. Cicero, A. Jacobson, and G. Winger act as emeritus members. DEC reports to the CPDD Liaison Committee for Drug Testing and Evaluation (Dr. F. I. Carroll, Chair). Members of both that CPDD committee and other CPDD committees as well as representatives from governmental agencies, attend DEC's meeting held during the Annual Scientific Meeting of the CPDD. One other DEC meeting was held in Michigan in May 2004 to discuss the work which has been accomplished and future plans. Separate meetings are held at VCU quarterly with the members of the VCU Analgesic Testing Group, as well as Drs. E. May and E. Bowman, Dr. A. Coop, and a NIDA representative (Dr. D. Thomas), to discuss the results obtained from the VCU testing and research program.
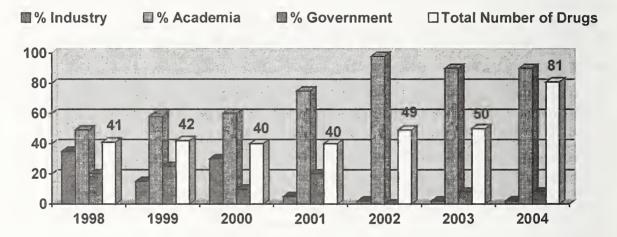
Data obtained under the auspices of DEC are held confidential for a maximum of three years, but can be released prior to the three-year limit with the permission of the submitter. Data were released for publication this year on 78 compounds evaluated by the Analgesic Testing Program (Figure 1). This figure is far larger than in previous years, and it is anticipated that a similar number of compounds will be released next year. Of these 78 compounds, 51 were evaluated at VCU (antinociceptive assays in mice - tail flick, hot plate, and phenylquinone, and the tail-flick antagonist assay, as well as substitution for morphine and precipitated withdrawal assays in rhesus monkeys), and 57 at UM (56 for binding affinity to the μ, δ, and κ opioid receptors and GTPγS functional studies, and one for self-administration in monkeys). Compounds were submitted primarily from academia; one compound was submitted from the pharmaceutical industry. Figure 1 clearly shows that the percentage of compounds originating from academia has been steadily increasing over the past few years, with the percentage from other sources correspondingly decreasing. It is noteworthy that a number of new industrial submitters have submitted compounds over the past year, thereby increasing the diversity of sources for compounds to be released in future years. In addition, several new academic submitters are represented this year, and it is anticipated that submissions from these sources will continue. Three compounds were released this year from the Stimulant/Depressant program which, when coupled to the three compounds released last year, represents a significant increase in compounds over the historical 1-2 releases per year.

Two joint publications based on the data gathered under DEC auspices were published since the last annual report (E. Greiner *et al.*, 2003; J. Schutz et al., 2003; Spetea *et al.*, 2004).

EXPERIMENTAL OBSERVATIONS

Compounds released for publication this year are listed in Table 1; their molecular structures and a summary of their *in vivo* and *in vitro* data are in Tables 2 to 10. Similar to previous years (Coop 2004), the examined compounds are classified according to their molecular structure: morphinans and 4,5-epoxymorphinans in Tables 2, 3 and 4; miscellaneous compounds in Table 5; 6,7-benzomorphans in Tables 6 and 7; esters and ethers of opioids in Table 8; opioid peptides in Table 9; compounds evaluated by the Stimulant/Depressant program are shown in Table 10. The more interesting compounds evaluated during the year are discussed below. For compounds that have been evaluated previously, the new data are discussed in relation to the published data.

FIGURE 1. DEC TESTING PROGRAMS: PERCENT AND SOURCE OF EXAMINED DRUGS AND TOTAL NUMBER OF COMPOUNDS (1998-2004)

The 14-phenylpropyloxy morphinans **NIH 11053 – NIH 11061** (Table 2) represent a unique class of opioids. They possess extraordinary potency as antinociceptive agents (10,000 x morphine), and high affinity for all three opioid receptors. As such, they can be considered of similar potency to the orvinols (Lewis, 1985, Casey and Parfitt, 1986). **NIH 11053 – NIH 11058** are 3-phenolic, and therefore the most potent, but the most interesting aspect of these compounds is that they are all mu opioid agonists. This is demonstrated through the Straub tail which was noted in most rodent assays, and also the reversal of the agonist actions by mu opioid antagonists. **NIH 11055** would be expected to have mu agonist actions due to the presence of the *N*-phenethyl group, but **NIH 11053** (*N*-propyl), **NIH 11054** (*N*-tetrahydrofuranyl), **NIH 11056** (*N*-cyclopropylmethyl), **NIH 11057** (*N*-cyclobutylmethyl), and **NIH 11058** (*N*-allyl) would all be expected to have mu opioid antagonist activity (Greiner et al., 2003). Although still very potent, **NIH 11055** is the least potent of the six compounds. These results suggest that the presence of a phenylpropyloxy group on the 14-position of these opioids leads to mu agonists of high potency, regardless of the nature of the N-substituent. The corresponding 3-methyl ethers display approximately 50-fold lower potency and affinity, but again the *N*-tetrahydrofuranyl (**NIH 11059**) and *N*-allyl (**NIH 11061**) possess greater potency than the *N*-phenethyl substituted **NIH 11060**.

The 3-ethers and esters of naltrexone in Table 3 have been discussed previously (Coop, 2002, 2004). These compounds were designed to possess a longer duration of action than naltrexone through the requirement for metabolism. The 3-ether **NIH11028** and the 3-cinnamoyl ester **NIH 11037** are neither particularly potent nor of longer duration. The 3-butyrate ester **NIH 11109** is of note for its increased potency which is estimated to be 5 times greater than naloxone. It is assumed that the increased lipophilicy of the drug as compared to naltrexone promotes rapid access to the CNS.

Table 4 contains several different morphinans and 4,5-epoxymorphinans. **NIH 11062** (an epoxymorphinan with N-propyl and 14-ethoxyl groups) shows again that N-propyl substituted opioids do not always possess a profile of mu antagonism. Indeed, **NIH 11062** is a potent mu opioid agonist (100 x morphine), but it should be remembered that the phenylpropyloxy derivative (NIH 11053, Table 2) is about 5000 times more potent than morphine. The corresponding 6,7-indole (**NIH 11063**, Table 4) is a derivative of naltrindole, the prototypical delta opioid

antagonist (Portoghese et al., 1990). This compound exhibits delta selectivity in binding assays and delta antagonism in GTPγS functional assays. **NIH 11063** may find use as a pharmacological tool for the study of delta receptors. Morphinans with 4-phenolic groups (such as **NIH 11066** Table 4) rarely possess significant opioid activity (Coop *et al.*, 1999), yet **NIH 11066** appears to possess similar potency to morphine in primates. The corresponding 4-methyl ether, **NIH 11065,** can be seen to possess the anticipated greater antinociceptive potency, being about 150 times more potent than morphine in rodents and 40 times more potent than morphine in primates. Interestingly, the corresponding *N*-cyclopropylmethyl substituted analog, **NIH 11076** Table 4, only possesses moderate morphine antagonism. Demonstrating again that traditional structure-activity relationships may not apply to this series, the *N*-methyl substituted 4-phenol with no 3-substituent, **NIH 11077** Table 4, possess excellent mu agonist potency, yet the corresponding *N*-cyclopropylmethyl substituted analog, **NIH 11075,** possesses 10-fold weaker antinociceptive activity, and no morphine antagonism.

NIH 10945 (Table 5) is similar to a benzomorphan, but with a nitrogen atom differently positioned. It was previously shown (Coop, 2002) that **NIH 10945** displayed weak antinociceptive activity in the anti-writing assay, yet possessed good affinity for both mu and kappa receptors. GTPγS functional assays have now shown this compound to be a partial agonist at both mu and kappa receptors of moderate potency. **NIH 11100** (Table 5) is a bridged indolomorphinan which was previously shown to possess moderate affinity for all three receptors. GTPγS assays have now shown this compound to have no mu agonist activity – a very unusual finding for a morphinan with an *N*-methyl substituent. **NIH 11031** (Table 5) has a long duration of action, but its activity changes as time progresses. It is initially a kappa agonist and manifests as a mu and kappa antagonist after 24-48 hours (Coop, 2004). New data in GTPγS functional assays is consistent with these findings and shows that **NIH 11031** is a potent partial agonist at both kappa and delta receptors, and possesses no agonist activity at mu receptors.

NIH 11161 (Table 5) is an analog of the prototypical delta agonist SNC80 (Calderon et al., 1997), but lacking the benzamide group generally considered important for activity (Calderon and Coop, 2004). **NIH 11161** showed weak reinforcing effects in primates experienced with mu agonists, and was estimated to be 30-fold less potent than the mu agonist alfentanyl. The presence of a phenolic group has previously been shown to lead to increased mu agonist activity, typified by BW373U86 (Calderon and Coop, 2004), so the fact that phenolic **NIH 11161** shows mu agonist activity is as expected.

The *N*-benzyl substituted benzomorphans (Table 6a) have garnered attention due to their unusual pharmacology (May et al., 1998; May et al., 2003). The corresponding homologs (*N*-phenethyl) tend to be potent mu agonists, yet the *N*-benzyl derivatives show little, if any, activity *in vivo*. Most of the analogs also display low affinity at opioid receptors, yet several of the compounds clearly show good affinity at mu and kappa receptors. The three *ortho* halogen substituted analogs (**NIH 11097** (*o*-F), **NIH 11093** (*o*-Cl), and **NIH 11081** (*o*-Br) Table 6a) were chosen for further study as all three possess good affinity (K_i <40 nM) at mu and kappa receptors, and all were inactive in both rodents and primates. GTPγS functional assays showed all three compounds to possess no agonist activity at mu, kappa, and delta receptors. Antagonist GTPγS studies confirmed that **NIH 11097** is an antagonist at both mu and kappa receptors. This still leaves the question as to why **NIH 11097** (for example) shows no activity in the rodent tail flick versus morphine nor exacerbate withdrawal in monkeys. In addition, it was also shown that **NIH 11097** did not antagonize a kappa agonist in rodents when administered s.c. One possible explanation for these apparent contradictions is that *N*-benzyl substituted benzomorphans do not readily cross into the CNS. Studies using **NIH 11097** administered by the i.c.v. route lead to an ED_{50} of 15 µM/brain in the tail flick assay. Further studies are warranted to examine the actions of **NIH 11097**, **NIH 11081**, and **NIH 11093** as antagonists when administered i.c.v. The (+)-isomer of **NIH 11097** (**NIH 11095,** Table 6b) also possesses significant affinity at kappa receptors. Again, GTPγS assays indicated no kappa agonist activity for this compound.

NIH 11082 (*N*-6-hydroxyhexyl substituted (-)-benzomorphan, Table 7a) possesses an unusual profile. The compound possesses good affinity at mu and kappa receptors, and lower affinity at delta receptors. It has antinociceptive activity in the anti-writing assay, that is reversed by the delta selective antagonist naltrindole. The *in vivo* studies indicate delta agonist actions which is not consistent with the low binding affinity at delta receptors. GTPγS functional assays complicate the matter further: **NIH 11082** acts as a weak partial mu agonist, a very weak kappa agonist of low efficacy, and at delta receptors very little stimulation is observed (9%) together with low potency. This would tend to suggest that the antinociceptive actions seen in PPQ are mu agonist actions. Why these actions were reversible with naltrindole remains to be determined.

The opioid ester **NIH 11044** (Table 8) was previously shown to possess a mixed agonist/antagonist profile in rodents (Coop, 2003), and overt signs in primates suggested a kappa agonist component. GTPγS functional assays have confirmed this profile, as **NIH 11044** is a kappa partial agonist and shows no stimulation in mu assays. The related analog lacking a terminal chlorine atom (**NIH 11045**, Table 8) possesses a similar profile of no stimulation in mu assays and kappa partial agonism, but with a weaker potency. In the case of **NIH 11045**, the kappa actions are so weak that they do not translate to activity in anti-writing assays.

Peptides **NIH 11086** and **NIH 11078** (Table 9) are analogs of the opioid peptide dynorphin. Severe convulsive effects were noted when these two compounds were administered i.c.v. The enkephalin analogs **NIH11089 - NIH11092** (Table 9) were also administered i.c.v. and exhibited varying degrees of antinociceptive activity in PPQ and TF. **NIH 11090** was notable for giving rise to convulsions and rigidity, but the other three peptides appear free from these undesired effects.

CPDD 0066 (5-Methoxy-N,N-diisopropyltryptamine) and **CPDD 0068** (2C-T-7) (Table 10) are hallucinogens of increasing concern to the Federal authorities, and they were shown to share discriminative stimulus effects with LSD. These compounds possess a profile which would suggest LSD-like effects in humans. **CPDD 0067** (phenylpiperazine) (Table 10) shares structural similarities to TFMPP and BZP (Coop, 2004). This compound shows no evidence of LSD-like effects.

IN CONCLUSION, DEC evaluated numerous interesting compounds this year. The 14-phenylpropylethers (Table 2) are extremely potent and have unique structure-activity relationships. The indolomorphinan (**NIH 11063**, Table 4) could prove useful as a delta selective antagonist, and the 4-phenols in Table 4 are some of only a very few available potent 4-phenolic opioids. **NIH 10945** (Table 5) is an opioid with a unique carbon-nitrogen skeleton, and **NIH 11161** (Table 5) is an analog of SNC80 which display mu agonism. The *N*-benzyl benzomorphans (Table 6a) have been shown to possess mu and kappa antagonism, and it is suggested that access to the CNS is one possible reason for their low potency *in vivo*. The hydroxyalkyl benzomorphan (**NIH 11082**, Table 7a) appears to show delta agonism *in vivo* and delta antagonism *in vitro*. The purported hallucinogens **CPDD 0066** and **CPDD 0068** (Table 10) have been shown to possess a profile which predicts LSD-like activity in humans.

TABLE 1. EVALUATED COMPOUNDS

NIH#	COMPOUND NAME	TABLE #-Evaluator
	ANALGESIC TESTING PROGRAM	
10945	(±)-(5S,8S,9R)-8-Amino-3-hydroxy-5,9-methano-9-(methoxymethyl)-5-methylbenzocyclooctene	5-UM
11001	4-(3-Hydroxyphenyl)-4-(1-oxopropyl)-1-(4-trifluoromethylbenzyl)piperidine.HCl	5-UM
11027	(-)-(1R,5R,9R)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-UM
11028	3-O-Methylnaltrexone.HCl	3-VCU
11031	17-Cyclopropylmethyl-7α-methyl-2'-[S]-phenyl-[5β,7β,3',5']-pyrrolidino-6,14-endo-ethenomorphinan.HCl	5-UM
11037	3-O-Cinnamoylnaltrexone.HCl	3-VCU
11041	(-)-(1R,5R,9R)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-UM
11044	(-)-1R,5R,9R-2'-Acetoxy-2-(3-cis-chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan.oxalate	8-UM
11045	(-)-(1R,5R,9R)-2'-Acetoxy-5,9-dimethyl-2-(propenyl)-6,7-benzomorphan.oxalate	8-UM
11050	6,7-Didehydro-3,14-dihydroxy-17-methyl-4,5α-epoxy-[(2-methyl)-pyrazolo-[6,7]]morphinan.2HCl	5-UM
11052	(-)-(1R,5R,9R)-5,9-Dimethyl-2-(propenyl)-2'-proprionoxy-6,7-benzomorphan.HCl	8-UM
11053	4,5α-Epoxy-3-hydroxy-14β-(3-phenylpropyloxy)-17-propyl-morphinan-6-one.HCl	2-VCU/UM
11054	4,5α-Epoxy-3-hydroxy-14β-(3-phenylpropyloxy)-17-([2-R,S-tetrahydrofuranyl)methyl)-morphinan-6-one.HCl	2-VCU/UM
11055	4,5α-Epoxy-3-hydroxy-17-phenethyl-14β-(3-phenylpropyloxy)morphinan-6-one.HCl	2-VCU/UM
11056	17-Cyclopropylmethyl-4,5-epoxy-3-hydroxy-14-(3-phenylpropyloxy)morphinan-6-one.HCl	2-VCU
11057	17-Cyclobutylmethyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl	2-VCU/UM
11058	17-Allyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl	2-VCU/UM
11059	4,5α-Epoxy-3-methoxy-14β-(3-phenylpropyloxy)-17-[(2-R,S-tetrahydrofuranyl)methyl]-morphinan-6-one.HCl	2-VCU/UM
11060	4,5α-Epoxy-3-methoxy-17-(2-phenethyl)-14β-(3-phenylpropyloxy)-morphinan-6-one.HCl	2-VCU/UM
11061	17-Allyl-4,5α-epoxy-3-methoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl	2-UM
11062	4,5α-Epoxy-14β-ethoxy-3-methoxy-17-(propyl)morphinan-6-one.HCl	4-VCU/UM
11063	4,5α-Epoxy-3-hydroxy-14β-methoxy-17-(propyl)indolo[2',3':6,7]morphinan-3-ol.HCl	4-UM
11065	5,6-Didehydro-14β-hydroxy-3,4-dimethoxy-17-methylmorphinan-6-carbonitrile	4-VCU/UM

TABLE 1. EVALUATED COMPOUNDS (continued)

11066	5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile	4- VCU/UM
11067	5,6-Didehydro-4-hydroxy-3,14β-dimethoxy-17-methylmorphinan-6-carbonitrile	4-VCU/UM
11068	17-Cyclobutylmethyl-4,5α-epoxy-14β-ethoxy-3-hydroxy-5β-methymorphinan-6-one	4-VCU/UM
11072	17-Cyclopropylmethyl-5,6-didehydro-14β-hydroxy-4-methoxymorphinan-6-carbonitrile	4-VCU/UM
11073	17-Cyclopropylmethyl-5,6-didehydro-4-hydroxy-3,14β-dimethoxymorphinan-6-carbonitrile	4-VCU/UM
11074	17-Cyclopropylmethyl-5,6-didehydro-4,14β-dihydroxy-3-methoxymorphinan-6-carbonitrile	4-VCU/UM
11075	17-Cyclopropylmethyl-5,6-didehydro-4,14β-dihydroxymorphinan-6-carbonitrile	4-VCU/UM
11076	17-Cyclopropylmethyl-5,6-didehydro-14β-hydroxy-3,4-dimethoxymorphinan-6-carbonitrile	4-VCU/UM
11077	5,6-didehydro-4,14β-dihydroxy-17-methylmorphinan-6-carbonitrile	4-VCU/UM
11078	7-Hydroxymethyl-8-methyl-6,7,8,9,10,10a-hexahydro-1H-2-oxa-8-aza-cycloocta[c,d]inden-3-ol	5-UM
11079	8-Hydroxymethyl-8-methyl-6,7,8,9,10,10a-hexahydro-1H-2-oxa-8-aza-cycloocta[c,d]inden-3-ol	5-UM
11081	(-)-(1R,5R,9R)- 2-(2-bromobenzyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-UM
11082	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan.HCl	7a-VCU/UM
11086	Dynorphin analog	9-VCU
11087	Dynorphin analog	9-VCU
11088	(+)-(1S,5S,9S)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	6b-UM
11089	Enkephalin analog	9-VCU
11090	Enkephalin analog	9-VCU
11091	Enkephalin analog	9-VCU
11092	Enkephalin analog	9-VCU
11093	(-)-(1R,5R,9R)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-UM
11095	(+)-(1S,5S,9S)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan. Oxalate	6b-UM
11096	(-)-(1R,5R,9R)-2'-Butyroxy-5,9-Dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	8-UM
11097	(-)-(1R,5R,9R)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.Oxalate	6a-VCU/UM
11098	(+)-(1S,5S,9S)-2'-Butryoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	8-VCU/UM

TABLE 1. EVALUATED COMPOUNDS (continued)

11100	18-(*E*)-Benzylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan.oxalate	5-UM
11101	18-Isopropylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan. oxalate	5-UM
11106	1'-Benzyloxymorphindole	5-VCU
11109	3-O-Butyrylnaltrexone.oxalate	3-VCU
11111	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanly)-6,7-benzomorphan.hemioxalate	6a-VCU
11112	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanly)-6,7-benzomorphan.hemioxalate	6b-VCU
11113	(+)-(1*S*,5*S*,9*S*)-2-Cyclopentylmethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6b-VCU
11114	(-)-(1*R*,5*R*,9*R*)-2-Cyclopentylmethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-VCU
11127	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(7-hydroxyheptyl)- 6,7-benzomorphan.HBr	7a-VCU
11128	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(7-hydroxyheptyl)-6,7-benzomorphan.HBr	7b-UM
11139	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl	7a-VCU
11140	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl	7b-VCU/UM
11161	(-)-3-{(*S*)-[(2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl](3-thienyl)methyl}phenol	5-UM
11163	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(5-hydroxypentyl)-6,7-benzomorphan.HCl	7b-UM
11164	(-)-(1*R*,5*R*,9*R*)-2-(5-Acetoxypentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7a-VCU/UM
11165	(+)-(1*S*,5*S*,9*S*)-2-(5-Acetoxypentyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	7b-VCU
11166	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(5-hydroxypentyl)-6,7-benzomorphan.HCl	7a-VCU
11167	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(1,3-dioxanylethyl)-2'-hydroxy-6,7-benzomorphan.HBr	6a-VCU
11168	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(1,3-dioxanylethyl)-2'-hydroxy-6,7-benzomorphan.HBr	6b-VCU
11176	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(1,3-dioxalanylethyl)-2'-hydroxy-6,7-benzomorphan. HCl	6a-VCU/UM
11177	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(1,3-dioxalanylethyl)-2'-hydroxy-6,7-benzomorphan. HCl	6b-UM
11178	(+)-(1*S*,5*S*,9*S*)- 5,9-Dimethyl-2'-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan.HCl	6b-UM
11179	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan.HCl	6a-VCU/UM
11180	(-)-(1*R*,5*R*,9*R*)-2-(3-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan. oxalate	7a-VCU/UM

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TABLE 1. EVALUATED COMPOUNDS (continued)

11181	(+)-(1S,5S,9S)-2-(3-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	7b-VCU/UM
11182	(+)-(1S,5S,9S)-2-(3-Acetoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	7b-VCU/UM
11183	(-)-(1R,5R,9R)-2-(3-Acetoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	7a-VCU/UM
11185	(-)-(1R,5R,9R)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-VCU/UM
11186	(+)-(1S,5S,9S)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6b-VCU/UM
11187	(-)-(1R,5R,9R)-2-(2-Ethylbutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-VCU/UM

CPDD# STIMULANT DEPRESSANT PROGRAM

0066	5-Methoxy-N,N-diisopropyltryptamine.HCl	9-SD
0067	Phenylpiperazine oxalate	9-SD
0068	2,5-Dimethoxy-4-(n)-propyl-thiophenethylamine.HCl	9-SD

NOTES FOR TABLES 2 - 9

Salt forms are shown. Rounded numbers are used (2 significant figures); precise values and details of the procedures are given in the VCU, UM, and Stimulant Depressant reports (Aceto *et al.*, 2005; Woods et al., 2005; France et al., 2005). "Inactive" is stated when an ED_{50} or AD_{50} is not obtained. NTI = naltrindole (delta antagonist); norBNI = norbinaltorphimine (kappa antagonist); β–FNA = β-funaltrexamine (mu antagonist).

1) Antinociceptive reference data:
Morphine ED_{50} (mg/kg): Hot Plate = 0.8; Phenylquinone = 0.23; Tail-Flick = 5.8; Tail-Flick Antagonism vs. morphine (naltrexone AD_{50} = 0.007; naloxone AD_{50} = 0.035).
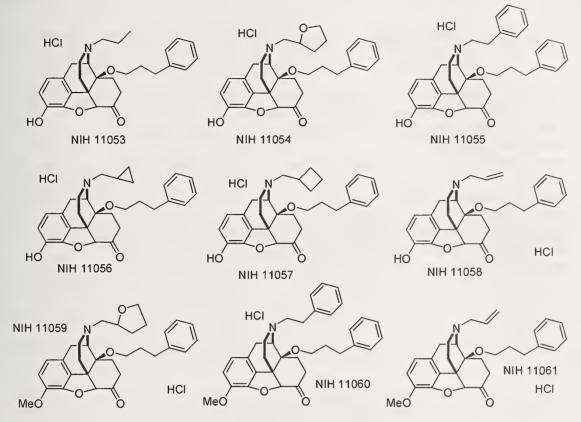
2) *In Vitro*:
Subtype selective binding affinity using recombinant receptors: μ (C_6 rat glioma cells expressing rat μ receptor), κ (CHO cells expressing human κ receptor), and δ (C_6 rat glioma cells expressing rat δ receptor). Affinity was assessed through the displacement of [^{3}H]-diprenorphine. K_i values for standard ligands: μ (DAMGO 7.6 nM, morphine 11.2 nM); δ (SNC80 0.8 nM); κ (U69593 0.3 nM)

[^{35}S]GTPγS functional data were obtained with the recombinant receptors described above. Values are given as EC_{50} with % stimulation compared to the standard full agonist (DAMGO, SNC80, U69,593), or the maximum stimulation achieved: μ (ED_{50}) morphine = 65 nM (100% stimulation), DAMGO = 34 nM (100% stimulation); δ (ED_{50}) SNC80 = 9 nM (100% stimulation), DPDPE = 8.3 nM (60% stimulation); κ (ED_{50}) U69,593 = 31 nM (100% stimulation), bremazocine = 0.5 nM (86% stimulation).

References to previous Drug Evaluation Committee annual reports are shown in parentheses, and refer to the year of publication.

TABLE 2. 14-PHENYLPROPYL SUBSTITUTED MORPHINANS AND 4,5-EPOXYMORPHINANS

NIH 11053 NIH 11054 NIH 11055 NIH 11056 NIH 11057 NIH 11058 NIH 11059 NIH 11060 NIH 11061

NIH #	MOUSE ANTINOCICEPTIVE ASSAYS				IN VITRO	MONKEY
	Hot Plate (ED$_{50}$, s.c., mg/kg)	Phenylquinone (ED$_{50}$, s.c., mg/kg)	Tail Flick (ED$_{50}$, s.c., mg/kg)	Tail Flick Antagonist (AD$_{50}$, s.c., mg/kg)	Binding Affinity, (K$_i$, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11053	0.0017	0.0009[a]	0.0016[b]	Inactive	μ=0.09, δ=0.93, κ=0.37	-
11054	0.0013	0.0017[c]	0.007[d]	Inactive	μ=0.20, δ=0.09, κ=0.08	-
11055	0.012	0.0094[e]	0.11	Inactive	μ=1.1, δ=1.25, κ=0.60	-
11056	0.0023	0.0062	0.0032	Inactive	–	Complete substitution for morphine at 0.04
11057	0.0037	0.0003[f]	0.0082	Inactive	μ=0.25, δ=0.46, κ=0.49	-
11058	0.0059	g	0.0056	Inactive	μ=0.20, δ=0.26, κ=0.11	-
11059	0.06[h]	0.0063[h]	0.084[h]	Inactive	μ=1.9, δ=5.4, κ=1.4	-

11060	0.68	i	0.76	Inactive	μ=3.8, δ=6.2, κ=61	-
11061	-	-	-	-	μ=1.7, δ=16, κ=4.1	-

a) Straub tail at 0.003 mg/kg. Subtype testing vs. ED_{80} of NIH 11053: β-FNA (mu) AD50 = 6.4 μg/brain; nor-BNI (kappa) 73% at 30 mg/kg; naltrindole (delta) inactive.

b) Clonic convulsions at 10 mg/kg (2/6 died); increased locomotor activity at 1 mg/kg.

c) Straub tail at 0.01 mg/kg.

d) Increased locomotor activity and clonic convulsions at 1 mg/kg. Naloxone vs. NIH 11054 in TF: AD_{50} = 0.14 mg/kg.

e) Straub tail, hyperactivity, and ataxia at 1 mg/kg.
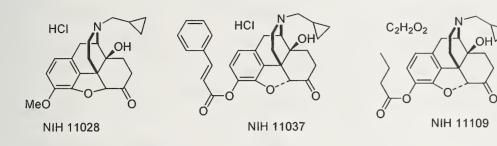
f) Straub tail, ataxia, and increased locomotion.

g) Non-dose related antinociception; Straub tail and increased locomotor activity at 1 mg/kg.

h) Straub tail in all rodent assays. Naloxone vs. NIH 11059 in TF: AD_{50} = 0.026 mg/kg.

i) Non-dose related antinociception; Straub tail noted.

TABLE 3. NALTREXONE ANALOGS
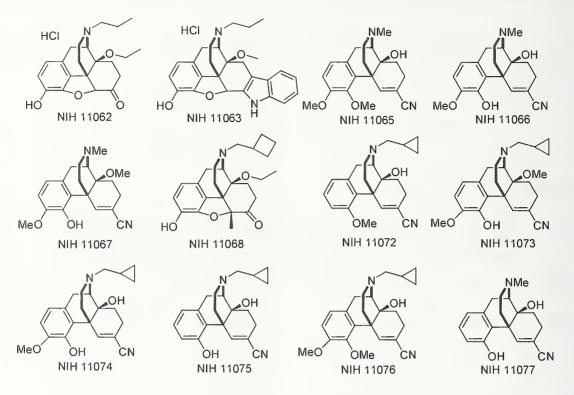
NIH 11028   NIH 11037   NIH 11109

NIH #	Hot Plate (ED$_{50}$, s.c., mg/kg)	Phenylquinone (ED$_{50}$, s.c., mg/kg)	Tail Flick (ED$_{50}$, s.c., mg/kg)	Tail Flick Antagonist (AD$_{50}$, s.c., mg/kg)	Binding Affinity, (K$_i$, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
	MOUSE ANTINOCICEPTIVE ASSAYS				***IN VITRO***	**MONKEY**
11028	Inactive[a]	-	Inactive[a]	0.47[a]	μ=31, δ=590, κ=95[a]	Exacerbated withdrawal at 4 and 16.[b]
11037	Inactive[c]	Inactive[c]	Inactive[c]	0.013[c,d]	μ=18, δ=385, κ=31[c]	Precipitated withdrawal at 0.03 and 0.15[c]
11109	Inactive[e]	Inactive[e]	Inactive[e]	0.0029[e,f]	μ=3.1, δ=63, κ=3.5[e]	Exacerbated withdrawal at 0.1.[f]

a) Reported previously (Coop, 2002, 2004). Tail flick: NIH 11028 vs. ED$_{80}$ of: enadoline (kappa agonist) AD$_{50}$ = 5.4 mg/kg; sufentanyl (mu agonist) AD$_{50}$ = 0.12 mg/kg; DPDPE (delta agonist) AD$_{50}$ = 1.8 mg/kg. NIH 11028 (p.o.) vs. ED$_{80}$ of morphine in tail flick: AD$_{50}$ = 2.3 mg/kg.

b) New data.

c) Reported previously (Coop, 2002). NIH 11037 vs. ED$_{80}$ of enadoline (kappa) AD$_{50}$ = 0.20 mg/kg; Four hour pretreatment study: Naloxone vs. morphine AD$_{50}$ = 1.92 mg/kg; NIH 11037 vs. morphine AD$_{50}$ = 2.69 mg/kg.

d) New data: NIH 11037 vs. ED$_{80}$ of DPDPE (delta, i.c.v.) inactive. Time course of NIH 11037 vs. morphine in tail flick: 20 minutes pretreatment, 70% antagonism; 2 hour pretreatment, 63% antagonism; 4 hours pretreatment, 2% antagonism.

e) Reported previously (Coop, 2004).

f) New data: time course in tail flick vs. morphine, loss of activity after four hours.

TABLE 4. MORPHINANS AND 4,5-EPOXYMORPHINANS

NIH 11062

NIH 11063

NIH 11065

NIH 11066

NIH 11067

NIH 11068

NIH 11072

NIH 11073

NIH 11074

NIH 11075

NIH 11076

NIH 11077

	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*		MONKEY
NIH #	Hot Plate (ED$_{50}$, s.c., mg/kg)	Phenyl-quinone (ED$_{50}$, s.c., mg/kg)	Tail Flick (ED$_{50}$, s.c., mg/kg)	Tail Flick Antagonist (AD$_{50}$, s.c., mg/kg)	Binding Affinity, (K$_i$, nM)	GTPγS Functional Assays (EC$_{50}$ and stimulation or K$_e$)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11062	0.062[a]	0.0022[a]	0.074[a]	Inactive	μ=1.6, δ=70, κ=6.1	-	-
11063	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	μ=270, δ=1.1, κ=110[b]	μ,κ,δ: no agonist stimulation. Antagonism of SNC80 (δ): K$_e$=0.24 nM	-
11065	0.15	0.026	0.018	Inactive	μ=12, δ=240, κ=380	-	Complete substitution at 0.1
11066	0.50	0.18	1.88	Inactive	μ=261, δ=3400, κ=4200	-	Complete substitution at 3
11067	0.25	0.11	0.21	Inactive	μ=22, δ=1000, κ=1500	-	Complete substitution at 0.3 and 1.2
11068	0.20	0.091	0.19	Inactive	μ=0.47, δ=31, κ=6.1	-	-
11072	Inactive	Inactive	Inactive	2.8	μ=69, δ=2100, κ=93	-	-

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TABLE 4. MORPHINANS AND 4,5-EPOXYMORPHINANS (continued)

11073	Inactive	2.4	8.0	Inactive	μ=240, δ=1600, κ=410	-	-
11074	Inactive	5.8	14	Inactive	μ=380, δ=4900, κ=370	-	-
11075	Inactive[c]	1.5[c]	8.65	Inactive	μ=23, δ=410, κ=12	-	-
11076	Inactive	Inactive	Inactive	5.5	μ=41, δ=1100, κ=49	-	-
11077	0.38	0.13	0.43[d]	Inactive[e]	μ=3.8, δ=420, κ=410	-	-

a)   Straub tail in all assays suggest mu agonism. Potency estimated to be 100 times greater than morphine.
b)   Previously reported (Coop, 2003).
c)   Rapid and heavy breathing; one convulsed and died in antiwrithing assay.
d)   Straub tail noted. Naloxone vs. ED_{80} of NIH 11077 AD_{50} = 0.06 mg/kg; naltrindole (delta) vs. ED_{80} of NIH 11077 inactive.
e)   Ataxia and increased locomotor activity at 30 mg/kg.
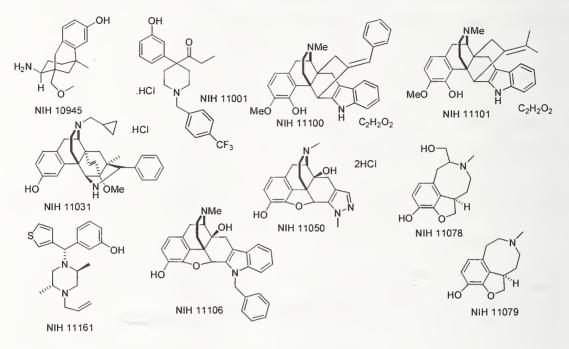
TABLE 5. MISCELLANEOUS DRUGS

Chemical structures: NIH 10945, NIH 11001, NIH 11100 ($C_2H_2O_2$), NIH 11101 ($C_2H_2O_2$), NIH 11031, NIH 11050 (2HCl), NIH 11078, NIH 11161, NIH 11106, NIH 11079
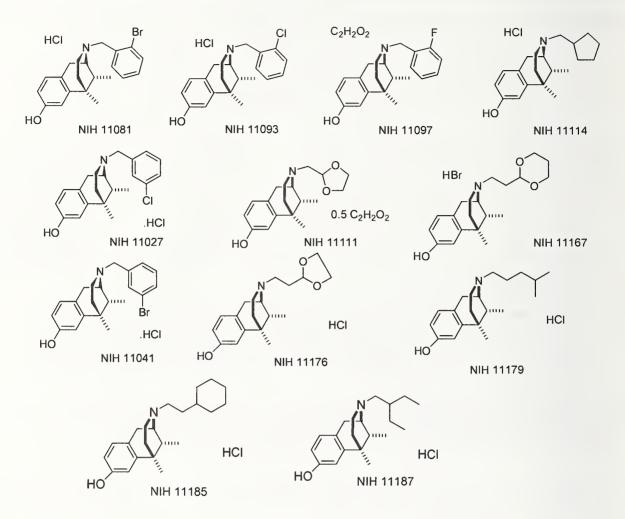
NIH #	Hot Plate (ED$_{50}$, s.c., mg/kg)	Phenylquinone (ED$_{50}$, s.c., mg/kg)	Tail Flick (ED$_{50}$, s.c., mg/kg)	Tail Flick Antagonist (AD$_{50}$, s.c., mg/kg)	Binding Affinity, (K$_i$, nM)	GTPγS Functional Assays (EC$_{50}$ and stimulation or K$_e$)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
10945	Inactive[a]	3.75[a]	Inactive[a]	Inactive[a]	μ=3.7, δ=160, κ=6.3[a]	μ EC$_{50}$ = 151 nM (60%); κ EC$_{50}$ = 66 nM (74%)	Partial suppression[a]
11001	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	μ=33, δ=290, κ=120[b,c].	μ,κ,δ: no agonist stimulation. Antagonism of μ: K$_e$ = 520 nM	No substitution[b]
11031	0.31[d]	0.018[d]	0.37[d]	Inactive[d]	μ=0.35, δ=0.95, κ=0.08[d]	μ: no stimulation; κ EC$_{50}$ = 0.36 nM (76%); δ EC$_{50}$ = 108 nM (35%)	Neither substitutes nor exacerbates withdrawal[d]
11050	-	-	-	-	μ=24, δ=23, κ=160[e]	μ EC$_{50}$ = 150 nM (89%); κ EC$_{50}$ = 250 nM (19%); δ EC$_{50}$ = 300 nM (27%)	-
11078	-	-	-	-	μ, δ, κ>10,000		-
11079	-	-	-	-	μ, δ, κ>10,000		-

Header group labels: MOUSE ANTINOCICEPTIVE ASSAYS — IN VITRO — MONKEY

TABLE 5. MISCELLANEOUS DRUGS (continued)

11100	-	-		-	$\mu=42$, $\delta=30$, $\kappa=60^i$	μ: no stimulation; κ EC_{50} = 2100 nM (64%); δ EC_{50} = 460 nM (41%)	-
11101	-	-	-	-	$\mu=270$, $\delta=150$, $\kappa=160^f$	μ EC_{50} = 2100 nM (64%); κ and δ no stimulation	-
11106	-	4.6^g	-	-	—	-	-
11161	-	-	-	-	—	-	Reinforcing effects in primates: 30-fold less potent and 30% less effective than alfentanyl.

a)   Previously reported (Coop, 2002).
b)   Previously reported (2001)
c)   Binding assays at mu performed in buffer with guanine nucleotides and sodium gave a K_i of 220 nM.
d)   Previously reported (2004). Subtype testing in tail flick vs. ED_{80} of NIH 11031: β-FNA (mu) inactive; nor-BNI (kappa) AD_{50} = 8.5 mg/kg; naltrindole (delta) inactive. Timecourse: Delayed mu and kappa antagonism; peaks at 48 hours, dissipated at 72 hours. Long term signs of jaw sag, ptosis, and ataxia in primate.
e)   Previously reported (Coop, 2003).
f)   Previously reported (Coop, 2004).
g)   Previously reported (Coop, 2003). Antagonism of ED_{80} of SNC80 in antiwrithing: inactive s.c. and i.c.v. New data: Naloxone vs. ED_{80} of NIH 11106 in antiwrithing AD_{50} = 0.02 mg/kg.

NIH 11081

NIH 11093

NIH 11097

NIH 11114

NIH 11027

NIH 11111

NIH 11167

NIH 11041

NIH 11176

NIH 11179

NIH 11185

NIH 11187

MOUSE ANTINOCICEPTIVE ASSAYS *IN VITRO* **MONKEY**

NIH #	Hot Plate (ED$_{50}$, s.c., mg/kg)	Phenylquinone (ED$_{50}$, s.c., mg/kg)	Tail Flick (ED$_{50}$, s.c., mg/kg)	Tail Flick Antagonist (AD$_{50}$, s.c., mg/kg)	Binding Affinity, (K$_i$, nM)	GTPγS Functional Assays (EC$_{50}$ and stimulation or K$_e$)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11027	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=25, δ=1360, κ=11[a]	μ,κ,δ: no stimulation; Antagonist assays: μ K$_e$ = 35 nM, κ K$_e$ = 23 nM.	Non-dose related exacerbation of withdrawal[a]

TABLE 6a. (-)-6,7-BENZOMORPHANS (continued)

11041	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=48, δ=1330, κ=10[a]	μ,κ,δ: no stimulation	Neither substituted nor exacerbated withdrawal at 4 and 16.[a]
11081	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	μ=40, δ=1200 κ=14[b]	μ,κ,δ: no stimulation	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16[b]
11093	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	μ=17, δ=600, κ=18[b]	μ,κ,δ: no stimulation	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16[b]
11097	Inactive[b]	Inactive[b]	Inactive[b,c]	Inactive[b]	μ=23, δ=330 κ=2.1[b]	μ,κ,δ: no stimulation; antagonist assays: μ K_e = 97 nM, κ K_e =17 nM	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16[b]
11111	Inactive[b]	1.9[b,d]	Inactive[b,d]	0.2[b]	–	-	Neither substituted nor exacerbated withdrawal at 0.15 and 0.6
11114	Inactive[b]	7.0[b,e]	Inactive[b]	2.4[b]	μ=0.8, δ=8.3, κ=0.2[b,e]	μ: no stimulation; κ EC_{50} = 11 nM (50%); δ EC_{50} = 250 nM (18%); antagonist assays: μ K_e = 2.4 nM	-
11167	Inactive	5.5	Inactive	Inactive	μ=20, δ=58, κ=67[b]	-	-
11176	Inactive	Inactive	Inactive	Inactive	μ=27, δ=53, κ=42	-	Attenuated withdrawal signs at 3 and 12
11179	Inactive	2.7	10	Inactive	μ=6.0, δ=60, κ=7.3	-	Tremors and convulsions prevented assessment
11185	8.5[f]	1.2[f]	3.0[f]	Inactive	μ=4.3, δ=43, κ=51	-	Attenuated withdrawal signs at 1.5 and 6
11187	Inactive[g]	1.4[g]	2.2[g]	Inactive	μ=9.2, δ=58, κ=5.9	-	Substituted for morphine at 1 and 4.[g]

a)   Previously reported (Coop, 2003).
b)   Previously reported (Coop, 2004).
c)   New data: tail flick (i.c.v.) ED_{50} = 15 μg/brain; NIH 11097 vs. ED80 of enadoline (kappa) in tail flick inactive.
d)   New data: norBNI (kappa) vs. ED_{80} of NIH 11111 in antiwrithing inactive; ED_{80} of NIH 11111 vs. DPDPE in TF AD_{50} = 0.27 mg/kg.
e)   New data: norBNI (kappa) vs. ED_{80} of NIH 11114 in antiwrithing inactive.
f)   Straub tail and increased locomotor activity noted.
g)   Straub tail and ataxia in rodents; Slowing, ataxia, eyelid ptosis, and jaw sag in monkeys.
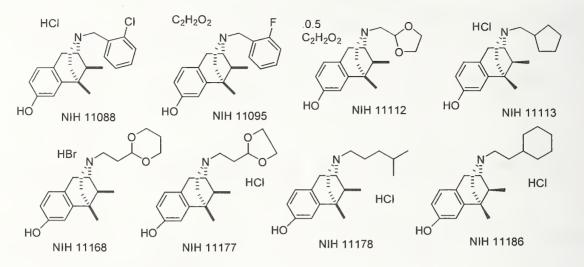
TABLE 6b. (+)-6,7-BENZOMORPHANS

NIH 11088 NIH 11095 NIH 11112 NIH 11113

NIH 11168 NIH 11177 NIH 11178 NIH 11186

NIH #	Hot Plate (ED$_{50}$, s.c., mg/kg)	Phenylquinone (ED$_{50}$, s.c., mg/kg)	Tail Flick (ED$_{50}$, s.c., mg/kg)	Tail Flick Antagonist (AD$_{50}$, s.c., mg/kg)	Binding Affinity, (K$_i$, nM)	GTPγS Functional Assays (EC$_{50}$ and stimulation or K$_e$)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
	MOUSE ANTINOCICEPTIVE ASSAYS				***IN VITRO***		**MONKEY**
11088	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=140, δ=3600, κ=23[a]	μ,κ,δ: no stimulation	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16[a]
11095	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=560, δ=4100, κ=47[a]	μ,κ,δ: no stimulation	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16[a]
11112	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=480, δ=1100, κ=190[a]	-	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16
11113	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=33, δ=610, κ=3.5[a]	-	-
11168	Inactive	Inactive	Inactive	Inactive	μ=1900, δ>10,000, κ=540[a]	-	-
11177	-	-	-	-	μ=670, δ=8700, κ=640	-	-
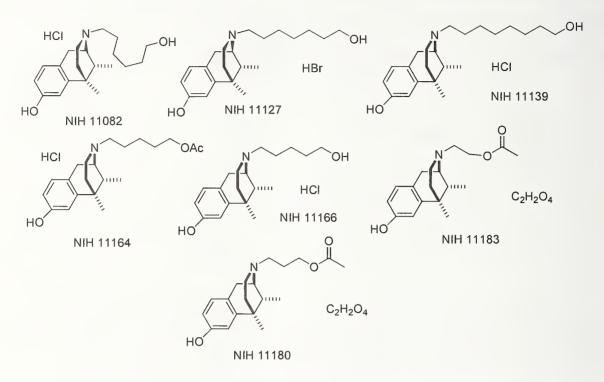
TABLE 6b. (+)-6,7-BENZOMORPHANS (continued)

11178	-	-	-	-	μ=610, δ=6100, κ=260	-	-
11186	Inactive	18	Inactive	Inactive	μ=140, δ=2800, κ=220		No effects on withdrawal signs at 4. At 16, one monkey convulsed

a)   Previously reported (Coop, 2004)

NIH 11082

NIH 11127

NIH 11139

NIH 11164

NIH 11166

NIH 11183

NIH 11180

	MOUSE ANTINOCICEPTIVE ASSAYS				IN VITRO		MONKEY
NIH #	Hot Plate (ED$_{50}$, s.c., mg/kg)	Phenylquinone (ED$_{50}$, s.c., mg/kg)	Tail Flick (ED$_{50}$, s.c., mg/kg)	Tail Flick Antagonist (AD$_{50}$, s.c., mg/kg)	Binding Affinity, (K$_i$, nM)	GTPγS Functional Assays (EC$_{50}$ and stimulation or K$_e$)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11082	Inactive[a]	1.93[a,b]	Inactive[a,b]	Inactive[a]	μ=10, δ=140, κ=29[a]	μ EC$_{50}$ = 300 nM (51%); κ EC$_{50}$ = 1300 nM (22%); δ EC$_{50}$ = 560 nM (9%).	Brief attenuation of withdrawal at 16
11127	Inactive[c]	2.9[c]	20[c]	Inactive[c]	μ=4.6, δ=200, κ=36[c]		Non-dose related attenuation of withdrawal signs
11139	Inactive	4.4	Inactive	Inactive	μ=5.8, δ=35, κ=8.8[c]		Attenuated some withdrawal signs at 3 and 15[d]
11164	Inactive	8.4	Inactive	Inactive	μ=15, δ=140, κ=55		-
11166	Inactive	Inactive	Inactive	Inactive	μ=33, δ=300, κ=260[c]		-
11180	Inactive	Inactive	Inactive	Inactive	μ=34, δ=290, κ=25		Precipitated withdrawal at 2 and 8[e]

TABLE 7a. (-)-6,7-BENZOMORPHANS (continued)

11183	Inactive	10	Inactive	8.8	$\mu=43$, $\delta=420$, $\kappa=60$		Exacerbated withdrawal at 4 and 16

a) Previously reported (Coop, 2003). Naltrindole (delta) vs. ED_{80} of NIH 11082 in antiwrithing AD_{50} = 0.75 mg/kg.
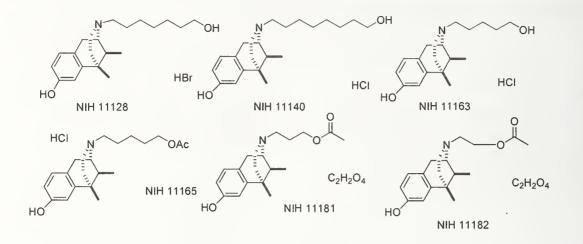
b) New data: norBNI (kappa) vs. ED_{80} of NIH 11082 in antiwrithing inactive; β-FNA (mu) vs. ED_{80} of NIH 11082 in antiwrithing inactive. Timecourse in antiwrithing 77% at 20 minutes, 26% at 1 hour. Effects additive with morphine in antiwrithing; no additive effects with morphine in tail flick.

c) Previously reported (Coop, 2004)

d) Did not block vocalization nor rigidity (mu effects).

e) Eyelid ptosis, slowing, and ataxia noted.

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TABLE 7b. (+)-6,7-BENZOMORPHANS
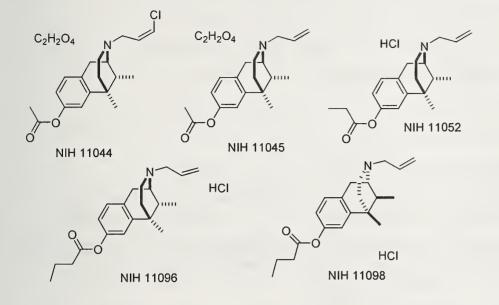
NIH 11128

NIH 11140

NIH 11163

NIH 11165

NIH 11181

NIH 11182

NIH #	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
	Hot Plate (ED$_{50}$, s.c., mg/kg)	Phenylquinone (ED$_{50}$, s.c., mg/kg)	Tail Flick (ED$_{50}$, s.c., mg/kg)	Tail Flick Antagonist (AD$_{50}$, s.c., mg/kg)	Binding Affinity, (K$_i$, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11128	-	-	-	-	μ=900, δ=5800, κ=1800	-
11140	Inactive	Inactive	Inactive	Inactive	μ=140, δ=200, κ=450	Neither substituted nor exacerbated withdrawal at 4 and 16
11163	-	-	-	-	μ,δ,κ>10,000	-
11165	Inactive	Inactive	Inactive	Inactive	μ=1400, δ=>10,000, κ=830[a]	-
11181	Inactive	Inactive	Inactive	Inactive	μ=4500, δ=>10,000, κ=4100	Attenuation of withdrawal at 4 and 16
11182	Inactive	4.7	Inactive	Inactive	μ=2000, δ=>10,000, κ=1800	No effects in SDS at doses up to 8

a)   Previously reported (Coop, 2004)

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TABLE 8. OPIOID ESTERS

NIH 11044

NIH 11045

NIH 11052

NIH 11096

NIH 11098

| MOUSE ANTINOCICEPTIVE ASSAYS | | | | | *IN VITRO* | | MONKEY |

NIH #	Hot Plate (ED$_{50}$, s.c., mg/kg)	Phenylquinone (ED$_{50}$, s.c., mg/kg)	Tail Flick (ED$_{50}$, s.c., mg/kg)	Tail Flick Antagonist (AD$_{50}$, s.c., mg/kg)	Binding Affinity, (K$_i$, nM)	GTPγS Functional Assays (EC$_{50}$ and stimulation or K$_e$)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11044	Inactive[a]	10.5[a]	Inactive[a]	0.24[a]	μ=15, δ=17, κ=3.0[a]	μ,δ: no stimulation; κ EC$_{50}$ = 23 nM (51%)	Slowing, eye-lid ptosis, jaw sag[a]
11045	Inactive[b]	Inactive[b]	Inactive[b]	1.35[b]	μ=136, δ=96, κ=29[b]	μ,δ: no stimulation; κ EC$_{50}$ = 130 nM (46%)	Slowing, eye-lid ptosis, jaw sag[b]
11052	-	-	-	-	μ=110, δ=91, κ=8.0[a]	μ,κ: no stimulation; δ EC$_{50}$ = 150 nM (37%)	-
11096	Inactive[c]	Inactive[c]	Inactive[c]	0.29[c]	μ=30, δ=37, κ=0.9[c]	μ EC$_{50}$ = 920 nM (11%), κ EC$_{50}$ = 66 nM (74%)	Precipitated withdrawal; potency equal to naloxone[c]
11098	Inactive[a]	9.6[a]	Inactive[a]	Inactive[a]	μ=600, δ=3100, κ=1700[a]	μ EC$_{50}$ = 950 nM (17%), κ: no stimulation	Attenuated withdrawal at 2 and 8

a)   Reported previously (Coop, 2003).
b)   Reported previously (Coop, 2003). AD$_{50}$ of NIH 11046 vs. ED80 of enadoline (kappa) = 2.7 mg/kg.
c)   Reported previously (Coop, 2004). Antagonism testing in tail flick vs. morphine – non-selective.

TABLE 9. OPIOID PEPTIDES

AcTyr-Lys-Trp-Trp-Le-Arg-Arg-D-Ala-Arg-Pro-Lys-NH$_2$ NIH 11086

AcPhe-Phe-Phe-Arg-Leu-Arg-Arg-D-Ala-Arg-Pro-Lys-NH$_2$ NIH 11087

(D)-Phe-N-piperonyl-Gly-(D)Nle-(D)Arg-NH$_2$ NIH 11089

(D)-Phe-(D)Nal-(D)Nle-NLys-NH$_2$ NIH 11090

NhPhe-(D)Phe-(D)Nle-(D)Arg-NH$_2$ NIH 11091

N-Pentyl-Gly-(D)Phe-(D)Nle-(D)Arg-NH$_2$ NIH 11092

	MOUSE ANTINOCICEPTIVE ASSAYS (I.C.V.)				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED$_{50}$, i.c.v., mg/kg)	Phenylquinone (ED$_{50}$, s.c., mg/kg)	Tail Flick (ED$_{50}$, s.c., mg/kg)	Tail Flick Antagonist (AD$_{50}$, s.c., mg/kg)	Binding Affinity, (K$_i$, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11086	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	–	-
11087	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	–	-
11089	Inactive[c]	Inactive[c]	2.5 µg/brain	Inactive	–	-
11090	Inactive	17 µg/brain[d]	0.29 µg/brain	Inactive[d]	–	-
11091	Inactive[e]	2.1 µg/brain[e]	Inactive[e]	Inactive	–	-
11092	Inactive	0.85 µg/brain	0.14 µg/brain	Inactive	–	-
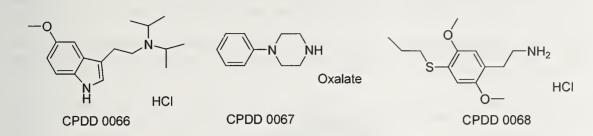
a)   Severe effects noted: hot plate (30 µg/brain) - tremors and whirling; antiwrithing unable to test higher doses; tail flick (30 µg/brain) tremors and sedation.

b)   Severe CNS effects noted: hot plate (3 mg/kg) - convulsions/death/ immobile; antiwrithing unable to test higher doses due to convulsions at 3; tail flick (10 mg/kg) immobility and loss of righting reflex.

c)   Insufficient drug for full analysis in hot plate and antiwrithing - highest dose was 3 µg/brain

d)   Antiwrithing: clonic extensions, hunched backs, convulsions, and rigidity; tail flick vs. morphine: convulsions, hunched back, rigidity.

e)   Sedation in all mice at 10 µg/brain, 3/8 moved in circles.

TABLE 10. COMPOUNDS EVALUATED BY STIMULANT DEPRESSANT PROGRAM

CPDD 0066   CPDD 0067   CPDD 0068

	Discriminative Stimulus Effects in Benzodiazepine-Trained Monkeys	Self-Administration in Cocaine-Maintained Monkeys	Drug Discrimination in Amphetamine-Trained Monkeys	Discriminative Stimulus Effects in LSD-Trained Rats	Binding affinity at 5HT receptors (pK$_i$)
0066	Shares no discriminative stimulus effects with either flumazenil or midazolam	No self-administration up to 0.3 mg/kg/inj	No amphetamine discriminative stimulus effects up to 10 mg/kg. At 17 mg/kg seizures were evident	LSD-like responding at 3 mg/kg	5-HT$_{1A}$ = 7.4 5-HT$_{2A}$ = 5.3 5-HT$_{2C}$ = 5.8
0067	Shares no discriminative stimulus effects with either flumazenil or midazolam	No self-administration up to 0.3 mg/kg/inj	-	No significant LSD-like responding	5-HT$_{1A}$ = 6.5 5-HT$_{2A}$ = 5.1 5-HT$_{2C}$ = 5.6
0068	Shares no discriminative stimulus effects with either flumazenil or midazolam	No self-administration up to 0.3 mg/kg/inj[a]	No amphetamine discriminative stimulus effects up to 3 mg/kg[b]	LSD-like responding at 1 mg/kg	5-HT$_{1A}$ = 5.9 5-HT$_{2A}$ = 6.9 5-HT$_{2C}$ = 7.4

a)   In the drug elicited head twitch response, CPDD-0068 acts as an agonist at 5-HT$_2$ receptors in the mouse with similar potency and effectiveness as the phenylisopropylamine hallucinogens DOM and DOI.

b)   A dose of 3 mg/kg was behaviorally active, with the subjects calm and staring

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ACKNOWLEDGEMENT

EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (2004)

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This report contains information on compounds that have been submitted to the Drug Evaluation Committee of the College and released for publication by the submitters. The information obtained usually involves *in vitro* evaluation in opioid-binding assays. In addition, the compounds may be evaluated for discriminative and reinforcing effects. Analgesic and respiratory function assays are also possible. These behavioral assessments are conducted in rhesus monkeys.

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia of Virginia Commonwealth University is currently administered by the Biological Coordinator, Dr. A. Coop, University of Maryland. The compounds come originally from pharmaceutical companies, universities, government laboratories, or international organizations.

At the UM and MCV of VCU laboratories, drug samples arrive from the Biological Coordinator with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information. After the evaluation is complete and the report sent to Dr. Coop, the submitter of the compound(s) is requested to release the chemical structure to include with the evaluation data in the ANNUAL REPORT. The submitter can withhold the structure for up to three years. When the structure is released all of the data on the compound are reported herein.

SUMMARY OF TESTS PERFORMED

The compounds that were evaluated at the University of Michigan during the past year are shown in the following Table. Also shown are dates of Reports to the Biological Coordinator, Dr. Coop.

NIH #	Date Submitted to Biological Coordinator	NIH #	Date Submitted to Biological Coordinator	NIH #	Date Submitted to Biological Coordinator
10945	09 September 2003	11067	15 January 2002	11128	10 April 2003
11001	04 August 2003	11068	15 January 2002	11140	14 March 2003
11027	31 July 2003	11072	15 January 2002	11161	31 January 2003
11031	31 July 2003	11073	14 March 2002	11163	10 April 2003
11041	04 August 2003	11074	14 March 2002	11164	10 April 2003
11044	31 July 2003	11075	14 March 2002	11176	31 July 2003
11045	04 August 2003	11076	14 March 2002	11177	31 July 2003
11050	09 September 2003	11077	14 March 2002	11178	31 July 2003
11053	24 October 2001	11078	23 October 2001	11179	31 July 2003
11054	24 October 2001	11079	23 October 2001	11180	31 July 2003
11055	24 October 2001	11081	04 August 2003	11181	31 July 2003
11057	01 November 2001	11082	01 August 2003	11182	31 July 2003
11058	01 November 2001	11088	01 August 2003	11183	31 July 2003
11059	20 November 2001	11093	04 August 2003	11185	31 July 2003
11060	20 November 2001	11095	04 August 2003	11186	31 July 2003
11061	20 November 2001	11096	09 September 2003	11187	31 July 2003
11062	05 December 2001	11097	04 August 2003		
11063	25 November 2001	11098	09 September 2003		
11065	03 December 2001	11100	31 July 2003		
11066	03 December 2001	11101	04 August 2003		

METHODS
Opioid Receptor Binding and In Vitro Efficacy Assessment

Details of the binding assay have been described previously (Lee *et al.*, 1999). Briefly, aliquots of a membrane preparation are incubated with [^{3}H]diprenorphine (0.3 nM) in the presence of different concentrations of the drug under investigation at 25° C for 1 hr. Specific, *i.e.*, opioid-receptor-related binding is determined as the difference in binding obtained in the absence and presence of 10μM naloxone. The potency of the drugs in displacing the specific binding of ^{3}H-ligand is determined from data using Graphpad Prism (GraphPAD, San Diego, CA) and

converted to Ki values by the method of Cheng and Prussoff (1973). Opioid binding is performed in membranes from C_6 rat glioma cells expressing recombinant μ (rat; Emmerson *et al.*, 1994) or δ (rat; Clark *et al.*, 1997) and CHO cells expressing the recombinant κ (human, Zhu *et al.*, 1997). The affinity (Kd) values of [^{3}H]diprenorphine at the receptors are: μ (0.15 nM); δ (0.45 nM); κ (0.25 nM).

The results of the selective binding assays are given as means ± SEM from three separate experiments, each performed in duplicate. Ki values for standard compounds using recombinant receptors and [^{3}H]diprenorphine as radioligand are: μ (DAMGO, 7.6 nM; morphine, 11.2 nM), δ (SNC80, 0.8 nM) and κ (U69593, 0.3 nM). If less than 50% displacement of [^{3}H]diprenorphine is seen at 10 μM, it is reported as > 10 μM and the percent displacement given in parentheses.

[^{35}S]GTPγS assays are carried out using membranes from C6 cells expressing either μ (Emmerson *et al.*, 1996) or δ (Clark *et al.*, 1997) receptors or CHO cells expressing δ receptors (Zhu *et al.*, 1997). Assays are performed as described by Traynor and Nahorski (1995). Values are given as EC_{50} with % effect compared to a standard agonist (DAMGO, SNC80, or U69593) or as maximal stimulation achieved at 10 μM. EC_{50} values (nM) for standard compounds are as follows: mu receptor (morphine, 65 nM; DAMGO, 34 nM; fentanyl, 13 nM), delta receptor (SNC80, 9 nM; DPDPE 8.3 nM), and kappa receptor (U69593, 31.0 nM; bremazocine, 0.5 nM)

DPDPE (60%) and bremazocine (86%) are partial agonists compared with the standards SNC80 and U69593. Morphine and DAMGO give equivalent responses.
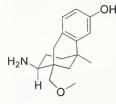
Antagonist activity is given as AD_{50} values or as pK_B values. AD_{50} refers to the concentration of test compound that reduces [^{35}S]GTPγS binding stimulated by an ED_{80} concentration of appropriate agonist (DAMGO, μ; DPDPE, δ; U69593, κ) by 50%. pK_B is the concentration of antagonist required to shift the dose-effect curve for appropriate agonist by 2-fold. It is a measure of the affinity of the antagonist for a receptor.

Self-Administration by Monkeys

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject alfentanil. Each of at least three monkeys is studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, observable changes in behavior are produced by the compound.

The schedule of intravenous drug delivery is a fixed-ratio 30; when a light above a lever is illuminated, the 30th response produce an intravenous drug injection accompanied by another light that is illuminated during drug delivery. After each injection, a 45 sec timeout period occurs. A component of the session ends after 20 injections have been received or 25 min have passed, whichever occurs first. Different doses of the drug are available during each of four components of a session. Other procedural details are given in Winger *et al.* (1989 and 1992).

NIH 10945   (±)-(5S,8S,9R)-8-Amino-3-hydroxy-5,9-methano-9-(methoxymethyl)-5-methylbenzocyclooctene

OPIOID RECEPTOR BINDING (nM) †

μ-receptor:	3.7 ± 0.2
δ-receptor:	156.0 ± 25.0
κ-receptor:	6.3 ± 0.4

[^{35}S]GTPγS ASSAY

Agonist Activity

μ-receptor: maximal stimulation = 59.6 ± 5.9% with EC_{50} = 151 ± 49 nM
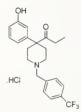κ-receptor: maximal stimulation = 74.4 ± 1.9% with EC_{50} = 66.1 ± 10.1 nM

SUMMARY

NIH 10945 has high affinity for both μ and κ opioid receptors. Affinity at δ receptors is over 20-fold less. NIH 10945 is also a partial agonist at μ and κ receptors that likely explains its activity in the PPQ assay in the mouse and its ability to partially substitute for morphine in the morphine-dependent monkey. ††

† Binding data previously reported in NIDA Monograph 182:141, 2002.
†† PPQ data reported previously in NIDA Monograph 182:168, 2002.

<p style="text-align:center">*   *   *</p>

NIH 11001   4-(3-Hydroxyphenyl)-4-(1-oxopropyl)-1-(4-trifluoromethylbenzyl)piperidine.HCl

OPIOID RECEPTOR BINDING (nM) †

μ-receptor:	32.9 ± 1.1
δ-receptor:	291 ± 83
κ-receptor:	118 ± 28

[^{35}S]GTPγS ASSAY

Agonist Activity

No significant stimulation of [^{35}S]GTPγS binding in C6 cells expressing the rat μ (C6μ) cells.

Antagonist Activity

Ke (μ) = 516 ± 121 nM

NIH 11001 (continued)
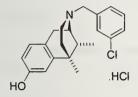
SUMMARY

NIH 11001 has affinity for $\mu > \kappa = \delta$, but showed no activity *in vivo* or *in vitro* as an agonist or μ antagonist in the mouse or monkey††. The present findings show that the compound has only very weak μ antagonist activity in spite of a reasonably high binding affinity. Note: repeat of the binding results in a buffer containing guanine nucleotides and Na^+ ions afforded a Ki at the μ receptor of 221 ± 71 nM, in line with the functional affinity measure.

† Binding data previously reported in NIDA Monograph 181:151, 2001
†† NIDA Monograph 181:197, 2001

* * *

NIH 11027   (-)-(1*R*,5*R*,9*R*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM) †

μ-receptor:	25.0 ± 9.9
δ-receptor:	1362 ± 53
κ-receptor:	11.1 ± 2.3

[^{35}S]GTPγS ASSAY

Agonist Activity

No stimulation of [^{35}S]GTPγS binding was observed.

Antagonist Activity
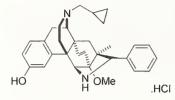
Ke (μ) 34.5 ± 17.5 nM
Ke (κ) 23.2 ± 6.2 nM

SUMMARY

NIH 11027 has affinity for κ and μ receptors with high selectivity ($\delta/\kappa = 123$; $\delta/\mu = 55$) for both of these over δ receptors. However, no activity as agonist or antagonist was seen in the mouse, although a non-dose-dependant exacerbation of withdrawal was observed in morphine-dependent monkeys†. The present findings show that the compound is an antagonist at both μ and κ receptors. However, the affinity (Ke) at μ receptors is approximately 10-fold less than that of naloxone. This may explain the *in vivo* results. Alternatively, the lack of *in vivo* activity may relate to the pharmacokinetic profile of this compound.

† Binding data previously reported in NIDA Monograph 183:175, 2003

NIH 11031   17-Cyclopropylmethyl-[5β,7β,3',5']-pyrrolidino-2'-[*S*]-phenyl-7α-methyl-6,14-*endo*-ethenomorphinan.HCl

OPIOID RECEPTOR BINDING (nM) †

μ-receptor = 0.35 ± 0.40
δ-receptor = 0.95 ± 0.08
κ-receptor = 0.08 ± 0.01

[³⁵S]GTPγS ASSAY

μ-receptor: <5% up to 10 μM
δ-receptor: maximal stimulation = 35.0 ± 5.7% with EC_{50} = 1.8 ± 0.5 nM
κ-receptor: maximal stimulation = 76.3 ± 11.0 with EC_{50} = 0.36 ± 0.03 nM

SUMMARY

The binding affinity (Ki) of NIH 11031 is very high at all three receptors. The opioid effects in the mouse and monkey†† may be explained by the highly potent agonist activity at κ receptors.

† Binding data previously reported in NIDA Monograph 194:155. 2004
†† NIDA Monograph 184:181-183, 2004

* * *

NIH 11041   (-)-(1*R*,5*R*,9*R*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM) †

μ-receptor: 47.7 ± 21.1
δ-receptor: 1326 ± 53.3
κ-receptor: 9.9 ± 1.4
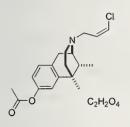
[³⁵S]GTPγS ASSAY
No significant stimulation of [³⁵S]GTPγS binding was observed up to a concentration of 10 μM.

SUMMARY

NIH 11041 has affinity for κ receptors and has 5-times lesser affinity at μ receptors and 26 times lesser at δ receptors. However, it has no activity in vivo or in vitro as an agonist or μ antagonist in the mouse or monkey.††
The present findings show that the compound has no agonist action and is likely to be a κ/μ antagonist. The affinity values suggest that it will be approximately 20-fold less potent as a : antagonist than naloxone. This may explain the lack of observed antagonist activity in vivo.

† Binding data previously reported in NIDA Monograph 183:177, 2003
†† Monkey data previously reported in NIDA Monograph 183:211, 2003

NIH 11044   (-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-2-(3-*cis*-chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan.oxalate

OPIOID RECEPTOR BINDING (nM) †

μ-receptor: 14.9 ± 2.5
δ-receptor: 17.4 ± 2.3
κ-receptor: 3.0 ± 0.1

[^{35}S]GTPγS ASSAY

μ-receptor: no stimulation up to 10 μM
δ-receptor: 5% stimulation at 10 μM
κ-receptor: maximal stimulation = $56.1 \pm 10.0\%$ with $EC_{50} = 22.7 \pm 7.3$ nM

SUMMARY
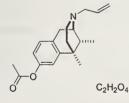
NIH 11044 has high affinity for κ opioid receptors > μ = δ receptors, with a selectivity of 5-fold for κ receptors over the other types. It acts as a partial agonist at κ opioid receptors. Its binding affinity (Ki) is high at all three receptors (see above), suggesting that it is also a potent μ and δ antagonist. This agrees with its *in vivo* profile in the mouse that it as μ antagonist activity but is antinociceptive in the PPQ†† test and that it has μ antagonist activity with some κ agonist properties in the monkey.

† Binding data previously reported in NIDA Monograph 183:178, 2003
†† NIDA Monograph 183:214, 2003

*   *   *

NIH 11045   (-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-5,9-dimethyl-2-(propenyl)-6,7-benzomorphan.oxalate

OPIOID RECEPTOR BINDING (nM) †

μ-receptor: 136 ± 34
δ-receptor: 96.2 ± 8.1
κ-receptor: 29.2 ± 1.6

[^{35}S]GTPγS ASSAY

μ-receptor: no stimulation up to 10 μM
δ-receptor: no stimulation up to 10 μM
κ-receptor: maximal stimulation = $45.5 \pm 5.6\%$ with $EC_{50} = 127 \pm 2.3$ nM

NIH 11045 (continued)

SUMMARY

NIH 11045 has affinity for κ opioid receptors but is only 3-4-fold selective for the κ over δ and μ receptors. In vivo, the compound is a μ and κ antagonist (versus morphine and enadoline, respectively) in the mouse but in the monkey is a μ antagonist with signs of κ agonism.†† The present findings show that the compound has partial agonist action at 6 receptors, which would explain the in vivo observation.
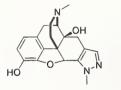
† Binding data previously reported in NIDA 183:179, 2003
†† See NIDA Monograph 183:215, 2003.

* * *

NIH 11050   17-Methyl-6,7-didehydro-3,14-dihydroxy-4,5α-epoxy-[(2-methyl)-pyrazolo-[6,7]]morphinan.2HCl

2HCl

OPIOID RECEPTOR BINDING (nM)⊥

μ-receptor: 23.9 ± 10.1
δ -receptor: 22.7 ± 3.3
κ-receptor: 157 ± 53

[³⁵S]GTP(S ASSAY)

μ-receptor: maximal stimulation = 89 ± 3% with EC_{50} = 154 ± 58 nM
δ-receptor: maximal stimulation = 27 ± 2% with EC_{50} = 302 ± 78 nM
κ-receptor: maximal stimulation =19 ± 7% with EC_{50} = 245 ± 54 nM

SUMMARY
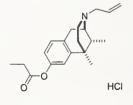
NIH 11050 has the same affinity for μ and δ receptors, but with no selectivity. It is approximately 7 times weaker at κ receptors. It is a relatively high efficacy agonist at μ receptors but has only low efficacy at δ and κ receptors. There is little selectivity in potency across the three receptors.

† Binding data previously reported in NIDA Monograph 183:179, 2003.

* * *

NIH 11052   (-)-(1R,5R,9R)-5,9-Dimethyl-2-(propenyl)-2'-proprionoxy-6,7-benzomorphan.HCl

HCl

OPIOID RECEPTOR BINDING (nM)⊥

μ-receptor: 107 ± 42
δ-receptor: 90.7 ± 15.4
κ-receptor: 7.9 ± 0.7

NIH 11052 (continued)

[^{35}S]GTPγS ASSAY

Agonist Activity

μ-receptor:	no stimulation up to 10 μM
δ-receptor:	no stimulation up to 10 μM
κ-receptor:	maximal stimulation = 37.3 ± 3.1% with EC_{50} = 147 ± 67nM
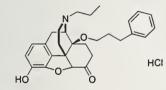
SUMMARY
NIH 11052 has high affinity for κ opioid receptors and is 12 times more selective for κ over μ or δ receptors. In the mouse and monkey, NIH 11052 was a μ antagonist, with weak antinociceptive properties in the mouse.†† The present findings show that the compound is likely to be a μ and δ antagonist with a partial agonist action at κ receptors, which would explain the weak antinociceptive properties observed in the mouse.

† Binding data previously reported in NIDA Monograph 183:180, 2003
†† NIDA Monograph 183:217, 2003

* * *

NIH 11053   17-Propyl-4,5α-epoxy-3-hydroxy-14-β-(3-phenylpropyloxy)morphinan-6-one.HCl

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.09 ± 0.05
δ-receptor: 0.93 ± 0.18
κ-receptor: 0.37 ± 0.17
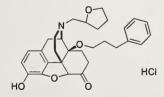
SUMMARY

NIH 11053 has very high affinity for all opioid receptors with selectivity ratios of κ/μ = 4 and δ/μ = 10.

* * *

NIH 11054   17-([2-*R*,*S*-Tetrahydrofuranyl)methyl)-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)
morphinan-6-one.HCl

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.20 ± 0.04
δ-receptor: 0.09 ± 0.02
κ-receptor: 0.08 ± 0.02
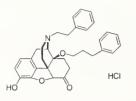
SUMMARY

NIH 11054 has very high affinity for all opioid receptors, but with no selectivity.

NIH 11055   17-Phenethyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl
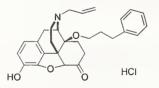

OPIOID RECEPTOR BINDING (nM)
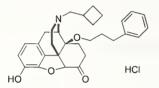
μ-receptor: 1.1 ± 0.4
δ-receptor: 1.25 ± 0.5
κ-receptor: 0.60 ± 0.2

SUMMARY

NIH 11055 has high affinity for all opioid receptors, but with no selectivity.

* * *

NIH 11057   17-Cyclobutylmethyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.25 ± 0.07
δ-receptor: 0.46 ± 0.16
κ-receptor: 0.49 ± 0.25

SUMMARY

NIH 11057 has very high affinity for all three opioid receptors.

* * *

NIH 11058   17-Cyclobutylmethyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl
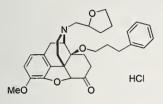
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.20 ± 0.01
δ-receptor: 0.26 ± 0.07
κ-receptor: 0.11 ± 0.05

SUMMARY

NIH 11058 has very high affinity for all three opioid receptors, but with no selectivity.

NIH 11059   17-[(2-*R,S*-Tetrahydrofuranyl)methyl]-4,5α-epoxy-3-methoxy-14β-(3-phenylpropyloxy) morphinan-6-one.HCl

OPIOID RECEPTOR BINDING (nM)
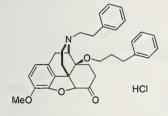
μ-receptor: 1.9 ± 0.38
δ-receptor: 5.4 ± 1.2
κ-receptor: 1.4 ± 0.67

SUMMARY

NIH 11059 has high affinity for all three opioid receptors.

*   *   *

NIH 11060   4,5α-Epoxy-3-methoxy-17-(2-phenyletheyl)-14β-(3-phenylpropyloxy)morphinan-6-one.HCl
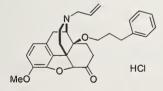

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3.8 ± 1.3
δ-receptor: 6.2 ± 0.2
κ-receptor: 61.4 ± 1.9

SUMMARY

NIH 11060 has high affinity for μ and δ receptors with 10- to 16-fold lower affinity for κ receptors.

*   *   *

NIH 11061   17-Allyl-4,5α-epoxy-3-methoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl
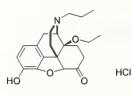
OPIOID RECEPTOR BINDING (nM)

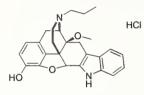μ-receptor: 1.7 ± 0.9
δ-receptor: 16.4 ± 5.2
κ-receptor: 4.1 ± 0.6

SUMMARY

NIH 11061 has high affinity for the three opioid receptors in the order μ > κ > δ.

141

NIH 11062 17-Allyl-4,5α-epoxy-3-methoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl
*********(CHECK FIGURE)*********

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1.6 ± 0.6
δ-receptor: 69.8 ± 21.2
κ-receptor: 6.13 ± 1.9

SUMMARY

NIH 11062 has high affinity for μ > κ receptors and δ receptor affinity. Its selectivity for μ receptors is 4-fold over κ and 44-fold over δ.

* * *

NIH 11063 4,5α-Epoxy-14β-ethoxy-3-hydroxy-17-(propyl)morphinan-6-one.HCl

OPIOID RECEPTOR BINDING (nM)⊥

μ-receptor: 270 ± 20.3
δ-receptor: 1.07 ± 0.18
κ-receptor: 108 ± 5.3

[^{35}S]GTPγS ASSAY

AGONIST ACTIVITY

No stimulation of [^{35}S]GTPγS binding was observed up to 10 μM.

ANTAGONIST ACTIVITY
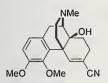
Ke (δ) = 0.24 ±0.05 nM

SUMMARY

NIH 11063 is a high affinity δ-antagonist. It is 100-fold selective for δ over κ and 250-fold selective for δ over μ in binding assays.

† Binding data previously reported in NIDA Monograph 183:180, 2003.

NIH 11065   5,6-Didehydro-14β-hydroxy-3,4-dimethoxy-17-methylmorphinan-6-carbonitrile
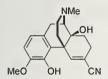

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 11.7 ± 1.0
δ-receptor: 342 ± 68
κ-receptor: 383 ± 89

SUMMARY

NIH 11065 has affinity for μ opioid receptors. It is 30-fold selective for μ receptors over κ receptors and δ receptors.

*   *   *

NIH 11066   5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 261 ± 30.4
δ-receptor: 3386 ± 138
κ-receptor: 4179 ± 629

SUMMARY

NIH 11066 has low affinity for the μ opioid receptor, but is 16-fold selective for μ over κ and 13-fold selective for μ over δ.

*   *   *

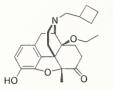**NIH 11067**   5,6-Didehydro-4-hydroxy-3,14β-dimethoxy-17-methylmorphinan-6-carbonitrile

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 22.3 ± 8.5
δ-receptor: 1006 ± 316
κ-receptor: 1480 ± 369

SUMMARY

NIH 11067 has μ receptor affinity with > 40-fold selectivity for the μ receptor compared with δ and κ receptors.

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NIH 11068   17-Cyclobutylmethyl-4,5α-epoxy-14β-ethoxy-3-hydroxy-5β-methymorphinan-6-one

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.47 ± 0.03
δ-receptor: 31.3 ± 9.3
κ-receptor: 6.1 ± 2.0

SUMMARY

NIH 11068 has very high μ receptor affinity with some (12-fold) selectivity over the κ receptor and 60-fold selectivity over the δ receptor.

* * *

NIH 11072   17-Cyclopropylmethyl-5,6-didehydro-14β-hydroxy-4-methoxymorphinan-6-carbonitrile
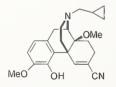

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 68.7 ± 21.6
δ-receptor: 2108 ± 434
κ-receptor: 93 ± 20

SUMMARY

NIH 11072 has approximately equal affinity for μ and κ receptors and 20-fold lower affinity for the δ receptor.

* * *

NIH 11073   17-Cyclopropylmethyl-5,6-didehydro-4-hydroxy-3,14β-dimethoxymorphinan-6-carbonitrile
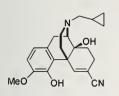

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 236 ± 14.6
δ-receptor: 1613 ± 370
κ-receptor: 411 ± 127

SUMMARY

NIH 11073 has low affinity for μ and κ receptors, with even lower affinity for δ receptors.

NIH 11074   17-Cyclopropylmethyl-5,6-didehydro-4,14β-dihydroxy-3-methoxymorphinan-6-carbonitrile

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 382 ± 25.5
δ-receptor: 4880 ± 881
κ-receptor: 368 ± 27

SUMMARY

NIH 11074 has low affinity for μ and κ receptors, with very low δ receptor affinity.

* * *

NIH 11075   17-Cyclopropylmethyl-5,6-didehydro-4,14β-dihydroxymorphinan-6-carbonitrile
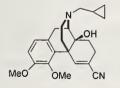

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 23.1 ± 6.1
δ-receptor: 405 ± 121
κ-receptor: 12.2 ± 5.5

SUMMARY

NIH 11075 has affinity for μ and κ receptors, with lower δ receptor affinity.

* * *

NIH 11076   17-Cyclopropylmethyl-5,6-didehydro-14β-hydroxy-3,4-dimethoxymorphinan-6-carbonitrile

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 40.9 ± 11.4
δ-receptor: 1138 ± 138
κ-receptor: 49 ± 15

SUMMARY

NIH 11076 has affinity for μ and κ receptors with low δ receptor affinity.

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NIH 11077 5,6-didehydro-4,14β-dihydroxy-17-methylmorphinan-6-carbonitrile

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3.8 ± 1.1
δ-receptor: 419 ± 92
κ-receptor: 408 ± 30

SUMMARY

NIH 11077 has high μ receptor affinity with 100-fold selectivity over the κ- and δ-opioid receptors.

* * *

NIH 11078 7-Hydroxymethyl-8-methyl-6,7,8,9,10,10a-hexahydro-1H-2-oxa-8-aza-cycloocta[c,d]inden-3-ol

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 22.4 ± 4.3% inhibition at 10 μM
δ-receptor: 22.6 ± 2.4% inhibition at 10 μM
κ-receptor: 27.0 ± 6.4% inhibition at 10 μM

SUMMARY

NIH 11078 has no affinity for opioid receptors.

* * *

NIH 11079 8-Methyl-6,7,8,9,10,10a-hexahydro-1H-2-oxa-8-aza-cycloocta[c,d]inden-3-ol
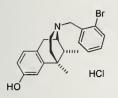

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 25.0 ± 2.5% inhibition at 10 μM
δ-receptor: 18.0 ± 9.0% inhibition at 10 μM
κ-receptor: 12.0 ± 2.5% inhibition at 10 μM

SUMMARY

NIH 11079 has no affinity for opioid receptors.

NIH 11081   (-)-(1*R*,5*R*,9*R*)- 2-(2-bromobenzyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM)⊥

μ-receptor: 40.2 ± 4.4
δ-receptor: 1227 ± 138
κ-receptor: 13.5 ± 2.0

[³⁵S]GTPγS ASSAY

Agonist Activity

No stimulation of [³⁵S]GTPγS binding was observed up to 10 μM.

SUMMARY

In binding assays, NIH 11081 has affinity for μ and κ receptors, but has no opioid effects in the mouse††. The present results suggest the compound to be a κ/μ antagonist with μ affinity 20-fold less than naloxone. This may explain the lack of observed in vivo activity.

†Binding data previously reported in NIDA Monograph 183:182, 2003.
†† NIDA Monograph 183:220, 2003

* * *

NIH 11082   (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM)†

μ-receptor: 10.2 ± 0.73
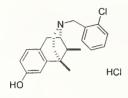δ-receptor: 140 ± 15.8
κ-receptor: 28.6 ± 4.5

[³⁵S]GTPγS ASSAY

Agonist Activity

μ-receptor: maximal stimulation = 50.5 ± 6.7% with EC_{50} = 303 ± 57
δ-receptor   maximal stimulation = 9.3 ± 4.7% with EC_{50} = 555 ± 149
κ-receptor: maximal stimulation = 21.7 ± 4.1% with EC_{50} = 1346 ± 514

SUMMARY

These data show that 11082 is a partial agonist at μ and κ receptors, but with low potency. It has almost no efficacy at δ receptors. These data help to explain why the compound is only active in the phenylquinone writing assay in mice††, but not in nociceptive tests using heat, even through the compound has high binding affinity.

† Binding data previously reported in NIDA Monograph 183:182, 2003
†† NIDA Monograph 183:221, 2003

NIH 11088   (+)-(1*S*,5*S*,9*S*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM) †

μ-receptor: 139 ± 33
δ-receptor: 3565 ± 1191
κ-receptor: 23.3 ± 2.4

[^{35}S]GTPγS ASSAY

Agonist Activity

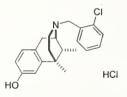NIH 11088 has no agonist activity at μ, δ, or κ opioid receptors.

SUMMARY

NIH 11088 has binding affinity for κ > μ > δ, with selectivity for κ over μ of 12-fold, but with no effects *in vivo* in the mouse††. It shows no agonism in the [^{35}S]GTPγS assay and may therefore be a κ antagonist with some selectivity.

† See NIDA Monograph 183:222, 2003)
†† See NIDA Monograph 184:190, 2004

* * *

NIH 11093   (-)-(1*R*,5*R*,9*R*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM) †

μ-receptor: 16.8 ± 2.1
δ-receptor: 600 ± 93
κ-receptor: 17.5 ± 5.4

[^{35}S]GTPγS ASSAY

Agonist Activity

No significant stimulation of [^{35}S]GTPγS binding was observed up to a concentration of 10 μM.

SUMMARY

In binding assays, NIH 11093 showed equal affinity for κ and μ, with low affinity for δ receptors. However, no activity as agonist or μ-antagonist was seen in the mouse or monkey. The present findings show that the compound has no agonist activity and is likely to be a μ/κ nonselective antagonist. However, the affinity values suggest that it will be approximately 10-fold less potent as a μ antagonist than naloxone. This may explain the lack of observed antagonist activity in vivo.

† Binding data previously reported in NIDA Monograph 183:184, 2003
†† NIDA Monograph 183:223, 2003

NIH 11095 (+)-(1*S*,5*S*,9*S*)- 5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy--6,7-benzomorphan.Oxalate

HO

$C_2H_2O_4$

OPIOID RECEPTOR BINDING (nM) †

μ-receptor: 560 ± 92
δ-receptor: 4129 ± 867
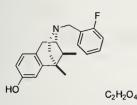κ-receptor: 47 ± 10.5

[^{35}S]GTPγS ASSAY

Agonist Activity

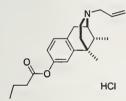No significant stimulation of [^{35}S]GTPγS binding was observed up to a concentration of 10 μM.

SUMMARY

In binding assays, NIH 11095 showed a 12-fold selectivity for κ over μ, with very low affinity for δ receptors. However, no activity as agonist or μ antagonist was seen in the mouse. †† The present findings show that the compound has no agonist activity and is likely to be an antagonist with a preference for the κ receptor. However, the affinity values suggest that it will be a weak antagonist.

† Binding data previously reported in NIDA Monograph 183:184, 2003.
††NIDA Monograph 183:223, 2003.

* * *

NIH 11096 (-)-(1*R*,5*R*,9*R*)- 2'-Butyroxy-5,9-Dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl

HCl

OPIOID RECEPTOR BINDING (nM)

μ receptor: 30.2 ± 13.5
δ receptor: 37.0 ± 1.7
κ receptor: 0.9 ± 0.05

[^{35}S]GTPγS ASSAY

Agonist Activity
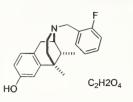
μ-receptor: maximal stimulation = 11 ± 7% with EC_{50} = 919 ± 685
κ-receptor: maximal stimulation = 74.4 ± 1.9% with EC_{50} = 66.1 ± 10.1

SUMMARY

NIH 11096 is a partial κ agonist with no significant μ efficacy. The binding affinity at the μ receptor suggests the compound would be a μ antagonist. These results are in keeping with the *in vivo* findings†† that the compound has μ and κ antagonist properties against high efficacy agonists.

† Binding data previously reported in NIDA Monograph 183:185, 2003
†† NIDA Monograph 184:193-194, 2004

OPIOID RECEPTOR BINDING (nM)⊥

μ-receptor: 23.3 ± 4.5
δ-receptor: 326 ± 40
κ-receptor: 2.1 ± 0.9

[^{35}S]GTPγS ASSAY

Agonist Activity

No stimulation of [^{35}S]GTPγS binding in C6 cells was observed.

Antagonist Activity

Ke (μ)   96.5 ± 17.4
Ke (κ)   17.4 ± 3.3

SUMMARY
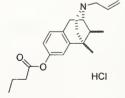
In binding assays, NIH 11097 showed a 10-fold selectivity for κ over μ. However, no activity as agonist or μ-antagonist was seen in the mouse. The present findings show that the compound is an antagonist at both μ and κ receptor with a small (~5-fold) preference for the κ receptor. However, the affinity (Ke) at μ receptors is approximately 10-fold less than that of naloxone, which may explain the previously reported lack of μ antagonist activity *in vivo*††. Alternatively, the lack of *in vivo* activity may relate to the pharmacokinetic profiles of the compound.

† Binding data previously reported in NIDA Monograph 183:185, 2003
†† NIDA Monograph 183:224, 2003

* * *

OPIOID RECEPTOR BINDING (nM) †

μ-receptor: 601 ± 10.8
δ-receptor: 3099 ± 405
κ-receptor: 1712 ± 167

[^{35}S]GTPγS ASSAY

Agonist Activity

μ-receptor: maximal stimulation = 17.8% with EC50 = 950 ± 307 nM
κ-receptor: no stimulation up to 10 μM

NIH 11098 (continued)
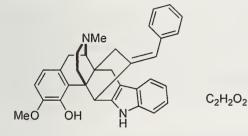
SUMMARY

NIH 11098 is a weak, very low efficacy μ agonist with no agonist activity at the κ receptor. The weak action in the PPQ assay in the mouse†† may be due to this μ activity, but could also be non-opioid.

† Binding data previously reported in NIDA Monograph 183:185, 2003.
†† NIDA Monograph 183: 224, 2003

* * *

NIH 11100   18-(*E*)-benzylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan.oxalate

$C_2H_2O_2$

OPIOID RECEPTOR BINDING (nM) †

μ-receptor: 41.8 ± 17.2
δ-receptor: 30.0 ± 3.6
κ-receptor: 60.0 ± 9.3

Agonist Activity

μ-receptor: no stimulation up to 10 μM
δ-receptor: maximal stimulation = $40.6 \pm 6.2\%$ with $EC_{50} = 463 \pm 38$ nM
κ-receptor: maximal stimulation = $64.0 \pm 18.7\%$ with $EC_{50} = 2063 \pm 324$ nM

SUMMARY
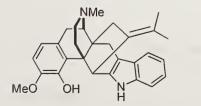
The binding affinity (Ki) of NIH 11100 is similar at all three receptors. However, its efficacy at the three receptors is different such that NIH 11100 is a partial agonist with low potency at δ receptors and very low potency at κ receptors. The results indicate that it would be a weak μ antagonist.

† See NIDA Monograph 184:156, 2004

* * *

NIH 11101   18-Isopropylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan.oxalate

$C_2H_2O_2$

OPIOID RECEPTOR BINDING (nM) †

μ-receptor: 267 ± 18
δ-receptor: 148 ± 33
κ-receptor: 158 ± 51

NIH 11101 (continued)

[^{35}S]GTPγS ASSAY

Agonist Activity

μ-receptor: maximal stimulation = 63.6 ± 3.1 with EC$_{50}$ = 2126 ± 587 nM (n=2)
δ-receptor: no stimulation up to 10 μM
κ-receptor: no stimulation up to 10 μM
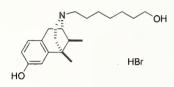
SUMMARY

NIH 11101 is a weak partial agonist at μ receptors. From its binding profile, it is also likely to be a low affinity δ/κ antagonist.

† Binding data previously reported in NIDA Monograph 184:156, 2004

* * *

NIH 11128   (+)-(1*S*,5*S*,9*S*)-5,9-dimethyl-2'-Hydroxy-2-(7-hydroxyheptyl)- 6,7-benzomorphan.HBr

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 907 ± 112
δ-receptor: 5822 ± 3500
κ-receptor: 1789 ± 379
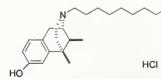
SUMMARY

NIH 11128 has very low affinity for μ, δ, and κ receptors.

* * *

NIH 11140   (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 136 ± 13.5
δ-receptor: 204 ± 33
κ-receptor: 449 ± 104
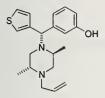
SUMMARY

NIH 11140 has low affinity for μ, δ, and κ opioid receptors nor is there evidence of selectivity.

NIH 11161   (-)-3-{(S)-[(2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl](3-thienyl)methyl}phenol

Four doses of NIH 11161 were evaluated in four rhesus monkeys. Each animal was tested at least twice per dose. This compound generated an inverted-U shaped dose-response curve (see rates in Table 1), and was self-administered by all four animals studied.

Table 1 shows absolute response rates (± SEM) for alfentanil and NIH 11161 self-administration, as well as their appropriate vehicles, aggregated across all four animals. Rates of response for NIH 11161 were high across a dose range approximately 30-fold higher than that required to engender contingent responding for alfentanil. The maximal rate of responding for NIH 11161 (at 0.01 mg/kg/inj) peaked at approximately 70% of alfentanil control, although rates for all doses tested were higher than those engendered by contingent saline or the NIH 11161 vehicle. By way of comparison, NIH 11661 is thus 30-fold less potent and 30% less effective than alfentanil in terms of reinforcing effects.

Dose (mg/kg/inj)	0.00003	0.0001	0.0003	0.001
Alfentanil	0.27 ± 0.13	0.95 ± 0.22	2.23 ± 0.48	2.06 ± 0.61
Saline	0.21 ± 0.11	0.20 ± 0.09	0.22 ± 0.14	0.14 ± 0.10

Dose (mg/kg/inj)	0.001	0.003	0.01	0.03
NIH11161	0.58 ± 0.34	1.33 ± 0.54	1.69 ± 0.47	0.45 ± 0.12
Vehicle	0.08 ± 0.03	0.14 ± 0.06	0.11 ± 0.08	0.08 ± 0.05

Table 1 – Response rates (responses per second) for alfentanil, NIH11161, and their infusion volume control vehicles across four doses (in mg/kg/inj) and expressed as mean ± SEM. Data were aggregated across four experimental subjects, and each dose condition was studied at least twice.

* * *

NIH 11163   (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(5-hydroxypentyl)-6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM)
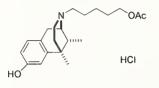
μ-receptor: 45 ± 2.0% displacement at 10 μM
δ-receptor: 10.3 ± 1.2% displacement at 10 μM
κ-receptor: 13.5 ± 6.5% displacement at 10 μM

SUMMARY

NIH 11163 has no affinity for opioid receptors.

NIH 11164   (-)-(1*R*,5*R*,9*R*) -2-(5-Acetoxypentyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM)
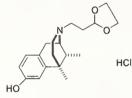
μ-receptor: 7.3 ± 2.9
δ-receptor: 140 ± 27
κ-receptor: 55.3 ± 4.2

SUMMARY

NIH 11164 has high affinity for μ receptors and some selectivity for μ over κ (7-fold) and δ (20-fold) receptors.

* * *

NIH 11176   (-)-(1*R*,5*R*,9*R*)- 5,9-Dimethyl-2-(1,3-dioxalanylethyl)- 2'-hydroxy-6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 26.6 ± 9.5
δ-receptor: 53.4 ± 5.9
κ-receptor: 41.9 ± 15.6
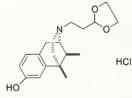
SUMMARY

NIH 11176 has affinity for all three opioid receptors with no selectivity.

* * *

NIH 11177   (+)-(1*S*,5*S*,9*S*)- 5,9-Dimethyl-2-(1,3-dioxalanylethyl)- 2'-hydroxy-6,7-benzomorphan.HCl
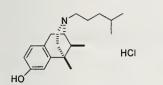
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 673 ± 95
δ-receptor: 8734 ± 2570
κ-receptor: 642 ± 70

SUMMARY

NIH 11177 has low, but equivalent, affinity for μ and κ opioid receptors and very low affinity for δ opioid receptors.

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NIH 11178   (+)-(1*S*,5*S*,9*S*)- 5,9-Dimethyl-2'-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM)
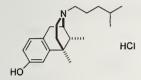
μ-receptor: 613 ± 163
δ-receptor: 6072 ± 4320
κ-receptor: 260 ± 83

SUMMARY

NIH 11178 has low affinity for μ and κ opioid receptors. It has very low affinity for δ opioid receptors.

* * *

NIH 11179   (-)-(1*R*,5*R*,9*R*)- 5,9-Dimethyl-2'-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 6.0 ± 1.2
δ-receptor: 59. ± 5.1
κ-receptor: 7.3 ± 2.2
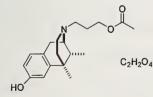
SUMMARY

NIH 11179 has high affinity for μ and κ opioid receptors, with 8- to 10-fold selectivity for these receptors over δ.

* * *

NIH 11180   (-)-(1*R*,5*R*,9*R*)- 2-(3-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate
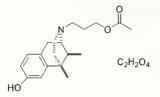
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 33.7 ± 1.8
δ-receptor: 285 ± 14
κ-receptor: 24.9 ± 3.7

SUMMARY

NIH 11180 has similar affinity for μ and κ opioid receptors with approximately 10-fold selectivity for these receptors over δ.

NIH 11181   (+)-(1*S*,5*S*,9*S*)- 2-(3-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate

C$_2$H$_2$O$_4$

OPIOID RECEPTOR BINDING (nM)
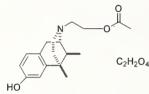
μ-receptor: 4478 ± 358
δ-receptor: 5% inhibition at 10 :M
κ-receptor: 4141 ± 778

SUMMARY

NIH 11181 has similar, very low affinity for μ and κ opioid receptors with no affinity for δ receptors.

* * *

NIH 11182   (+)-(1*S*,5*S*,9*S*)-2-(3-Acetoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate

C$_2$H$_2$O$_4$

OPIOID RECEPTOR BINDING (nM)
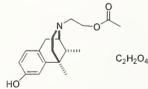
μ-receptor: 1951 ± 198
δ-receptor: 22% inhibition at 10 μM
κ-receptor: 1830 ± 269

SUMMARY

NIH 11182 has similar, very low affinity for μ and κ opioid receptors. It shows no appreciable binding to δ receptors.

* * *

NIH 11183   (-)-(1*R*,5*R*,9*R*)- 2-(3-Acetoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate

C$_2$H$_2$O$_4$
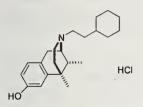
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 42.6 ± 6.9
δ-receptor: 421 ± 41
κ-receptor: 60.1 ± 17

SUMMARY

NIH 11183 has similar affinity for μ and κ opioid receptors, with low affinity for δ receptors.

NIH 11185   (-)-(1*R*,5*R*,9*R*)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

HCl

HO

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 4.3 ± 0.8
δ-receptor: 42.8 ± 5.1
κ-receptor: 51.0 ± 15.5
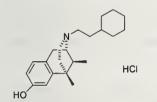
SUMMARY

NIH 11185 has high affinity for μ opioid receptors and is 10- to 12-fold selective over δ and κ receptors.

* * *

NIH 11186   (+)-(1*S*,5*S*,9*S*)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

HCl

HO

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 142 ± 10.5
δ-receptor: 2793 ± 430
κ-receptor: 215 ± 246
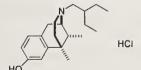
SUMMARY

NIH 11186 has similar, low affinity for μ and κ opioid receptors and very low affinity for δ receptors and very low affinity for δ receptors.

***

NIH 11187   (-)-(1*R*,5*R*,9*R*)-2-(2-Ethylbutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

HCl

HO

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 9.2 ± 0.8
δ-receptor: 58.2 ± 4.7
κ-receptor: 5.9 ± 0.3

SUMMARY

NIH 11187 has high affinity for μ and κ opioid receptors and low affinity for δ receptors. It has no selectivity between μ and κ.

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AFFILIATION

The Drug Abuse Basic Research Program, Departments of Pharmacology and Psychology, University of Michigan, Ann Arbor, MI 48109-0632.

DEPENDENCE STUDIES OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (2004)

M.D. Aceto, E.R. Bowman, L.S. Harris, L.D. Hughes, B. R. Kipps, S. L. Lobe, and E.L. May

Department of Pharmacology and Toxicology, School of Medicine, Virginia Commonwealth University, Richmond, VA

When originally submitted by the Biological Coordinator, Dr. Andrew Coop of the University of Maryland, School of Pharmacy, the identity of all the compounds was unknown to us. These studies were conducted under the auspices of the Drug Evaluation Committee in association with the College on Problems of Drug Dependence. See summary of new data in Table 1. All animals received care according to the "Guide for the Care and Use of Laboratory Animals" (1996). These facilities are certified by the American Association for the Accreditation of Laboratory Animal Care (AAALAC).

Dependence-Liability Studies in Rhesus Monkeys

Substitution-for-morphine (SDS) Test. Male and female rhesus monkeys (M. mulatta) weighing 2.5-7.5 kg were used, and they received 3 mg/kg, s.c., of morphine SO_4 every 6 hr. All the animals had received morphine for at least 3 months and were maximally dependent on morphine (Seevers and Deneau 1963). A minimal 2-week recuperation period was allowed between tests. Unless otherwise noted, at least 3 monkeys/dose were used. The assay (Aceto and co-workers, 1977 and 1978) was initiated by a subcutaneous injection of the test drug or control substances (morphine and vehicle) into animals in a group that had not received morphine for 14-15 hr and showed definite signs of withdrawal. Each animal was randomly chosen to receive one of the following treatments: a) a dose of the compound under investigation; b) morphine control, 3.0 mg/kg; and c) vehicle control, 1 ml/kg. The animals were scored for suppression of withdrawal signs during a 2.5-hr observation period. The observer was "blind" regarding the assignment of treatments. The mean cumulative score ± SEM was calculated and the data illustrated in figure form. If indicated, the data were analyzed using the Kruskal-Wallis ANOVA and post hoc Mann-Whitney U-Tests.

Precipitated-Withdrawal (PPT-W) Test. This evaluation was done under the same conditions as described above, except that the animals were administered a test compound 2-3 hr after the last dose of morphine. These animals were not then in withdrawal. Naloxone·HCl (0.05 mg/kg, s.c.) served as the positive control.

Table 1. List of NIH compounds included in this report as well as an indication of the tests that were conducted on each compound.

NIH #.	CHEMICAL NAME OR GENERIC CLASS	MOUSE DATA				MONKEY DATA	
		TF	TF vs M	PPQ	HP	SDS	PPT-W
11028	3-O-methylnaltrexone	T [a,b]	T	T	T	T	T
11037	3-O-Cinnamoylnaltrexone	T [c,d]	T [e]	T	T		T
11053	4,5-Epoxymorphinan-6-one	T	T [f]	T	T		
11054	4,5-Epoxymorphinan-6-one	T [g]	T	T	T		
11055	4,5-Epoxmorphinan-6-one	T	T	T	T		
11056	4,5-Epoxmorphinan-6-one	T	T	T	T	T	
11057	4,5-Epoxymorphinan-6-one	T	T	T	T		
11058	4,5-Epoxymorphinan-6-one	T	T	T	T		
11059	4,5-Epoxymorphinan-6-one	T [g]	T	T	T		
11060	4,5-Epoxymorphinan-6-one	T	T	T	T		
11062	4,5-Epoxymorphinan-6-one	T	T	T	T		
11065	Morphinan-6-carbonitrile	T	T	T	T	T	
11066	Morphinan-6-carbonitrile	T	T	T	T	T	
11067	Morphinan-6-carbonitrile	T	T	T	T	T	
11068	4,5-Epoxymorphinan-6-one	T	T	T	T		
11072	Morphinan-6-carbonitrile	T	T	T	T		
11073	Morphinan-6-carbonitrile	T	T	T	T		
11074	Morphinan-6-carbonitrile	T	T	T	T		
11075	Morphinan-6-carbonitrile	T	T	T	T		
11076	Morphinan-6-carbonitrile	T	T	T	T		
11077	Morphinan-6-carbonitrile	T	T [h]	T	T		
11082	6,7-Benzomorphan	T [i]	T [j]	T	T	T	
11086	Dynorphan analog	T	T	T	T		
11087	Dynorphan analog	T	T	T	T		
11090	Enkephalin analog	T	T	T	T		
11091	Enkephalin analog	T	T	T	T		
11097	6,7-Benzomorphan	T [k]	T	T	T	T	
11098	6,7-Benzomorphan	T	T	T	T	T	
11106	N'-Benzyloxymorphindole	T	T [l]	T	T		
11109	O-Butyrylnaltrexone	T	T	T	T	T	
11111	6,7-Benzomorphan	T	T [m]	T	T	T	
11112	6,7-Benzomorphan	T	T	T	T	T	
11113	6,7-Benzomorphan	T	T	T	T		
11114	6,7-Benzomorphan	T	T [n]	T	T	T	
11127	6,7-Benzomorphan	T	T	T	T	T	
11139	6,7-Benzomorphan	T	T	T	T	T	
11140	6,7-Benzomorphan	T	T	T	T	T	
11164	6,7-Benzomorphan	T	T	T	T		
11165	6,7-Benzomorphan	T	T	T	T		
11166	6,7-Benzomorphan	T	T	T	T		
11167	6,7-Benzomorphan	T	T	T	T		
11168	6,7-Benzomorphan	T	T	T	T		
11176	6,7-Benzomorphan	T	T	T	T	T	
11179	6,7-Benzomorphan	T	T	T	T	T	

Table 1. (continued)

11180	6,7-Benzomorphan	T	T	T	T		T
11181	6,7-Benzomorphan	T	T	T	T		
11182	6,7-Benzomorphan	T	T	T	T	T	
11183	6,7-Benzomorphan	T	T	T	T	T	
11185	6,7-Benzomorphan	T	T	T	T	T	
11186	6,7-Benzomorphan	T	T	T	T	T	
11187	6,7-Benzomorphan	T	T	T	T	T	

T = Test Performed

[a]Special: NIH 11028 (p.o.) vs morphine in TF; naltrexone and NIH 11028 (6 hr pretreatment) vs ED80 of morphine in TF; [b]Special: Naloxone (p.o.) vs ED80 of NIH 11028 in TF; [c,d]Special: Naltrexone and NIH 11037 vs ED80 of morphine in TF, [e]AD50 of NIH 11037 vs ED80 of DPDPE in PPQ; [f]Special: NIH 11053 vs β-FNA, nor-BNI and naltrindole In PPQ; [g]Special: Naloxone vs NIH 11054 in TF; Naloxone vs NIH 11159 in TF. [h]Special: Naltrindole vs ED80 of NIH 11077 in PPQ. [i]Special time-course for NIH 11082 in PPQ, co-administration of NIH 11082 and morphine in PPQ. [j]Naltrindole, nor-BNI and β-FNA vs ED80 of NIH 11082 in PPQ; [k]Enadoline vs ED80 of NIH 11097 in TF; [l]Naloxone vs ED80 of NIH 11106 in PPQ; mNor-BNI vs ED80 of NIH 11111 in PPQ; nNor-BNI vs ED80 of NIH 11114 in PPQ.

Primary-Physical-Dependence (PPD) Study. Drug-naive monkeys were medicated with drug, using escalating dose regimens, periodically challenged with naloxone or placed in abrupt withdrawal. They were observed for overt behavioral signs during drug administration and when they were challenged with the antagonist, naloxone, or abruptly withdrawn from the drug.

Rat-Infusion Studies

The continuous-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Rats were anesthetized after which each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted into the peritoneal cavity. The cannula was anchored at both ends with nylon sutures and attached to a flow-through swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7-10 ml of solution every 24 hr.

Substitution-for-Morphine (SM) Test. The rats received morphine·SO_4 (50 mg/kg/24 hr on the first day, 100 mg/kg/24 hr on the second day, and 200 mg/kg/24 hr from days 3 and 4). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of sterile water for injection. The animals were observed for changes in body weight and for behavioral-withdrawal signs for 0.5 hr at 6, 24, 48, 72 and/or 96 hr after stopping the infusion of morphine.

Primary-Physical-Dependence (PPD) Study. The rats received test compound, as specified above, for 4-6 days and then, were placed in abrupt withdrawal and observed for overt behavioral signs.

Mouse-Antinociception Tests

Male mice, weighing 20-30 g, were used. All drugs were dissolved in distilled water or in the vehicle indicated and injected subcutaneously (s.c.). At least three doses were tested, and 6-10 animals per dose were used. When applicable, ED50's or AD50's were calculated by using computerized probit analysis (Bliss, 1967). The results obtained with reference compounds are summarized in Table 2. Occasionally, when requested, drugs were given orally (p.o.) or intravenously (i.v.), intracerebroventricular (i.c.v) and the pretreatment times are indicated in the text.

Tail-Flick (TF) and (TF vs M) Assays. The procedure and modifications were described (D'Amour and Smith, 1941 and Dewey et al., 1970 and 1971) in the literature. Briefly, the mouse's tail was placed in a groove which contained a slit under which was located a photoelectric cell. When the heat source or noxious stimulus was turned on, it focused on the tail, and the animal responded by flicking its tail out of the groove. Thus, light passed though the slit and activated the photocell which, in turn, stopped the recording timer. The heat source was adjusted to produce tail flick of 2-4 sec under control conditions. Mice were injected with drug or vehicle and tested 20 min later. In the assays for antagonism of the antinociceptive effect, the potential antagonists were administered 10 min before the agonist, and evaluation occurred 20 min later.

Phenylquinone Abdominal-Stretching (PPQ) Assay. The procedure was reported previously (Pearl and Harris, 1966). The mice were injected with test drug and 10 min later received 2.0 mg/kg intraperitoneally (i.p.) of a freshly prepared paraphenylquinone (PPQ) solution. The mice were then placed in cages in groups of three each. Ten min after the PPQ injection, the total number of stretches per group were counted over 1-min periods. A stretch was characterized by an elongation of the mouse's body, development of tension in the abdominal muscles, and extension of the hindlimbs. The antinociceptive response was expressed as the percent inhibition of the PPQ-induced stretching response.

Hot-Plate (HP) Assay. The method was also reported previously (Eddy and Leimbach, 1953 and Atwell and Jacobson, 1978). The hot plate was held at 56°C. Mice were placed on the hot plate and activity was scored if the animal jumped, lifted its back feet, or licked its front paws.

Table 2

Comparative Data (ED50, mg/kg s.c.) [95% C.L.] of Selected Standards in 4 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick	Tail-Flick Antagonist	Phenylquinone	Hot-Plate
Pentazocine	15% at 10.0	18 (12 - 26)	1.7 (1.0 - 2.5)	13% at 30.0
Cyclazocine	17% at 1.0[a]	0.03 (0.02 - 0.78)	0.01 (0.005 - 0.03)	25% at 9.0
Nalorphine·HCl	None at 10.0	2.6 (0.7-1.0)	0.6 (0.03 - 1.44)	13% at 30.0
Naloxone·HCl	None at 10.0	0.04 (0.0 - 0.09)	No Activity	- - - -
Naltrexone·HCl	None at 10.0	0.007 (.002 - 0.02)	No Activity	- - - -
Morphine·S0$_4$[b]	1.92 (0.89 - 4.14)	Inactive	0.4[b] (0.2-0.8)	0.85 (0.39 -1.86)
Codeine·P0	17.5 (15.4 - 19.9)	Inactive	8.2 (5.12 -13.29)	6.4 (2.4 -16.8)
Meperidine·HCl	8.4 (4.6 - 15.23)	Inactive	2.2 (1.7 - 2.9)	4.6 (1.2 - 11.7)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but there was no further increase in reaction time
[b]ICR - Harlan-Sprague-Dawley Inc.

Calculation of Apparent pA2 . Using the tail-flick or PPQ assay, the apparent pA$_2$ and 95% confidence limits were calculated using Schild and constrained plots as described in Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 2nd ed., Springer Verlag, NY, 1987).

Briefly, mice were pretreated with vehicle or various doses of antagonist followed 10 min later by an injection of agonist. The mice were tested 30 min after receiving the antagonist. Dose-response lines for antinociception were plotted using at least 3 doses of each opioid agonist in the presence of vehicle or one of the selected doses of antagonist. ED5Os were estimated according to the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Ther., 96, 399, 1949). Each dose ratio (x) was calculated by dividing the ED50 of the opioid in the presence of a given dose of antagonist by that of the agonist alone. Log (x - 1) was plotted against the negative logarithm of the molar dose of the antagonist. At least 3 logs (x - l) were plotted. The pA$_2$ values for the antagonists were calculated from the point of intersection of the regression line with the abscissa. See Table 3 for summary of results.

Table 3. Apparent pA_2 values[a] using the mouse tail-flick assay

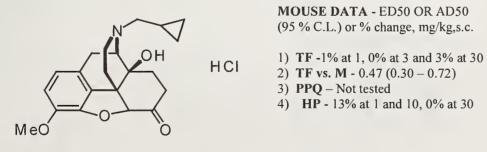| Treatment Antagonist/Agonist	Schild Plot pA_2 (95% C.L.) Slope	Constrained Plot pA_2(95% C.L.)
1) Naloxone/Morphine	7.2 (7.0-7.4)-1.2	7.3 (7.1 - 7.6)
2) Naloxone/Sufentanil	7.0 (6.5 - 7.5)-1.0	7.0 (6.8 - 7.1)
3) Naloxone/Mirfentanil	7.6 (7.3 - 8.0)-0.7	7.2 (6.9 - 7.5)
4) Naloxone/NIH 10672 (Enadoline) (selective kappa agonist)	6.1 (5.6 - 6.6)-1.2	6.6 (6.3 - 7.0)
5) Naloxone/U-50,488 (kappa agonist)	6.6 (6.3 - 6.9)-1.1	6.2 (5.9 - 7.3)
6) Naloxone/(-)-Nicotine	5.3 (5.3-5.3)-0.5	-
7) Nalmefene/Morphine	8.0 (7.6 - 8.3)-1.1	8.0 (7.7 - 7.6)
8) Naltrexone/Morphine	7.7 (4.9 - 10.5)-0.8	7.6 (7.1 - 8.3)
9) (-)-Quadazocine/Morphine	6.8 (6.7 - 7.0)-0.9	6.8 (6.1 - 7.6)
10) (-)-Quadazocine/Enadoline	6.2 (6.1 - 6.2)-1.7	6.7 (6.6 - 6.8)
11) nor BNI/Enadoline	6.5 (5.9 - 7.0)-1.3	6.6 (5.9 - 7.3)
12) Mecamylamine/(-)-Nicotine	6.6 (6.2 - 6.9)-0.9	-

[a]Negative logarithm of the molar concentrations of antagonist required to produce a two-fold shift of the agonist dose-response curve to the right. Competitive antagonism can be assumed when slope = -1. pA_2 provides a measure of the relative potency and affinity of the antagonist. When the slope differs significantly from unity, this may indicate non-equilibrium conditions, interactions with multireceptors, receptor sensitization, precoupling mechanisms, or multiple drug properties. With a constrained plot, the slope of the regression line is restricted to slope of - 1.

Special Intracerebroventricular (i.c.v.) Tail-Flick and PPQ Assays. In order to develop an in-vivo agonist and antagonist model to correlate with the in-vitro binding data of the various opioid receptor types (mu, kappa and delta), we chose the mouse Tail-Flick and PPQ tests and a variety of routes of administration. The intracerebroventricular (i.c.v.) route was chosen to test drugs that did not cross the blood-brain barrier.

Special in vivo opioid agonist and antagonist subtype testing. To further characterize an opioid, special subtype testing is conducted. Compounds are tested for mu, kappa and delta opioid agonist and antagonist properties using the opioid selective agonists sufentanil (mu), enadoline (kappa) and/or DPDPE (delta) and the selective opioid antagonists beta-funaltrexamine (mu), nor-binaltorphamine(kappa) and/or naltrindole(delta).

NIH 11028 3-O-Methylnaltrexone.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** -1% at 1, 0% at 3 and 3% at 30
2) **TF vs. M** - 0.47 (0.30 – 0.72)
3) **PPQ** – Not tested
4) **HP** - 13% at 1 and 10, 0% at 30

Special Tests: 1) NIH 11028 (p.o.) vs ED80 of morphine (s.c.) in TF: AD50 = 2.31 (1.73 –3.09)

Note: Naloxone (p.o.) AD50 vs ED80 of morphine (s.c.): 1.44 (0.51 – 4.03)

Table 1. Naltrexone (AD50) and NIH 11028 (ED50) versus ED80 mu-, kappa-, and delta-opioid agonists in TF test.

	Enadoline	Enadoline	Sufentanil	Sufentanil	DPDPE	DPDPE
Naltrexone (AD 50) versus 80% response of Opioid Agonists						
		(repeat)		(repeat)		(repeat)
AD_{50}	0.523	0.552	0.003	0.013	0.062	0.045
range	(0.162 -1.687)	(.265 - 1.028)	(0.001 - 0.009)	(0.004 - 0.039)	(0.023 - 0.171)	(0.033 - 0.062)

	Enadoline	Sufentanil	DPDPE
NIH 11028 (AD50) *vs* 80% Response of Opioid Agonists			
AD_{50}	5.44	0.121	1.77
range	(1.58 - 18.69)	(0.033 - 0.448)	(1.15 - 2.73)

MONKEY DATA (SDS)

As shown in the figure below, at doses of 4 and 16 mg/kg, NIH 11028 neither attenuated withdrawal nor substituted for morphine in rhesus monkeys. Instead, it exacerbated withdrawal in a dose dependent manner.
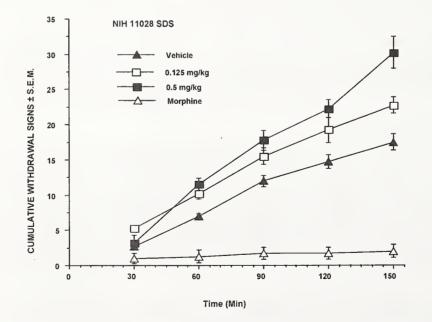
Fig NIH 11028-SDS. Results of study in which single doses of NIH 11028 were substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 11028 (continued)

MONKEY DATA (PPt-W)

NIH 11028 precipitated abstinence signs in monkeys dependent on morphine. Its action was dose related. However, the drug is much less potent than naloxone, The drug acted promptly and its duration of action was longer than that of naloxone. Potency estimate was about 1/20 that of naloxone, the reference standard.
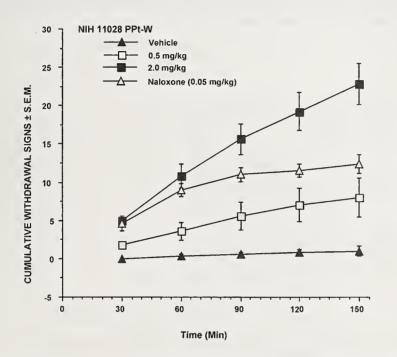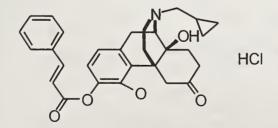
Fig. NIH 11028-PPt-Withdrawal. Results of study in which morphine-dependent monkeys were given single doses of NIH 11028 two hr after morphine.

Comment: The results show that NIH 11028 is a much weaker mu-, kappa- and delta-opioid receptor antagonist than naltrexone. Duration of action is waning at 6 hr.

NIH 11037 3-O-Cinnamoylnaltrexone.HCl

HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30[a]
2) **TF vs. M** - 0.013 (0.003 - 0.04) 30 min
3) **PPQ** - Inactive at 30[a]
4) **HP** - 13% at 30[a]

Special 4-hr pretreatment study (s.c.): Naltrexone and NIH 11037 (AD50s) vs morphine.

Naltrexone	NIH 11037
AD50 = 1.92 (0.69 - 5.31)	2.69 (0.99 - 7.30)

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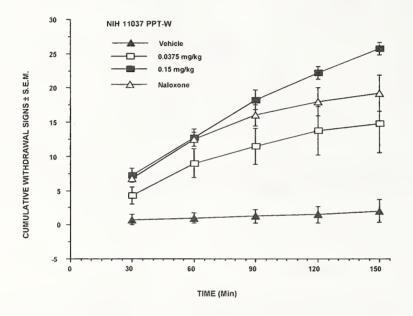
NIH 11037 (continued)

Opioid subtype testing (kappa antagonist):

AD50 vs ED80 of enadoline, a kappa agonist = 0.196 (0.045 - 0.849).

MONKEY DATA (PPT-W)
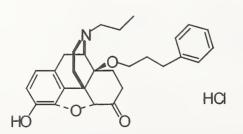
NIH 11037 precipitated withdrawal in morphine-dependent monkeys at doses of 0.03 and 0.15 mg/kg. As shown in the accompanying figure, this drug appeared to be more potent than naloxone, the reference standard. Onset of action was rapid and offset seemed longer than that of naloxone.

Fig. NIH 11037 Results of study in which NIH 11037 was administered to morphine-dependent monkeys (PPT-W).

Comment: Based on the results of studies in mice and morphine-dependent monkeys, we conclude that NIH 11037 is a potent mu- and kappa-opioid receptor antagonist. Whether or not this drug also has delta-opioid receptor antagonist activity remains to be determined.

NIH 11053 17-Propyl-4,5α-epoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.
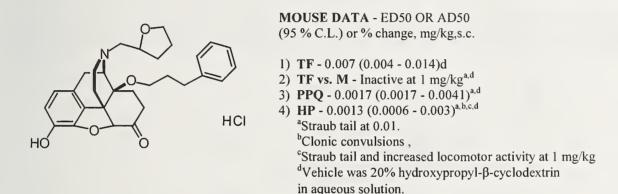
1) **TF** - 0.0016 (0.0009 - 0.0027)[a],[d]
2) **TF vs. M** - Inactive at 1[a],[b,d]
3) **PPQ** - 0.0009 (0.0005 - 0.0017)[a,d]
4) **HP** - 0.0017 (0.0008 - 0.0036)[a,b,c]
    [a]Straub tail at 0.003 mg/kg.
    [b]Increased locomotor activity.
    [c]Clonic convulsions at 10 mg/kg, 2/6 died.
    [d]Vehicle was 15% hydroxypropyl-β-cyclodextrin in water.

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Opioid subtype testing:

a) β-FNA (i.c.v.) vs ED80 of NIH 11053 (s.c.,) in TF test: AD 50 = 6.48 (2.3 - 18) μg/brain.

b) nor-BNI (s.c.,) vs ED80 of NIH 11053) in TF test: Inactive at 1, 10 and 30.

c) Naltrindole (s.c.,) vs ED80 of NIH 11053,) in TF test: Inactive at 1, 10 and 30.
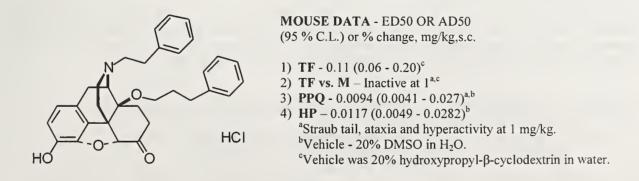
Comment: The results indicate that NIH 11053 is a very potent opioid with mu-receptor selective activity.

NIH 11054 17-([2-R,S-Tetrahydrofuranyl)methyl)-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.007 (0.004 - 0.014)d
2) **TF vs. M** - Inactive at 1 mg/kg[a,d]
3) **PPQ** - 0.0017 (0.0017 - 0.0041)[a,d]
4) **HP** - 0.0013 (0.0006 - 0.003)[a,b,c,d]
   [a]Straub tail at 0.01.
   [b]Clonic convulsions ,
   [c]Straub tail and increased locomotor activity at 1 mg/kg
   [d]Vehicle was 20% hydroxypropyl-β-cyclodextrin
   in aqueous solution.

Special Test: Naloxone vs ED80 NIH 11054 in TF: AD50 = 0.14 (0.06 - 0.30).
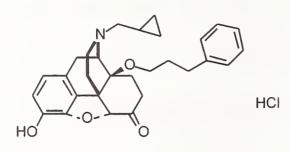
Comment: NIH 11054 is a very potent opioid with mu-receptor agonist properties. Onset of action was prompt.

NIH 11055 17-(2-Phenethyl)-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

HCl

**MOUSE DATA** - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.11 (0.06 - 0.20)[c]
2) **TF vs. M** – Inactive at 1[a,c]
3) **PPQ** - 0.0094 (0.0041 - 0.027)[a,b]
4) **HP** – 0.0117 (0.0049 - 0.0282)[b]
   [a]Straub tail, ataxia and hyperactivity at 1 mg/kg.
   [b]Vehicle - 20% DMSO in H_2O.
   [c]Vehicle was 20% hydroxypropyl-β-cyclodextrin in water.

Comment: NIH 11055 has potent opioid-agonist activity. Mu-receptor properties of rapid onset are indicated.

NIH 11056 17-2-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14β-(3- phenylpropyloxy)morphinan-6-one.HCl

HCl

MOUSE DATA - ED50 OR AD50 AD,
(95% C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.0032 (0.0016 - 0.0062).[a,]
2) **TF vs. M** - 14% at 1, 18% at 10 and 47% at 30.[a,b,c,d]
3) **PPQ** - 0.0062 (0.0031 -0.0125).[a,b,d]
4) **HP** - 0.0023 (0.0011 - 0.0047).[a,b]
   [a]Vehicle was 1% lactic acid aqueous solution
   [b]Straub tail and increased locomotor activity at 0.1
   [c]Mild Straub tail at 0.01
   [d]Mild Sedation at 10 and heavy sedation at 30

MONKEY DATA (SDS)

As depicted in the figure, NIH 11056 substituted completely for morphine at 0.04 mg/kg s.c. Potency estimate is approximately 100 times that of morphine sulfate. Jaw sag and scratching were noted in 1 monkey receiving 0.02 mg/kg s.c.
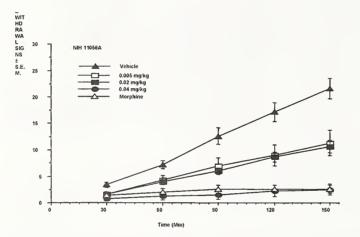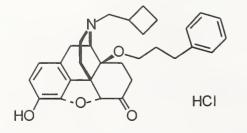
Fig NIH 11056 SDS. Results of study in which single doses of NIH 11056 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: The mouse data indicated that NIH 11056 is a potent opioid agonist with prominent mu-opioid receptor properties. Potency estimate is approximately 3000 times that of morphine sulfate. In the monkey, NIH 11056 substituted completely for morphine with a potency estimate of 100 times that of morphine sulfate.

NIH 11057 17-Cyclobutylmethyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

HCl
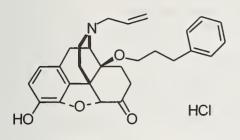
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.0082 (0.0034 - 0.02)[a,b]
2) **TF vs. M** - Inactive at 1[b]
3) **PPQ** - 0.0003 (0.00002 - 0.006)[a,b]
4) **HP** - 0.0037 (0.0008 - 0.0172)[b]
[a]Straub tail, ataxia and increased locomotor activity.
[b]Vehicle was 20% DMSO (dimethylsulfoxide) aqueous solution.

Comment: The results suggest that NIH 11057 has very potent opioid agonist activity with a mu-opioid component. The drug acts promptly.

NIH 11058 17-Allyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.0056 (0.003 - 0.011)[a,b]
2) **TF vs. M** - Inactive at 1[b]
3) **PPQ** - 74% at 0.003, 42% at 0.005, 39% at 0.01, 95% at 0.021 and 100% at 0.03 and 1[a,b]
4) **HP** - 0.0059 (0.0037 - 0.0094)[b]
   [a]Straub tail and increased locomotor activity at 1 mg/kg
   [b]Vehicle - 20% hydroxypropyl-β-cyclodextrin plus sonication

Comment: There was an erratic dose-response in the PPQ test. Overall, the results indicate that NIH 11058 has potent opioid agonist properties and that mu-opioid receptor system is involved.

NIH 11059 17,[(2-R,S-Tetrahydrofuranyl)methyl]-4,5α-epoxy-3-methoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl
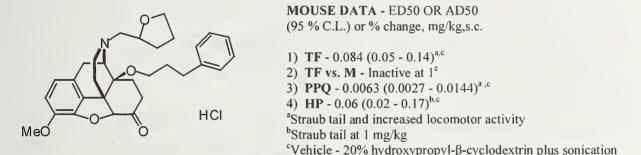

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.084 (0.05 - 0.14)[a,c]
2) **TF vs. M** - Inactive at 1[c]
3) **PPQ** - 0.0063 (0.0027 - 0.0144)[a,c]
4) **HP** - 0.06 (0.02 - 0.17)[b,c]
   [a]Straub tail and increased locomotor activity
   [b]Straub tail at 1 mg/kg
   [c]Vehicle - 20% hydroxypropyl-β-cyclodextrin plus sonication

Special Test: Naloxone vs NIH 11059 in TF: AD50 = 0.026 (0.009 - 0.076).

Comment: This compound has opioid agonist properties. Mu-opioid receptors seem to be involved.

NIH 11060 4,5 -Epoxy-3-methoxy-17-(2-phenylethyl)-14β -(3-phenylpropyloxy)morphinan-6-one.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.
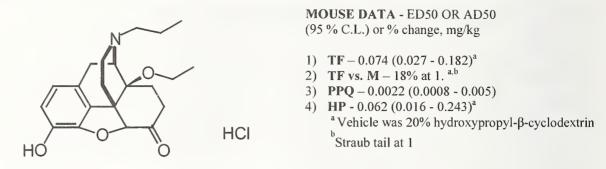
1) **TF** - Not Requested - Limited Supplies
2) **TF vs. M** - Not Requested - Limited Supplies
3) **PPQ** - 29% at 0.001, 34% at 0.01, 3% at 0.03, 37% at 0.1, 24% at 0.3, 97% at 1 and 100% at 10[a,b]
4) **HP** - 0.68 (0.29 - 1.61)[b]

Comment: This compound produced an erratic dose-effect curve in the PPQ test. NIH 11060 has opioid agonist propertries of which the mu-opioid receptor subtype is involved.

NIH 11062 4,5-Epoxy-3-hydroxy-14-ethoxy-17-propylmorphinan-6-one.HCl

HCl
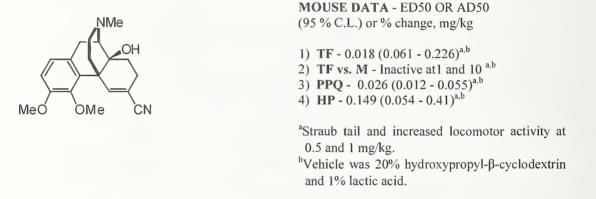
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg

1) **TF** – 0.074 (0.027 - 0.182)[a]
2) **TF vs. M** – 18% at 1. [a,b]
3) **PPQ** – 0.0022 (0.0008 - 0.005)
4) **HP** - 0.062 (0.016 - 0.243)[a]
     [a] Vehicle was 20% hydroxypropyl-β-cyclodextrin
     [b] Straub tail at 1

Comment: The profile of activity is reminiscent of that of morphine. The potency estimate is 100 times that of morphine sulfate.

NIH 11065 5,6-Didehydro-14 beta -hydroxy-3,4-dimethoxy-17-methylmorphinan-6-carbonitrile

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg

1) **TF** - 0.018 (0.061 - 0.226)[a,b]
2) **TF vs. M** - Inactive at 1 and 10 [a,b]
3) **PPQ** - 0.026 (0.012 - 0.055)[a,b]
4) **HP** - 0.149 (0.054 - 0.41)[a,b]

[a]Straub tail and increased locomotor activity at
  0.5 and 1 mg/kg.
[b]Vehicle was 20% hydroxypropyl-β-cyclodextrin
  and 1% lactic acid.

MONKEY DATA (SDS)

At doses of 0.07 and 0.35 mg/kg, NIH 11065 substituted completely for morphine in physically-dependent monkeys in withdrawal (see figure) The drug acted promptly; however, duration of action appeared to be waning after 60 min. Potency estimate at 1 hr was 40 times that of morphine sulfate.
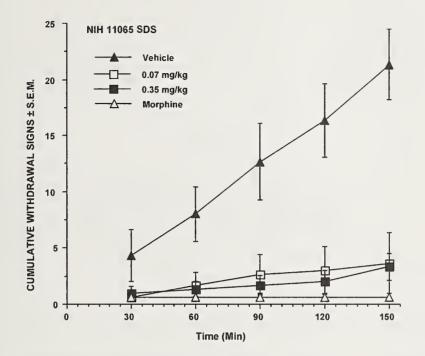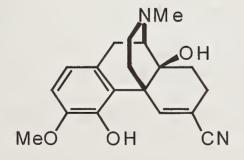
Fig NIH 11065 SDS. Results of study in which single doses of NIH 11065 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity suggests that NIH 11065 is a potent mu-opioid agonist. It is 100 to 150 times more potent than morphine sulfate in the mouse. In the monkey, its potency is about 40 times that of morphine sulfate.

NIH 11066 5,6-Didehydro-4,14 beta -dihydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 1.88 (1.25 - 2.83)[a,b]
2) **TF vs. M** - Inactive at 1 and 10[a,b]
3) **PPQ** - 0.178 (0.076 - 0.42)[a,b]
4) **HP** - 0.5 (0.12 - 2.02)[a,b]

[a]Straub tail at 3 and 10 mg/kg.
[b]Vehicle was 20% hydroxypropyl-β-cyclodextrin in water and 1% lactic acid.

MONKEY DATA (SDS)

NIH 11066 substituted completely for morphine at 3 mg/kg (n = 2). Limited drug supply prevented a complete study. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.
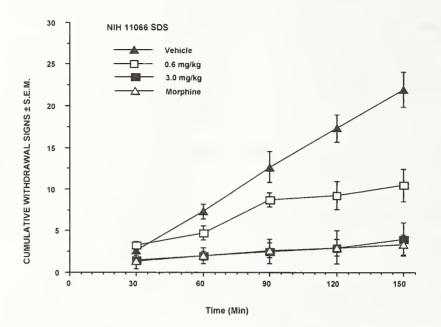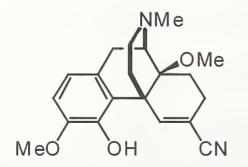
Fig NIH 11066 SDS. Results of study in which single doses of NIH11066 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 11066 exhibits a profile of activity not unlike that of morphine sulfate.

NIH 11067   5,6-Didehydro-4-hydroxy-3α,14β-dimethoxy-17-methylmorphinan-6-carbonitrile

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.209 (0.109 - 0.4)[a,b]
2) **TF vs. M** - Inactive at 1 and 10[a,b]
3) **PPQ** - 0.108 (0.072 - 1,64)[a,b]
4) **HP** - 0.253 (0.072 - 1.64)[a,b]
[a]Straub tails at 1 and 10 mg/kg.
[b]Vehicle was 20% hydroxypropyl-β-cyclodextrin in water and 1% lactic acid

MONKEY DATA (SDS)

At doses of 0.3 and 1.2 mg/kg, NIH 11067 substituted completely for morphine sulfate in morphine-dependent monkeys in withdrawal (see accompanying figure). Onset was prompt and duration of action was at least as long as that of the reference standard.
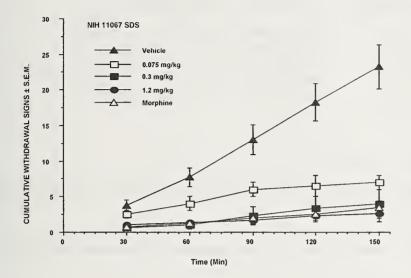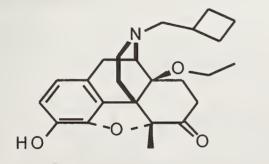
Fig NIH 11067 SDS. Results of study in which single doses of NIH 11067 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: This compound (NIH 11067) acts like a typical mu-opioid receptor agonist.   Potency is about 10 times that of morphine sulfate.

NIH 11068 17-Cyclobutylmethyl-4,5α-epoxy-14β -ethoxy-3-hydroxy-5β-methymorphinan-6-one
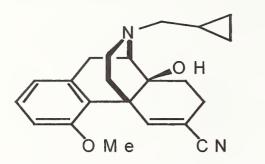
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg.s.c.

1) **TF** - 0.192 (0.071 - 0.515).[a]
2) **TF vs. M** - Inactive at 1 and 10.[a,b]
3) **PPQ** - 0.091 (0.062 - 0.134).[a]
4) **HP** - 0.198 (0.134 - 0.292).[a]
[a]Vehicle was 1% lactic acid in water.
[b] Insufficient drug for testing higher doses.

Comment: The results suggest a morphine-like profile of activity. It is 10 times more potent than morphine sulfate.

NIH 11072 17-Cyclopropylmethyl-5,6-didehydro-14β-hydroxy-4-methoxymorphinan-6-carbonitrile

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** – Inactive at 1 and 10, 23% at 30.[a]
2) **TF vs. M** – 2.77 (1.23 - 6.25).[a]
3) **PPQ** – Inactive at 1 and 10, 7% at 30.[a]
4) **HP** - 13% at 1, 0% at 10 and 37% at 30.[a]
[a]Vehicle was 1% lactic acid aqueous solution.
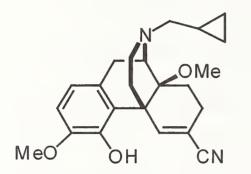
NIH 11072 s.c. in TF versus ED80 of Enadoline: AD50 = 6.3 (2.62 - 15.17) mg/kg.

Comment: NIH 11072 has very weak mu-opioid antagonist activity. It is approximately 100 times less potent than naloxone. It also has kappa-opioid antagonist activity.

NIH 11073 17-Cyclopropylmethyl-5,6-didehydro-4-hydroxy-3,14β -dimethoxymorphinan-6-carbonitrile
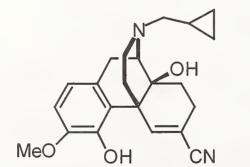
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 7.99 (2.78 - 22.84)[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[a]
3) **PPQ** - 2.43 (0.89 - 6.62)[a]
4) **HP** - 13% at 1 , 25% at 10 and 13% at 30[a]
   [a]Vehicle was 1% lactic acid aqueous solution.

Comment: NIH 11073 has weak analgesic properties. Whether or not it has opioid effects, would require further testing.

NIH 11074 7-Cyclopropylmethyl-5,6-didehydro-4,14β-dihydroxy-3-methoxymorphinan-6-carbonitrile

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.
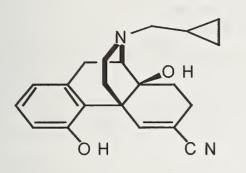
1) **TF** - 13.6 (6.7 - 27.5)
2) **TF vs. M** - 6% at 1, 0% at 10 and 11% at 30
3) **PPQ** - 5.84 (2.65 - 12.88)
4) **HP** - 13% at 1, 25% at 10 and 37% at 30

Vehicle was 1% lactic acid acid in water.

Comment: NIH 11074 is weakly active antinociceptively; however, additional testing would be required to characterize its mechanism of action.
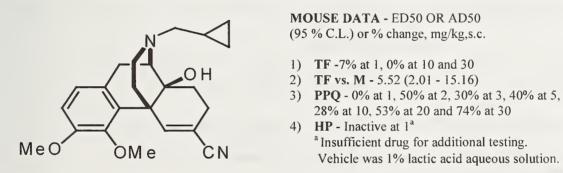
NIH 11075 17-Cyclopropylmethyl-5,6-didehydro-4,14β -dihydroxymorphinan-6-carbonitrile

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg

1) **TF** - 8.65 (2.16 - 34.64)[a]
2) **TF vs. M** - 0% at 1, 3% at 10 and 9% at 30
3) **PPQ** - 1.47 (1.15 - 1.89)[b]
4) **HP** - 0% at 1, 37% at 10 and 50% at 30[c]
[a]Slight ataxia.
[b]Rapid and heavy breathing; 1 convulsed and died at eight min.
[c]Labored breathing.
Vehicle was 1% lactic acid in water.
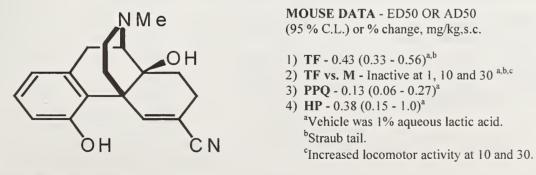
Comment: NIH 11075 has weak antinociceptive properties. Subtype testing might define its mechanism(s) of action.

NIH 11076 17-Cyclopropylmethyl-5,6-didehydro-14β -hydroxy-3,4-dimethoxymorphinan-6-carbonitrile

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** -7% at 1, 0% at 10 and 30
2) **TF vs. M** - 5.52 (2.01 - 15.16)
3) **PPQ** - 0% at 1, 50% at 2, 30% at 3, 40% at 5, 28% at 10, 53% at 20 and 74% at 30
4) **HP** - Inactive at 1[a]
   [a] Insufficient drug for additional testing.
   Vehicle was 1% lactic acid aqueous solution.

Comment: The evidence suggests that NIH 11076 is a weak mu-opioid receptor antagonist in the mouse. Drug supply was exhausted.

NIH 11077 5,6-didehydro-4,14β-dihydroxy-17-methylmorphinan-6-carbonitrile

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.43 (0.33 - 0.56)[a,b]
2) **TF vs. M** - Inactive at 1, 10 and 30 [a,b,c]
3) **PPQ** - 0.13 (0.06 - 0.27)[a]
4) **HP** - 0.38 (0.15 - 1.0)[a]
   [a]Vehicle was 1% aqueous lactic acid.
   [b]Straub tail.
   [c]Increased locomotor activity at 10 and 30.

Opioid subtype testing:

Naltrindole (s.c.) vs ED80 of NIH 11077 in PPQ: 8% at 1, 8% at 3, 0% at 10 and 53% at 30.

Comment: The antinociceptive profile of activity and Straub tail suggest that NIH 11077 has mu-opioid receptor agonist activity. Potency is approximately 10 times that of morphine sulfate. It also has weak delta-opioid agonist properties.

NIH 11082 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1 and 10 and 20% at 30[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[a]
3) **PPQ** - 1.93 (0.70 - 5.34)[a]
4) **HP** - Inactive at 1, 10, and 30[a]
[a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Opioid subtype testing:

a) Naltrindole (s.c.) vs ED80 of NIH 11082 in PPQ = 0.75 (0.26 - 2.20).

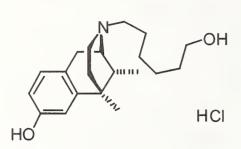b) nor-BNI vs ED80 of NIH 11082 in PPQ = 0% at 9% at 10 and 26% at 30 mg/kg.

c) β-FNA vs ED80 of NIH 11082 in PPQ = 3% at 1, 9% at 3, 18% at 10 and 38% at 30 mg/kg.

Table 1. NIH 11082 ED80 time-course study in the PPQ assay

Dose (ED80) 10 mg/kg s.c.				
TIME	20 min	1 hr	4 hr	6 hr
% Inhibition	77	26	Inactive	Inactive

Table 2. Co-administration of ED50 of NIH 11082 and ED50 of morphine in the tail-flick assay

Treatment (ED50, mg/kg s.c.) in 10% hydoxypropyl β-cyclodextrin in water	Percent Inhibition
Morphine (4.0)	59
Morphine (4.0) + NIH 11082 (1)	54

Table 3. Co administration of ED50 of NIH 11082 and ED50 of morphine in the PPQ assay[a]

Treatment (ED50, mg/kg s.c.) in 10% hydoxypropyl β-cyclodextrin in water	Percent Inhibition
Morphine (0.35)	29
NIH 11082 (1.0)	43
Morphine (0.35) + NIH11082 (1.0)	89

[a] Preliminary

NIH 11082 (continued)

Table 4. Co-administration of ED25 of NIH 11082 and ED25 of morphine in the PPQ assay. (n = 12)
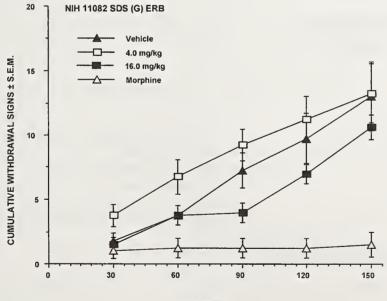
Treatment (ED 25, mg/kg sc) in 10% hydoxypropyl-β-cyclodextrin in water	Percent Inhibition
Morphine (0.3)	41
NIH 11082 (0.2)	13
Morphine (0.3) + NIH 11082 (0.2)	78

Table 5. Co-administration of ED50 of NIH 11082 and ED50 morphine in the PPQ assay. (n = 12)

Treatment (ED 50, mg/kg sc) in 10% hydoxypropyl-β-cyclodextrin in water	Percent Inhibition
Morphine (0.35)	49
NIH 11082 (6.0)	49
Morphine (0.35) + NIH 11082 (6.0)	87

MONKEY DATA (SDS)

As shown in the figure, NIH 11082 briefly attenuated withdrawal signs in morphine-dependent monkeys at a dose of 16 mg/kg.

Fig NIH 11082 SDS. Results of study in which single doses of NIH 11082 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results indicate that NIH 11082 lacks significant mu-opioid properties in mice; and morphine-dependent monkeys. However, in mice, delta-opioid agonist activity is impressive. Unlike other delta-opioid agonists no convulsions were noted.

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NIH 11086 Dynorphin analog

AcTyr-Lys-Trp-Trp-Le-Arg-Arg-
D-Ala-Arg-Pro-Lys-NH2

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, μg/brain, i.c.v.

1) **TF** - 16% at 0.3, 42% at 1, 17% at 3, 29% at
   10 and 8% at 30[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[b]
3) **PPQ** - 2% at 0.3, 36% at 1, 62% at 3 and 50% at10[c]
3) **HP** - Inactive at 1, 10 and
   [a] At 30, 3/6 had slight tremors, 2/6 were heavily sedated.
   [b] At 30, 2/6 were heavily sedated, 1/6 had slow righting
   reflex at 30.
   [c] Insufficient drug to run higher doses.
   [d] At 30, 1/6 had tremors, 2/6 whirled about on the hot-plate.

Comment: Although NIH 11086 showed some effects on the central nervous system in mice, antinociceptive activity was not evident. Insufficient drug supply precluded further testing.

NIH 11087 Dynorphin analog

AcPhe-Phe-Phe-Arg-Leu-Arg-
Arg-D-Ala-Arg-Pro-Lys-NH2

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, μg/brain, i.c.v.

1) **TF** - 5% at 0.3, 27% at 1 and 24% at 3[a,d]
2) **TF vs. M** - Inactive at 1 and 10[b,d]
3) **PPQ** - 5% at 0.1, 45% at 0.3, 52% at 1 and 69% at 3[c,d]
4) **HP** - 25% at 1 and 2/8 were positive[e,d]

[a] At 3 ug/brain, tumbling in 5/6, immobility 1/6 and clonic convulsions in 2/6.
[b] At 10 ug/brain, loss of righting reflex and immobility in 2/6.
[c] At 3 ug/brain, immediate convulsion in 1/6 and intermittent convulsions thereafter.
[d] Insufficient drug for further testing.
[e] At 1 ug/brain, convulsion in 1/8, and tumbling in 2/8; At 3 ug/brain, 2/8 tested positive, 1/8 could not be tested, 1/8 died, 5/8 convulsed, 3/8 lost righting reflex and 2/8 were immobile.

Comment: Severe central nervous system effects precluded further testing of NIH 11087.

NIH 11090 Enkephalin analog

MOUSE DATA - ED50 OR AD50
(95 % C.L.) and % change, µg/brain, i.c.v.

(D)-Phe-(D)Nal-(D)Nle-NLys-NH2

1) **TF** - 0.29 (0.094 - 0.92) (i.c.v.)
2) **TF vs. M** -11% at 1 and inactive at 10 and 30 (i.c.v.)[a]
3) **PPQ** - 28% at 0.1, 59% at 0.3 and 1, 0% and 91% at 3, 47% at 10 and 91% at 30 (i.c.v.)[b]
4) **HP** - 13% at 1 and 3, 50% at 10 and 25% at 30 (i.c.v.)
   [a]30 µg/brain, hunched backs in 4/6, rigidity in 2/6 and convulsions in 2/6.
   [b]At 30 µg/brain, clonic extensions in 4/6, hunched backs and rigidity in 2/6 and convulsions in 1/6.

Comment: The evidence suggests that NIH 11090 is active antinociceptively. This drug might have mu- and/or delta-opioid receptor agonist activity. Because supply was exhausted, additional testing was not possible.

NIH 11091 Enkephalin analog
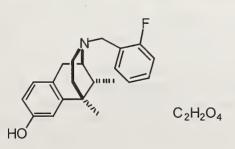
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, □g/brain, i.c.v.

NhPhe-(D)Phe-(D)Nle-(D)Arg-NH2

1) **TF** - 34% at 0.1, 59% at 0.3, 61% at 1, 55% at 3 and 68% at 10 (i.c.v.)[a]
2) **TF vs. M** - Inactive at 1 and10 (i.c.v.)[a,b]
3) **PPQ** - 2.14 (1.01 - 4.56) (i.c.v.)[a,c]
4) **HP** -13% at 1 and 38% at 10 (i.c.v.)[a,b,c]
   [a]At 10 µg/brain, 6/6 were sedated.
   [b]At 10 µg/brain 1/6 convulsed.
   [c]At 10 µg/brain, 3/8 moved in circles.

Comment: NIH 11091 is active antinociceptively in the PPQ test and has prominent central nervous system effects. Additional testing might provide insights regarding its mechanism of action.

NIH 11097 (-),(1R,5R,9R)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate

$C_2H_2O_4$

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, ug/brain,i.c.v.,or s.c.

1) **TF** - 14.8 (8.14 – 26.9) ug/brain,i.c.v.
   - Inactive at 1, 10 and 30, s.c.
2) **TF vs. M** - 0% at 1, 18% at 10 and 0% at 30
3) **PPQ** - 7% at 1, 10% at 10 and 27% at
4) **HP** - 13% at 1 and 10, 0% at 30

Vehicle was 20% hydroxypropyl-β-cyclodextrin in water

Opioid subtype testing:

Enadoline s.c. vs ED80 of NIH 11097 s.c. in TF; 20% at 1, 8% at 10 and 7% at 30 mg/kg.

NIH 11097 (continued)

<u>MONKEY DATA</u> (SDS)

Because of limited supplies, only 2 subjects per dose regimen were tested. These results suggest that NIH 11097 did not attenuate withdrawal or substitute for morphine and that it may have exacerbated withdrawal (see Fig).
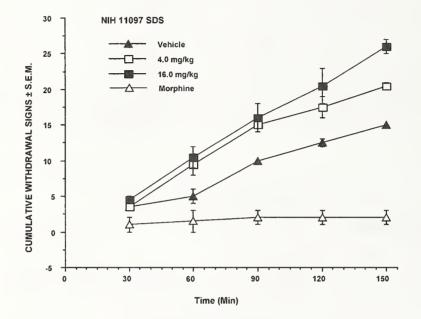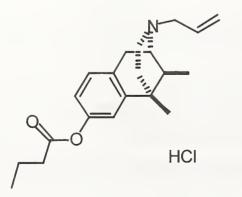
Fig NIH 11097-SDS. Results of study in which single doses of NIH 11097 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: This profile of activity is not indicative of significant mu-opioid receptor properties.

NIH 11098   (+),(1S,5S,9S)-2'-Butryoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30[a,d]
2) **TF vs. M** - Inactive at 1, 10 and 30[a,b,d]
3) **PPQ** - 9.6 (4.4 - 21.0)[a,c,d]
4) **HP** - Inactive at 1, 13% at 10 and inactive at 30[a,c,]
    [a]At 30 mg/kg, ataxia and mild Straub tail.
    [b]At 20 mg/kg, ataxia prior to morphine, Straub tail.
    [c]Ataxia at 3, 10 and 30, increased respiration at 30.
    [d]Vehicle was 20% hydroxypropyl-β-cyclodextrin in water.

<u>MONKEY DATA</u> (SDS)

NIH 11098 attenuated withdrawal (see accompanying fig.). The response was dose related and delayed.
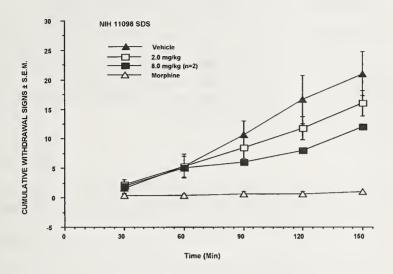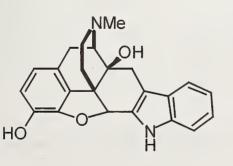
Fig NIH 11098-SDS. Results of study in which single doses of NIH 11098 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: This so-called Straub tail is probably associated with the ataxia. NIH 11098 does not display activity reminiscent of mu-opioid receptor agonists. However, it may have delta-opioid agonist activity.

NIH 11106 (BU 99041) N'-Benzyl-4,5,6,7-tetrahydrooxymorphindole

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,or µg/brain
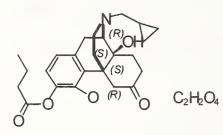
1) **TF** - Not Tested
2) **TF vs. M** - Not tested
3) **PPQ** - 4.63 (1.55 – 13.8)
4) **PPQ** - **NIH 11106 vs NIH 10815 (SNC80)**
    a) - 0% at 10 and 30 mg/kg (s.c.)[a]
    b) Inactive at 1, 10 and 30 mg/kg (s.c.) [b]
    c) 21% at 1 and 53% at 10 µg/brain (i.c.v.)[b,c]
5) **HP** - Not Tested
    [a]30 min pretreatment and
    [b] 24 hr pretreatment.
    [c]At 30 µg /brain one mouse convulsed and another died.

Special Test:

Naloxone AD50 vs. ED80 of NIH 11106 in PPQ = 0.02 (0.031 - 0.047).

Comment: Initially, NIH 11106 had opioid agonist activity in the PPQ test. It exhibited delayed delta-opioid antagonist activity when given centrally.

NIH 11109 3-O-Butyrylnaltrexone.oxalate

$C_2H_2O_4$

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30[a]
2) **TF vs. M** - 0.0029 (0.0013 - 0.0067)[a]
3) **PPQ** - Inactive at 1, 10 and 30[a]
4) **HP** - Inactive at 1, 10 and 30[a]

[a]Solubilized with sonification in 20% hydroxypropyl-β-cyclodextrin.

MONKEY DATA (SDS)

NIH 11109 did not substitute for morphine or attenuate withdrawal in morphine-dependent monkeys. Instead, it exacerbated withdrawal.
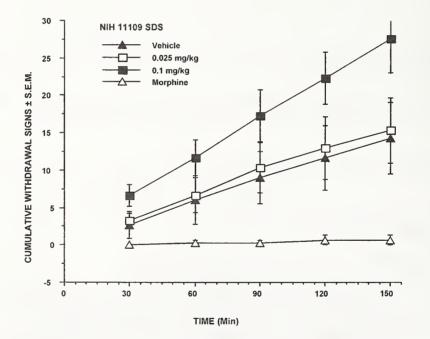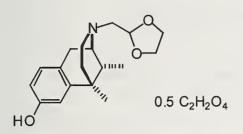

Fig NIH 11109-SDS. Results of study in which single doses of NIH 11109 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results in mice and morphine-dependent monkeys indicate that NIH 11109 has potent mu-opioid antagonist properties.

NIH 11111 (-),(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanyl)-6,7-benzomorphan.hemioxalate

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg

1) **TF** -13% at 1, 12% at 10, and inactive at 30[a,c]
2) **TF vs. M** - 0.2 (0.06 - 0.65)[c]
3) **PPQ** - 1.85 (0.43 - 8.0)[a,c]
4) **HP** - Inactive at 2, 25% at 6 and inactive at 20 and 30[a,b,c]
    [a]At 30 mg/kg, ataxia and sedation.
    [b]At 20 mg./kg, slight ataxia and Straub tail.
    [c]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

0.5 C$_2$H$_2$O$_4$

Opioid subtype testing:

Nor-BNI (s.c.) vs ED80 of NIH 11111 in PPQ: 6% at 1, 22% at 3, 25% at 10 and 17% at 30.

MONKEY DATA (SDS)

At doses of 0.15 and 0.6 mg/kg, NIH 11111 neither substituted for morphine nor exacerbated withdrawal in morphine-dependent monkeys.
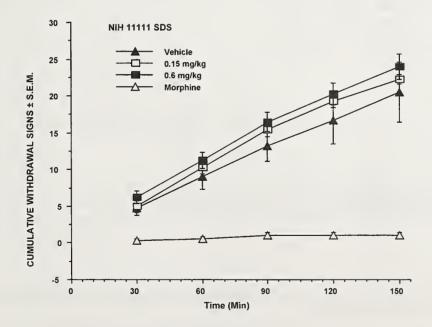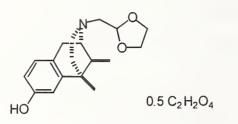
Fig NIH 11111-SDS. Results of a study in which single doses of NIH 11111 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 11111 is active in the PPQ test and has mu-opioid antagonist effects in the mouse. This compound may also have delta opioid agonist activity.

NIH 11112 (+),(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanyl)-6,7-benzomorphan.hemioxalate

0.5 $C_2H_2O_4$

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1 and 10, 4% at 30[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[a]
3) **PPQ** - 23% at 1 and 10, 19% at 30[a]
4) **HP** - Inactive at 1, 10 and 30[a]
    [a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water

MONKEY DATA (SDS)

Although the data illustrated in the figure seem provocative, no conclusion is possible because of insufficient supplies to test higher doses.
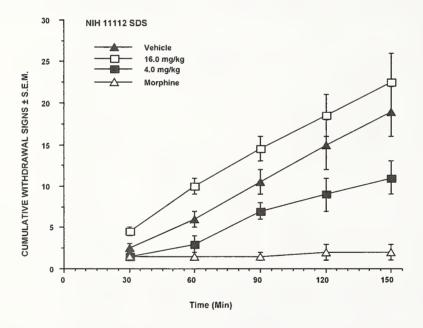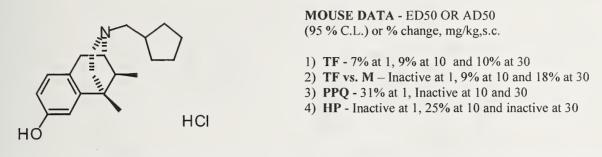

Fig NIH 11112-SDS. Results of study in which single doses of NIH 11112 were substituted for morphine in morphine-dependent monkeys in withdrawal.
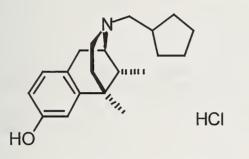
Comment: As tested, NIH 11112 appears devoid of mu-opioid agonist/antagonist properties.

NIH 11113 (+),(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-cyclopentylmethyl-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 7% at 1, 9% at 10 and 10% at 30
2) **TF vs. M** – Inactive at 1, 9% at 10 and 18% at 30
3) **PPQ** - 31% at 1, Inactive at 10 and 30
4) **HP** - Inactive at 1, 25% at 10 and inactive at 30

HCl

Comment: The profile of activity of NIH 11113 does not portend significant opioid agonist/antagonist activity.

NIH 11114 (-),(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-cyclopentylmethyl-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 16% at 1, 14% at 10 and 4% at 30[a,c]
2) **TF vs. M** - 2.44 (1.03 - 5.78)[a,c]
3) **PPQ** - 7.0 (2.73 - 18.56) [a,b,c]
4) **HP** - Inactive at 1, 3, 10 and 30[a,c]
   [a]Vehicle was 20% hydroxypropyl-β-cyclodextrin in water.
   [b]At 30 mg/kg, mild ataxia.
   [c]This sample contained small black and brown particles.

HCl

Opioid subtype testing:

Nor-BNI (s.c.) vs ED80 of NIH 11114 in PPQ: 0% at 1, 12% at 3, 3% at 10 and 30.

MONKEY DATA (SDS)

As shown in the figure, NIH 11114 dose-dependently attenuated withdrawal in morphine-dependent monkeys at 1 and 4 mg/kg. However, at these doses it had little effect on two important withdrawal signs that are crucial for characterizing mu-opioid agonists in this test. It failed to block vocalization and abdominal muscle rigidity associated with abdominal palpation.
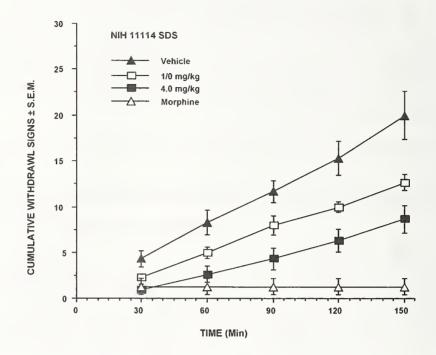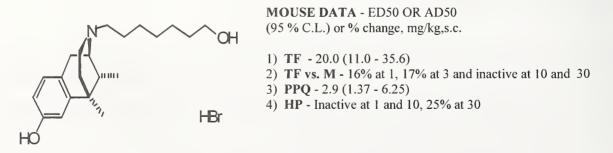
Fig NIH 11114-SDS. Results of study in which single doses of NIH 11114 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: In the mouse, NIH 11114 displayed agonist antinociceptive properties, lacking kappa-opioid agonist involvement. It also displayed weak mu-opioid antagonist effects. However, in morphine-dependent monkeys, neither agonist nor antagonist mu-opioid effects were evident because it failed to block vocalization when their abdomens were palpated and it failed to exacerbate withdrawal, respectively.

NIH 11127 (-),(1R,5R,9R)-5,9-dimethyl-2'-Hydroxy-2-(7-hydroxyheptyl)- 6,7-benzomorphan.HBr

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 20.0 (11.0 - 35.6)
2) **TF vs. M** - 16% at 1, 17% at 3 and inactive at 10 and 30
3) **PPQ** - 2.9 (1.37 - 6.25)
4) **HP** - Inactive at 1 and 10, 25% at 30

<u>**MONKEY DATA**</u> (SDS)

Although this compound lowered the incidence of withdrawal scores the results were not dose-related. In addition, the responses to abdominal palpation were not alleviated suggesting that NIH 11127 either lacked mu-opioid agonist properties or that a high enough dose was not tested.

NIH 11127 (continued)
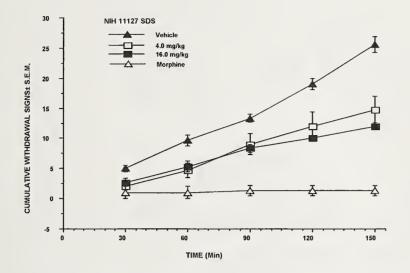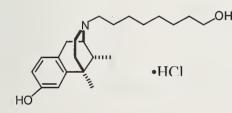
Fig NIH 11127-SDS. Results of study in which single doses of NIH 11127 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results in mice and monkeys suggest that NIH 11127 does not have remarkable mu-opioid agonist or antagonist effects.

NIH 11139 (-),(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30[a]
 2) **TF vs. M** - Inactive at 1, 10 and 30[a]
3) **PPQ** - 4.4 (2.2 – 8.6)[a]
4) **HP** - 0% at 1 and 10, 13% at 30[a]
        [a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water

MONKEY DATA (SDS)

Although NIH 11139 attenuated many withdrawal signs, it did not substitute completely for morphine because the monkeys had rigid abdominal muscles and vocalized when their abdomens were palpated.

189
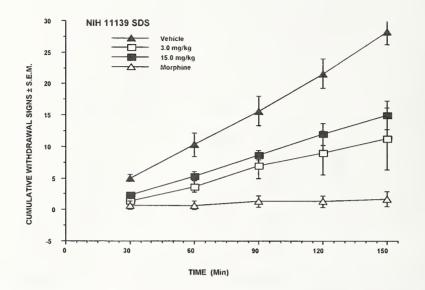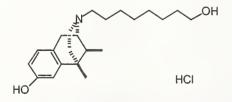
Fig NIH 11139-SDS. Results of study in which single doses of NIH 11139 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results do not portend remarkable mu-opioid agonist or antagonist properties. It may have delta-opioid agonist activity.

NIH 11140 (+),(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** – Inactive at 1, 10 and 30[a]
2) **TF vs. M** – Inactive at 1, 10 and 30[a]
3) **PPQ** – 41% at 1, 68% at 3, 38% at 10 and 30[a]
4) **HP** - Inactive at 1, 10 and 30[a]
   [a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

MONKEY DATA (SDS)

As shown in the accompanying figure, at doses of 4 and 16 mg/kg, NIH 11140 neither substituted for morphine nor exacerbated withdrawal in withdrawn morphine-dependent monkeys.

190
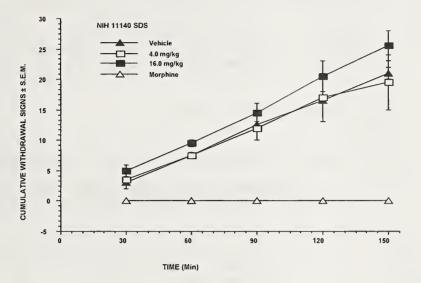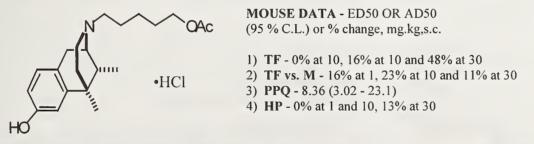
Fig NIH 11140-SDS. Results of study in which single doses of NIH 11140 were substituted for morphine in morphine-dependent monkeys in withdrawal.
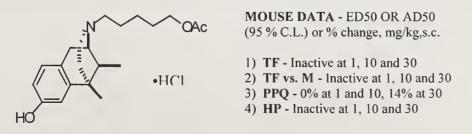
Comment: This compound (NIH 11140) is essentially devoid of mu-opioid activity in both species.

NIH 11164 (-),(1R,5R,9R) -2-(5-Acetoxypentyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg.kg,s.c.

1) **TF** - 0% at 10, 16% at 10 and 48% at 30
2) **TF vs. M** - 16% at 1, 23% at 10 and 11% at 30
3) **PPQ** - 8.36 (3.02 - 23.1)
4) **HP** - 0% at 1 and 10, 13% at 30
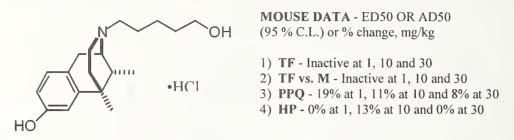
Comment: These data suggest very weak, if any, mu-opioid properties. NIH 11164 may have delta-opioid agonist effects.

NIH 11165 (+),(1S,5S,9S)- 2-(5-Acetoxypentyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - 0% at 1 and 10, 14% at 30
4) **HP** - Inactive at 1, 10 and 30
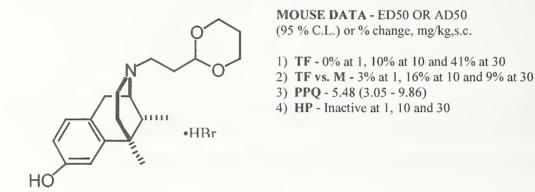
Comment: Most likely, NIH 11165 is devoid of opioid properties.

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NIH 11166 (-),(1R,5R,9R)- 5,9-Dimethyl-2'-hydroxy-2-(5-hydroxypentyl)-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - 19% at 1, 11% at 10 and 8% at 30
4) **HP** - 0% at 1, 13% at 10 and 0% at 30
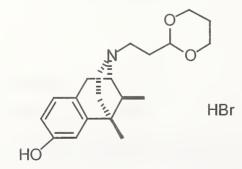
Comment: These results do not predict opioid activity for NIH 11166.

NIH 11167 (-),(1R,5R,9R)- 5,9-Dimethyl-2-(1,3-dioxanylethyl)- 2'-hydroxy-6,7-benzomorphan.HBr

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0% at 1, 10% at 10 and 41% at 30
2) **TF vs. M** - 3% at 1, 16% at 10 and 9% at 30
3) **PPQ** - 5.48 (3.05 - 9.86)
4) **HP** - Inactive at 1, 10 and 30

Comment: These results do not indicate that NIH 11167 has mu-opioid properties; however delta-opioid effects have not been ruled out.

NIH 11168 (+),(1S,5S,9S)- 5,9-Dimethyl-2-(1,3-dioxanylethyl)- 2'-hydroxy-6,7-benzomorphan.HBr

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.
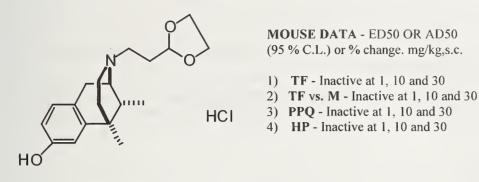
1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - 2% at 1, 8% at 10 and 0% at 30
3) **PPQ** - 21% at 1, 47% at 10 and 41% at 30
4) **HP** - 0% at 1 and 10, 13% at 30

Comment: Very weak, if any, opioid activity is apparent.

192

NIH 11176 (-),(1R,5R,9R)- 5,9-Dimethyl-2-(1,3-dioxalanylethyl)- 2'-hydroxy-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change. mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - Inactive at 1, 10 and 30
4) **HP** - Inactive at 1, 10 and 30

HCl

MONKEY DATA (SDS)

NIH 11176 dose dependently attenuated withdrawal in morphine-dependent monkeys at 3 and 12 mg/kg (see fig). Unfortunately, drug supply was exhausted and additional doses could not be tested.
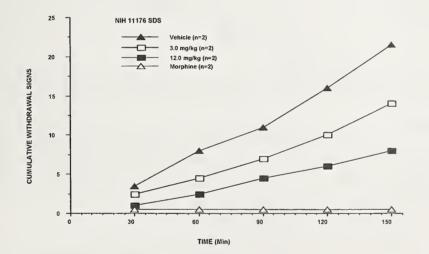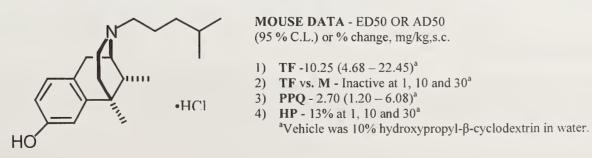

Fig NIH 11176-SDS. Results of study in which single doses of NIH 11176 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The drug appears inactive in the mouse and produces some attenuation of withdrawal signs in the monkey. However, insufficient supplies did not permit a full evaluation.

NIH 11179 (-),(1R,5R,9R)- 5,9-Dimethyl-2'-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** -10.25 (4.68 – 22.45)[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[a]
3) **PPQ** - 2.70 (1.20 – 6.08)[a]
4) **HP** - 13% at 1, 10 and 30[a]
   [a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

•HCl

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MONKEY DATA (SDS)

In the preliminary test, cumulative doses of 1, 2 and 4 mg/kg, spaced 15 min apart, respectively, NIH 11179 produced tremors and convulsions of short duration.

As depicted in the figure, some non dose-related attenuation of withdrawal signs was observed in the SDS assay. It should be noted that tremors were observed in 1 monkey and, brief convulsions, in another, receiving the high dose.
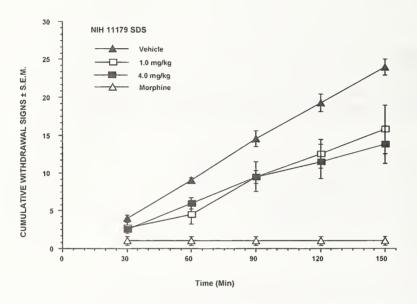
Fig NIH 11179-SDS. Results of study in which single doses of NIH 11179 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Further work would be required to characterize NIH 11179.

NIH 11180 (-),($1R,5R,9R$)-2-(3-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate

$C_2H_2O_4$

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - 4.83 (3.77 – 6.19)
2) **PPQ** - 2% at 1, 34% at 10 and 45% at 30
3) **HP** - 0% at 1 and 10, 13% at 30

MONKEY DATA (PPt-W)

As shown in the accompanying figure, a dose-related precipitated withdrawal was observed. Onset of action was prompt and duration of action was at least as long as that of naloxone, Eyelid ptosis, slowing and ataxia were observed at both doses. Potency estimate is 1/100 that of naloxone.
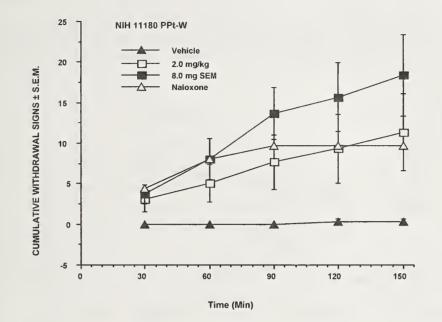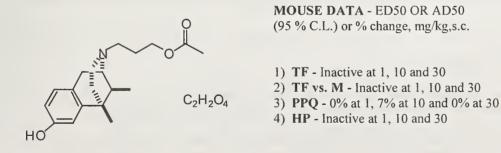
Fig. NIH 11180-PPt-Withdrawal. Results of study in which morphine-dependent monkeys were given single doses of NIH 11180 two hr after morphine.

Comment: The results in mice and monkeys suggest weak mu-opioid antagonist properties. It is possible that NIH11180 may also have some weak kappa- and delta-opioid antagonist effects.

**NIH 11181** (+),(1S,5S,9S)-2-(3-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate

$C_2H_2O_4$

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - 0% at 1, 7% at 10 and 0% at 30
4) **HP** - Inactive at 1, 10 and 30

MONKEY DATA (SDS)

Because of limited supplies, only 2 monkeys per dose regimen were tested. In spite of the large standard deviations, NIH 11181 appeared to attenuate withdrawal signs in rhesus monkeys in spontaneous withdrawal.
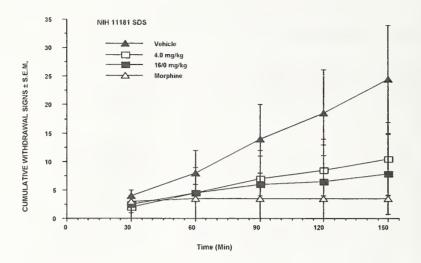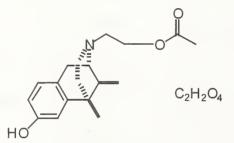
Fig NIH 11081 SDS. Results of study in which single doses of NIH 11081 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Overall, these results do not indicate that NIH 11181 has mu- opioid properties.

NIH 11182 (+),(1S,5S,9S)-2-(2-Acetoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.
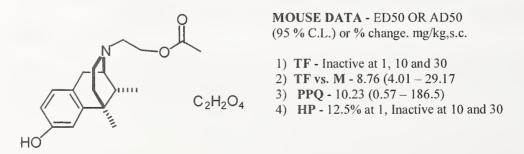
1) **TF** - Inactive at 1,10 and 30
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - 4.74 (3.22- 6.97)
4) **HP** - Inactive at 1,10 and 30

$C_2H_2O_4$

MONKEY DATA (SDS-Preliminary Study)

Limited supplies, permitted a preliminary study only. Over a period of 45 min, doses of 1, 2, 4, and 8 mg/kg, given at 15 min intervals respectively, produced no remarkable effects in morphine-dependent rhesus monkeys.

Comment: These results do not predict kappa- or mu-opioid agonist effects. However, they do not exclude delta-opioid properties. If warranted, subtype testing with naltrindole would settle the issue.

NIH 11183 (-),(1R,5R,9R)- 2-(2-Acetoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change. mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - 8.76 (4.01 – 29.17)
3) **PPQ** - 10.23 (0.57 – 186.5)
4) **HP** - 12.5% at 1, Inactive at 10 and 30

$C_2H_2O_4$

NIH 11183 (continued)

<u>MONKEY DATA</u> (SDS)

At doses of 4 and 16 mg/kg, NIH 11183 did not substitute for morphine. Instead, it exacerbated withdrawal. Due to limited supplies, only 2 monkeys were tested at the high dose regimen. Thus, the cumulative number of withdrawal signs in the figure was lower when compared to vehicle because the latter treatment group consisted of 5 subjects.
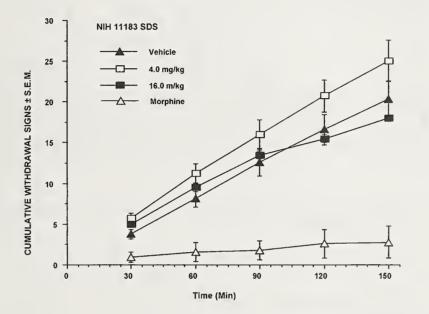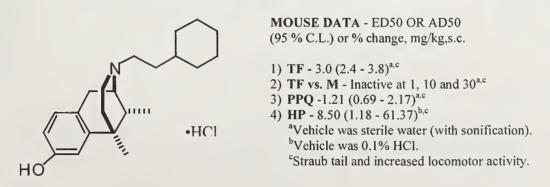

Fig NIH 11183-SDS. Results of study in which single doses of NIH 11183 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The evidence indicates that NIH 11183 has rather weak mu-opioid antagonist properties.

NIH 11185   (-),(1R,5R,9R)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 3.0 (2.4 - 3.8)[a,c]
2) **TF vs. M** - Inactive at 1, 10 and 30[a,c]
3) **PPQ** -1.21 (0.69 - 2.17)[a,c]
4) **HP** - 8.50 (1.18 - 61.37)[b,c]
   [a]Vehicle was sterile water (with sonification).
   [b]Vehicle was 0.1% HCl.
   [c]Straub tail and increased locomotor activity.

<u>MONKEY DATA</u> (SDS)

As shown in the figure, NIH11185 attenuated withdrawal signs in monkeys in spontaneous withdrawal at doses of 1.5 and 6.0 mg/kg. Complete substitution was not seen.

197
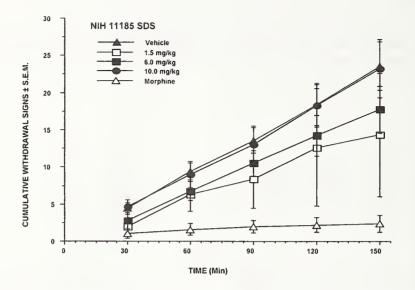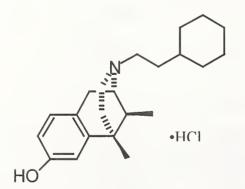
Fig NIH 11185-SDS. Results of study in which single doses of NIH 11185 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Overall, the results indicate that NlH 11185 has mu-opioid agonist properties.

NIH 11186 (+),(1S,5S,9S)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.
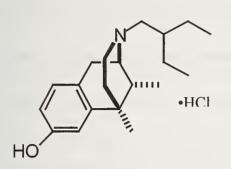
1) TF - 0% at 1, 2% at 10 and 17% at 30a
2) TF vs. M - lnactive at 1, 10 and 30
3) PPQ - 17.95 (2.08 – 154.85)
4) HP - 0% at 1, 12.5% at 10 and 0% at 30
   aSlightly ataxic at 30 mg/kg.

MONKEY DATA (SDS)

Only one experiment could be conducted because drug supply was exhausted. At 4 mg/kg, the monkey behaved essentially as the vehicle control. One-half hr after receiving 16 mg/kg, convulsions were noted in one monkey. The convulsions were quickly terminated following an injection of pentobarbital.

Comment: These results do not portend mu- and or kappa-opioid agonist or mu-opioid antagonist properties. Further testing in the mouse might reveal delta-opioid agonist effects.

NIH 11187 (-),(1R,5R,9R)-2-(2-Ethylbutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 2.21 (1.69 – 2.90)[a,b]
2) **TF vs. M** - 10% at 1, 0% at 10 and 30% at 30[a,c]
3) **PPQ** - Inactive at 0.3, 48% at 0.6. 50% at 1 and 98% at 3
4) **HP** - 12.5% at 1, 25% at 10 and 37.5% at 30[a,b,c]
[a]Straub tail at 10 and 30, [b]Increased locomotor activity at 10, and
[c]Ataxia at 30.

MONKEY DATA (SDS)

At doses of 1 and 4 mg/kg, NIH 11187 substituted completely for morphine (see accompanying figure). Dose-related signs designated slowing, ataxia, jaw sag and eyelid ptosis were observed.

This cluster of side effects along with its ability to substitute for morphine usually heralds mu- and kappa-opioid agonist activity.
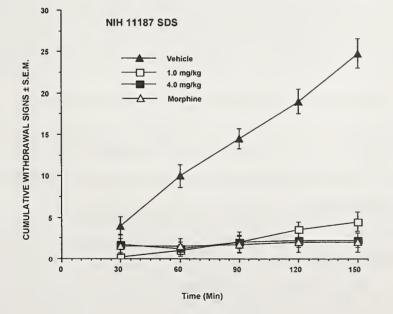

Fig NIH 11187-SDS. Results of study in which single doses of NIH 11187 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profiles of activity in mice and rhesus monkeys suggest that NIH 11187 has mixed opioid effects. probably mu- and kappa. Some weak mu opioid-antagonist effects were also observed at the highest dose in mice.

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PROGRESS REPORT FROM THE TESTING PROGRAM FOR STIMULANT AND DEPRESSANT DRUGS (2004)

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INTRODUCTION

A research group within the Drug Evaluation Committee has been involved in the evaluation of stimulant and depressant compounds for approximately 20 years. The group currently includes laboratories at The University of Texas Health Science Center at San Antonio (UTHSCSA; France, McMahon), the University of Michigan (UM; Fantegrossi, Woods), The University of Mississippi Medical Center (UMMC; Woolverton), and the State University of New York at Buffalo (SUNYB; Winter). As part of the Drug Evaluation Committee (Woods, Chair) of the College on Problems of Drug Dependence (CPDD), research is supported by both the CPDD and the National Institute on Drug Abuse (NIDA). One of the purposes of this group is to evaluate new compounds, generally classified as either stimulants or depressants, for their abuse liability and physical dependence potential. Compounds are received, coded and distributed by the Biologic Coordinator (Coop, University of Maryland School of Pharmacy at Baltimore) for blind testing in the various laboratories. Drugs are then evaluated for reinforcing effects in monkeys with histories of drug self-administration (UM), and for discriminative stimulus effects in monkeys that discriminate amphetamine (UMMC), midazolam (UTHSCSA), or flumazenil (UTHSCSA). This year, compounds were also tested for the capacity to induce the head-twitch response in mice (UM), and for LSD-like discriminative stimulus effects in rats (SUNYB) as well as binding to serotonin receptors in rat brain (SUNYB). This report includes the results of evaluation of CPDD 0066, CPDD 0067 and CPDD 0068. All studies were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committees at UTHSCSA, UM, UMMC, SUNYB and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

METHODS

Reinforcing Effects in Rhesus Monkeys (UM)

Subjects and Apparatus

Three adult rhesus monkeys (*Macaca mulatta*) experienced with self-administration of cocaine were surgically prepared with indwelling silicone rubber catheters using 10.0 mg/kg i.m. ketamine and 2.0 mg/kg i.m. xylazine as anesthetics. Catheters were implanted in either a jugular (internal or external), femoral, or brachial vein as necessary. Catheters passed s.c. to the mid-scapular region, exited the body, and continued through a hollow restraining arm to the outside rear of the cage. During these studies, each animal wore a Teflon mesh jacket (Lomir, Québec, Canada) connected to a flexible stainless steel spring arm attached to the rear of the cage. Animals were individually housed in 83.3 x 76.2 x 91.4 cm-deep stainless steel cages. A side-mounted panel was present in each cage, equipped with a row of three stimulus lamps (red-green-red) across the top, and two response levers (one mounted under each red light.) Animals were fed 10-12 Purina monkey chows twice per day along with fresh fruit and other preferred foods; water was available continuously. Environmental enrichment toys were provided on a regular rotating basis.

Procedure

Two experimental sessions were conducted each day: 1000 and 1600 hours. A red stimulus light signaled the onset of each session. In the presence of this light, the tenth lever press (fixed ratio [FR] 10) resulted in the operation of the infusion pump and delivery of 1 ml of saline or drug over 5 seconds. During the 5-second infusion, the red

stimulus light was extinguished, the center green light was illuminated, and further lever presses had no programmed consequence. For studies on CPDD 0066, immediately following each infusion, all stimulus lights were extinguished for a 10-second timeout during which lever presses had no programmed consequence. For studies on CPDD 0067 and CPDD 0068, this timeout was increased to 60 seconds. Session lengths for CPDD 0066 tests were approximately 120 minutes; CPDD 0067 and CPDD 0068 were examined in 60-minute test sessions.

Under baseline conditions, animals could respond for a dose of 0.01 mg/kg/injection of cocaine following the above outlined schedule requirements. To ensure that responding was maintained by drug, saline was substituted for cocaine every third or fourth session, usually for two consecutive sessions. CPDD 0066, CPDD 0067, and CPDD 0068 were studied two to three times per week, except on weekends. Drugs were studied in an ascending order of dose and saline was tested for at least three consecutive sessions prior to drug tests. Typically, each dose of each test compound was assessed at least twice in each animal.

Drugs

CPDD 0066, CPDD 0067, and CPDD 0068 were dissolved in sterile 0.9% saline. Test compounds were assessed over a dose range from 0.003 to 0.3 mg/kg/injection.

Discriminative Stimulus Effects in Rhesus Monkeys (amphetamine discrimination, UMMC)

Subjects and Apparatus

Three adult rhesus monkeys that had received other drugs prior to these studies were individually housed in stainless-steel cages with water available continuously. Feeding consisted of 110-200 g of Teklad monkey chow approximately 3 hours after each session and monkeys received a chewable vitamin 3 days per week. During experimental sessions, each monkey was seated in a restraint chair and placed in a sound-attenuating cubicle that had two response levers, a white light above each lever, and a white house light mounted on the ceiling. Shoes were attached to the chairs and were fitted with brass plates through which electric shock could be delivered. Experimental events were programmed and recorded using an Apple Macintosh computer in an adjacent room.

Procedure

Monkeys had been trained in a discrete-trials paradigm to discriminate amphetamine (1.0 mg/kg) from saline (Woolverton et al., 1994). Each monkey was placed in the chair and moved to the test room where their feet were placed in shoes and held in place with a Velcro strap. Monkeys received an infusion of either saline (0.25 ml/kg) or the training drug, followed by 2 ml of flush i.g. via a nasogastric tube. Monkeys remained in the chair in the test room for 55 minutes then were placed in the experimental chambers. The session began with a 5-minute timeout, after which the house light and lever lights were illuminated (trial) and responding on the correct lever either prevented electric shock (8515 and Ou3) or delivered a 1-g banana-flavored food pellet (M163), and extinguished the lights. Responding on the incorrect lever reset the response requirement on the correct lever. The correct lever was determined by the pre-session infusion (drug or saline). If the response requirement (FR2, 8515; FR 5, M163, Ou3) was not satisfied on the correct lever within 10 seconds of the onset of the lights, then shock (250 millisecond duration, 5 mA intensity) was delivered (8515 and Ou3 only). If the response requirement was not satisfied within 4 seconds after this shock, then a second shock was delivered and the trial ended. For M163, if the response requirement was not satisfied within 10 seconds, the trial ended. Sessions terminated after two consecutive trials in which 2 shocks were received or food was not received. Trials were separated by a 30-second timeout, and sessions lasted for 30 trials or 20 minutes, whichever occurred first.

Training sessions were conducted five days a week according to the following two-week schedule: SDDSS, DSSDD, where S denotes sessions preceded by saline infusion and D denotes sessions preceded by drug infusion. Discrimination training continued until at least 80% of the responses in the first trial were on the correct lever and at least 90% of the total trials (27/30) were avoidance trials (8515 and Ou3 only) for seven out of eight consecutive sessions. Test sessions were conducted according to the following two-week schedule: SDTST, DSTDT, where T denotes test sessions. If the criteria for stimulus control were not satisfied during the training sessions, test sessions

were not conducted and the training sequence continued. Test sessions were identical to training sessions except that completion of the response requirement on either lever was reinforced.

Drugs

d-Amphetamine sulfate (Abbott Laboratories, N. Chicago, IL) was dissolved in sterile 0.9% saline to an infusion volume of 0.25 ml/kg. CPDD 0066 was prepared in sterile water. The dose of 1.0 mg/kg was administered in 0.1 ml/kg. Doses of 3.0 and 10 mg/kg were administered in the standard infusion volume of 0.25 ml/kg. A dose of 17 mg/kg was administered to one monkey in 1.0 ml/kg. CPDD 0068 was prepared in sterile water with doses administered in the standard infusion volume of 0.25 ml/kg. Doses of CPDD 0066 and CPDD 0068 were tested the day after a saline or a drug-training session. If in that test responding occurred predominately on the drug lever, the dose was tested again the day after the opposite training session.

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations, UTHSCSA)

Subjects and Apparatus

Seven adult rhesus monkeys, weighing between 4.6 and 9.0 kg, were housed individually in stainless steel cages. Water was available continuously and monkeys received primate chow (Harlan Teklad, Madison, WI) daily as well as fresh fruit and peanuts several days per week.

Monkeys were seated in chairs that provided restraint at the neck. During experimental sessions, chairs were located in sound-attenuating, ventilated chambers that were equipped with two response levers, a food cup and stimulus lights. Chairs were equipped with shoes containing brass electrodes, to which brief (250 ms) electric shock could be delivered from an a.c. shock generator.

Procedure

Flumazenil Discrimination. Monkeys consumed 5.6 mg/kg of diazepam in fruit punch 3 hours prior to daily sessions in which they discriminated between s.c. injections of 0.1 mg/kg (two monkeys) or 1.78 mg/kg (one monkey) of flumazenil and vehicle while responding under an FR 5 schedule of food presentation (Gerak and France, 1999). Daily training sessions consisted of several discrete, 15-minute cycles. Each cycle comprised a 10-minute pretreatment period, during which the chamber was dark and lever presses had no programmed consequence, followed by a 5-minute response period, during which the chamber was illuminated green and monkeys could receive a 300 mg banana-flavored food pellet by responding five times on the appropriate lever as determined by the s.c. injection administered during the first minute of the 10-minute timeout (e.g., left lever after vehicle, right lever after flumazenil). Responses on the incorrect lever reset the response requirement on the correct lever. Test sessions were identical to training sessions except that various doses of flumazenil, CPDD 0066, CPDD 0067, or CPDD 0068 were administered during the first minute of the timeout and five consecutive responses on either lever resulted in the delivery of food. CPDD 0066, CPDD 0067, and CPDD 0068 were studied up to 2 hours after administration in tests comprising eight 15-minute cycles.

Midazolam Discrimination. Monkeys discriminated between s.c. injections of 0.32 mg/kg of midazolam and saline while responding under an FR 10 schedule of stimulus-shock termination (Lelas et al., 1999). Daily sessions comprised multiple, 15-minute cycles. Each cycle comprised a 10-minute pretreatment period, during which the chamber was dark and lever presses had no programmed consequence, followed by a response period, during which the chamber was illuminated red and monkeys could postpone scheduled shock for 30 seconds by responding ten times on the appropriate lever as determined by the s.c. injection administered during the first minute of the 10-minute timeout (e.g., left lever after saline, right lever after midazolam). Failure to satisfy the response requirement within 15 seconds resulted in the delivery of a brief shock. The response period ended after 5 minutes or 4 shocks, whichever occurred first. Responses on the incorrect lever reset the response requirement on the correct lever. Test sessions were identical to training sessions except that various doses of midazolam, CPDD 0066, CPDD 0067, or CPDD 0068 were administered during the first minute of the timeout and ten consecutive responses on either lever postponed the shock schedule. CPDD 0066, CPDD 0067, and CPDD 0068 were studied up to 2 hours after administration in tests comprising eight 15-minute cycles.

Diazepam (Zenith Laboratories, Northvale, NJ) was suspended in 42-48 ml (depending on body weight) of fruit punch containing suspending Agent K to yield a dose of 5.6 mg/kg/daily drinking episode. Flumazenil (F. Hoffman LaRoche, LTD, Basel, Switzerland) was dissolved in a vehicle of 10% ethanol, 40% propylene glycol and 50% saline; midazolam hydrochloride (Roche Pharma, Inc., Manati PR) was purchased as a commercially-prepared solution. CPDD 0066, CPDD 0067 and CPDD 0068 were dissolved in sterile 0.9% saline and were studied up to doses of 1.0, 10.0, and 0.32 mg/kg s.c., respectively.

Discriminative Stimulus Effects in Rats (LSD discrimination, SUNYB)

Subjects and Apparatus

Male Fischer 344 rats were obtained at an age of approximately 6 weeks from Harlan Sprague-Dawley Inc. (Indianapolis, IN, U.S.A.), housed in pairs under a 12-hour light-dark cycle beginning at 0600 hours, and allowed free access to water in their home cages. All training and testing occurred during the light cycle. Caloric intake was controlled to maintain a mean body weight of 250 g. Subjects were fed standard rat chow following experimental sessions. Caloric control has been shown to lengthen the life span and decrease the incidence of a variety of pathologies in Fischer 344 rats (Keenan et al. 1994).

Small animal test chambers [MED Associates ENV-008] were used for all experiments and were housed in larger light-proof, sound-insulating boxes which contained a house light and an exhaust fan. Chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper which delivered 0.1 ml of sweetened condensed milk diluted 2:1 with tap water. Sessions were managed by a micro-computer using operant control software [MED-PC State Notation, Version IV].

Procedure

After learning to drink from the dipper, rats were trained to press first one, and then the other, of the two levers. The number of responses for each reinforcer was gradually increased from 1 to 10. During this time, the reinforced lever was alternated on a random basis. All subsequent training and testing sessions used an FR 10 schedule of reinforcement. Subjects were then trained to discriminate LSD (0.1 mg/kg i.p., 15 min pretreatment; Hirschhorn and Winter 1971). Following the administration of LSD, every tenth response on the LSD-appropriate lever was reinforced. Similarly, responses on the saline-appropriate lever were reinforced on an FR 10 schedule following the injection of saline. For half of the subjects, the left lever was designated as the drug-appropriate lever. During discrimination training, drug and saline were alternated on a daily basis. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, at least 83% of all responses prior to the delivery of the first reinforcer were on the appropriate lever, i.e., no more than 2 incorrect responses prior to completion of the FR10 on the correct lever.

After stimulus control with LSD was established, tests of generalization were conducted once per week in each animal. Tests were balanced between subjects trained on the previous day with saline and drug, respectively. During test sessions, no responses were reinforced and the session was terminated after the emission of 10 responses on either lever. The distribution of responses between the two levers was expressed as the percentage of total responses emitted on the drug-appropriate lever. Response rate was calculated for each session by dividing the total number of responses emitted prior to lever selection, that is, prior to the emission of 10 responses on either lever, by elapsed time. Data for any subject failing to emit 10 responses within the 10-minute test session were not considered in the calculation of the percent drug-appropriate responding but were included in the calculation of response rates.

Drugs

Lysergic acid diethylamide [(+)-LSD (+)-tartrate (2:1)] and [-]-2,5-dimethoxy-4-methylamphetamine (DOM) were generously provided by the National Institute on Drug Abuse (Rockville, MD). Doses of LSD and DOM were expressed as mg/kg of the salts; both drugs were dissolved in sterile 0.9% saline. A stock solution of pirenpirone (1

mg/ml) was prepared in a minimal volume of a 45 percent w/v aqueous solution of 2-hydroxy-propyl-β-cyclodextrin and solutions for i.p. injections were made by diluting the stock with sterile 0.9% saline.

Head-twitch Response in Mice (UM)

Subjects and Apparatus

Male NIH Swiss mice (Harlan Sprague Dawley Inc., Indianapolis, IN) weighing approximately 20-30 g were housed 12 animals per 44.5 x 22.3 x 12.7 cm Plexiglas cage in a room that was maintained at $22 \pm 2°C$ and 45-50% humidity under a 12-hour light/dark cycle. Animals were fed Lab Diet rodent chow (Laboratory Rodent Diet #5001, PMI Feeds, Inc., St. Louis, MO) and water *ad libitum* until immediately before testing. Neither food nor water was available during the tests. Animals were not used in experiments until at least two days after arrival in the laboratory. Each animal was used only once, and was sacrificed immediately after use.

Procedure

The drug elicited head-twitch response is a selective behavioral model for $5-HT_2$ agonist activity in the rodent, and several previous studies have established that direct and indirect 5-HT agonists induce this effect (Peroutka *et al.* 1981; Colpaert and Janssen 1983; Green *et al.* 1983; Goodwin and Green 1985; Darmani *et al.* 1990a, 1990b, 1992). Further, $5-HT_2$ receptor antagonists selectively block the head-twitch response (Lucki *et al.* 1984; Handley and Singh 1986) with a potency that is highly correlated with affinity for $5-HT_2$ receptors (Peroutka *et al.* 1981; Ortmann *et al.* 1982).

On test days, mice were weighed, marked, and returned to the home cage. Individual animals were subsequently removed from the home cage, received saline i.p., and then placed into a 15.24 x 25.40 x 12.70 cm Plexiglas mouse cage. Ten minutes after the initial injection, mice received an injection of either saline or one of several doses of R(-)-DOM, CPDD-0066 or CPDD-0068 and were returned to the observation cage. Five minutes after this second injection, a camera mounted above the observation cage began recording behavior for 10 minutes. Videotapes were later scored for the head-twitch response (defined as a rapid rotational jerk of the head that is not contiguous with any grooming or scratching behaviors) by two observers who were blind to treatment.

Drugs

R(-)-DOM (National Institute on Drug Abuse, Research Technology Branch, Research Triangle Park, NC), CPDD 0066 and CPDD 0068 were dissolved in sterile 0.9% saline. All injections were i.p. at a volume of 1 ml/100 g.
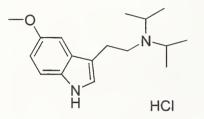
Competition Binding in Rat Brain (SUNYB)

Receptor Binding

The frontal cortex ($5-HT_{2A}$ receptors), hippocampus ($5-HT_{1A}$ receptors), or brain stem ($5-HT_{2C}$ receptors) from male CDF rats (Charles Rivers Laboratories) was homogenized (Dounce tissue grinder) in 50 mM Tris-HCl (pH 7.4). The homogenates were then centrifuged at 40,000 g for 15 minutes at 4°C. The resulting pellets were resuspended in the Tris buffer and stored at $-80°C$. On the day of the assays tissue samples were thawed and centrifuged at 40,000 g for 15 minutes at 4°C. The resulting pellets were resuspended in 30 ml warm 50 mM Tris-HCl (pH 7.4) and incubated for 10 minutes at 37°C to remove endogenous serotonin. Samples were again centrifuged at 40,000 g for 15 minutes at 4°C. Final resuspension of the pellets (frontal cortex: 6.7 mg/ml; hippocampus: 5 mg/ml; brain stem 13.3 mg/ml) was in Tris assay buffer (50 mM Tris-HCl, pH 7.4, containing 4 mM $MgCl_2$, 10μM pargyline and 0.1% ascorbate). For [^{3}H]8-OH-DPAT binding, assays were carried out for 30 minutes at 37°C in a final volume of 0.5 ml containing Tris assay buffer, 1 nM radioligand (129 Ci/mmole; Perkin-Elmer, Boston MA), appropriate drugs, and hippocampal membranes (2 mg wet weight/tube). For [^{3}H]ketanserin binding, assays were carried out for 30 minutes at 30°C in a final volume of 0.5 ml containing Tris assay buffer, 1.5 nM radioligand (88 Ci/mmole; Perkin-Elmer, Boston MA), 100 nM prazosin to prevent binding to α_1-adrenergic receptors, appropriate drugs, and frontal cortical membranes (2 mg wet weight/tube). For [^{3}H]mesulergine binding, assays were carried out for 45 minutes at 37°C in a final volume

of 0.5 ml containing Tris assay buffer, 2 nM radioligand (77 Ci/mmole; Amersham Biosciences), 100 nM spiperone to prevent binding to 5-HT$_{2A}$ and dopamine D$_2$ receptors, appropriate drugs, and membranes from the brain stem (4 mg wet weight/tube). Reactions were terminated by rapid vacuum filtration (Brandel harvester) through GF/B glass fiber filters presoaked in 0.1% polyethylenimine. Filters were washed twice with cold 50 mM Tris-HCl (pH 7.4) with the amount of bound radioactivity measured by scintillation spectrophotometry. Nonspecific binding was defined as the difference in the amount of radioligand binding in the absence and presence of either 10 μM 5-HT ([^{3}H]8-OH-DPAT binding), 20 μM 5-HT ([^{3}H]mesulergine binding) or 100 μM cinanserin ([^{3}H]ketanserin binding). Data were analyzed by nonlinear regression using the program EBDA/LIGAND (Elsevier BIOSOFT).

RESULTS

CPDD 0066: 5-Methoxy-N,N-diisopropyltryptamine HCL

Reinforcing Effects in Rhesus Monkeys

A dose of 0.01 mg/kg/injection of cocaine maintained high rates of responding in all monkeys with an average of more than 100 injections of cocaine received per session. Up to five doses of CPDD 0066 were evaluated in three rhesus monkeys. Figure 1 shows the mean (± SEM) effects obtained with CPDD 0066. No animal self-administered this compound at rates greater than those engendered by saline.
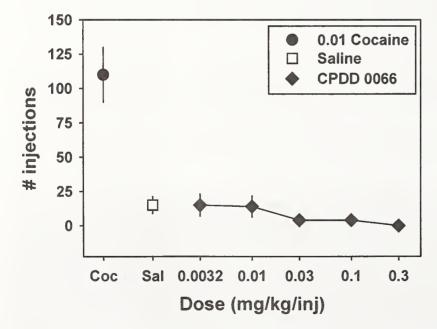

Figure 1. Self-administration studies with CPDD 0066.

Discriminative Stimulus Effects in Rhesus Monkeys (amphetamine discrimination)

When administered 60 minutes before the session, CPDD 0066 generally lacked amphetamine-like discriminative stimulus effects up to a dose of 10 mg/kg (Table 1). Partial substitution at 3.0 mg/kg in monkey Ou3 was the result of averaging full substitution during the initial test session with no substitution when this dose was retested. This variable effect, and the lack of amphetamine-like responding at any dose in other monkeys, suggests that the full substitution seen in the initial test in Ou3 was a spurious result. CPDD 0066 was administered to an untrained monkey at a dose of 17 mg/kg. After 2-3 minutes the monkey began to seize. Seizures were controlled with diazepam and isoflurane and the monkey was conscious and sitting 4-5 hours later. Therefore, doses of CPDD 0066 larger than 10 mg/kg were not tested in trained monkeys.

Subject	TABLE 1 CPDD 0066 (D0SE) MG/KG				
	AMPH	SALINE	1.0	3.0	10.0
8515	100 / 1.4	1.5 / 1.8	0 / 1.0	0 / 0.8	0 / 1.1
M163	100 / 1.8	5 / 1.4	0 / 2.3	0 / 2.5	0 / 1.7
Ou3	100 / 2.3	0 / 2.7	0 / 1.6	0 / 2.1	48 / 2.1

CPDD 0066 was administered via nasogastric tube 60 minutes prior to testing.

AMPH = amphetamine

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations)

Flumazenil Discrimination. In monkeys receiving 5.6 mg/kg/day of diazepam and discriminating between 0.1 mg/kg (JI) or 0.178 mg/kg (JE) of flumazenil and vehicle, flumazenil dose-dependently increased responding on the drug-associated lever with a dose of 0.1 mg/kg occasioning greater than 80% drug-lever responding in each monkey (Table 2). Over the doses studied, flumazenil decreased response rate in JI and increased response rate in JE.

Subject	TABLE 2 Flumazenil Dose (mg/kg)			
	Veh	0.01	0.032	0.1
JI	0 / 1.76	0 / 1.79	27 / 1.46	82 / 0.83
JE	0 / 0.46	0 / 0.38	74 / 0.90	88 / 1.04

Data represent percent drug-appropriate responding / response rate (responses / second)
Veh, vehicle

CPDD 0066 did not substitute (i.e., did not occasion at least 80% drug-lever responding) for the flumazenil discriminative stimulus (Table 3) up to doses (0.32 mg/kg in JE and 0.56 mg/kg in JI) that suppressed responding.

Data shown are an average of responding at 30 minutes after administration of CPDD 0066.

Subject	TABLE 3 CPDD 0066 Dose (mg/kg)			
	Veh	0.1	0.32	0.56
JI	0 / 1.36	10 / 1.69	0 / 1.84	* / 0
JE	0 / 0.47	0 / 0.36	* / 0	NT

Data represent percent drug-appropriate responding / response rate (responses / second)
Veh, vehicle
*Discrimination data are not presented when response rate was <20% of control response rate
NT, not tested

At the largest doses (0.56 mg/kg in JI and 0.32 mg/kg in JE), the onset of action for CPDD 0066 to suppress responding was 15-30 minutes and the duration of action was 30-60 minutes (Table 4).

Subject (mg/kg of CPDD 0066)	TABLE 4 Min after CPDD 0066				
	15	30	45	60	75
JI (0.56)	14 / 1.60	* / 0	* / 0	65 / 1.53	0 / 1.80
JE (0.32)	* / 0	* / 0	* / 0	* / 0	0 / 0.76

See Table 3 for details

Midazolam Discrimination. In monkeys discriminating between 0.32 mg/kg of midazolam and vehicle, midazolam dose-dependently increased responding on the drug-associated lever with doses of 0.1 mg/kg and 0.32 mg/kg occasioning greater than 80% drug-lever responding in LI and GI, respectively (Table 5). Over the doses studied, midazolam increased response rate in LI and decreased response rate in GI. CPDD 0066 did not substitute (i.e., did not occasion at least 80% drug-lever responding) for the midazolam discriminative stimulus (Table 6) up to a dose (1.0 mg/kg) that markedly decreased responding and that produced pupil dilation and hyperventilation. Data shown are from 30 minutes after administration of CPDD 0066.

Subject	TABLE 5 Midazolam Dose (mg/kg)				
	Veh	0.01	0.032	0.1	0.32
LI	0 / 1.59	0 / 1.39	0 / 1.47	100 / 2.05	NT
GI	0 / 1.94	0 / 1.60	0 / 1.22	1 / 0.99	100 / 0.95

NT, not tested
See Table 3 for details

| Subject | TABLE 6 CPDD 0066 Dose (mg/kg) | | | |
	Veh	0.32	0.56	1.0
LI	0 /1.34	0 / 1.58	0 / 1.43	* / 0
GI	0 / 1.98	0 / 2.62	0 / 1.70	* / 0.06

See Table 3 for details

At the largest dose (1.0 mg/kg), the onset of action for CPDD 0066 to suppress responding was 15 minutes and the duration of action was at least 30 min (Table 7).

| Subject (mg/kg of CPDD 0066) | TABLE 7 Min after CPDD 0066 | | | | |
	15	30	45 60	75	
LI (1.0)	* / 0	* / 0	0 / 2.00	0 / 1.92	0 / 2.15
GI (1.0)	* / 0	* / 0.06	1 / 1.09	0 / 1.59	0 / 1.38

See Table 3 for details

Discriminative Stimulus Effects in Rats (LSD discrimination)

Up to a dose of 3 mg/kg, CPDD 0066 substituted partially for the LSD discriminative stimulus and also decreased rate of responding (Figure 2). Moreover, the partial LSD-like discriminative stimulus effects of 1 mg/kg of CPDD 0066 were completely attenuated by pretreatment with 0.16 mg/kg of pirenpirone.

Head-twitch Response in Mice

R(-)-DOM generated a biphasic dose-response function on the head-twitch response, consistent with previous studies in mice (Fantegrossi et al., 2004a). R(-)-DOM-induced head-twitches peaked at a mean of approximately 14 twitches in 10 minutes at a dose of 1.0 mg/kg (Table 8). CPDD 0066 induced a similar biphasic dose-response function for the head-twitch response, although this compound was less effective than DOM, eliciting a maximum of 8.5 twitches at a dose of 1.0 mg/kg.
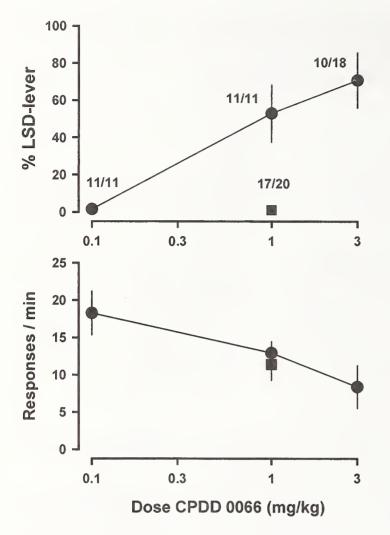
Figure 2. Discriminative stimulus (upper) and rate-altering (lower) effects of CPDD 0066 administered alone (circles) or 60 minutes after administration of 0.16 mg/kg of pirenpirone (squares) in rats discriminating between 0.1 mg/kg of LSD and saline. Ordinates: upper, average percentage of responses on the LSD-associated lever; lower, rate of lever pressing in responses/minute. Abscissa: dose in mg/kg body weight. CPDD 0066 was administered 15 minutes before testing. Other values (X/Y) indicate number of animals responding / number of animals studied.

Dose	Saline	DOM	CPDD 0066	CPDD 0068
0.0	0.67 ± 0.33	-		
0.3	-	5.67 ± 0.76	1.67 ± 0.49	2.83 ± 0.60
1.0	-	14.17 ± 1.40	8.50 ± 1.38	15.60 ± 2.41
3.0	-	10.33 ± 3.77	6.33 ± 0.80	7.33 ± 0.95
10.0	-	7.17 ± 2.09	Not studied	Not studied

Table 8. Head-twitch response for DOM, CPDD 0066 and CPDD 0068. Each value is the mean ($\pm$ SEM) number of twitches per 10-minute observation period for different groups of mice.
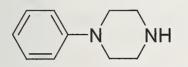
Competition Binding in Rat Brain

CPDD 0066 displaced binding in all three assays indicating binding affinity for 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_{2C}$ receptors in rat brain (Table 9); CPDD 0066 had highest affinity for 5-HT$_{1A}$ receptors.

CPDD #	pK$_I$ [^{3}H]8-OH-DPAT	pK$_I$ [^{3}H]ketanserin	pK$_I$ [^{3}H] mesulergine

0066	7.44 ± 0.04	5.25 ± 0.04	5.77 ± 0.36
0067	6.51 ± 0.01	5.11 ± 0.06	5.57 ± 0.07
0068	5.93 ± 0.08	6.92 ± 0.17	7.41 ± 0.02

Table 9. Binding affinities at 5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors. Affinities of the various compounds at [^{3}H]8-OH-DPAT binding sites in hippocampus [5-HT$_{1A}$], [^{3}H]ketanserin binding sites in frontal cortex [5-HT$_{2A}$], and [^{3}H] mesulergine binding sites in brain stem [5-HT$_{2C}$] were measured as described in the Methods section. Data are expressed as the mean ($\pm$ SEM; n=3-5) negative log of the equilibrium dissociation constant (pK$_i$).

CPDD 0067: Phenylpiperazine Oxalate

Oxalate

Reinforcing Effects in Rhesus Monkeys

Four doses of CPDD 0067 were evaluated in three rhesus monkeys. Figure 3 shows the mean ($\pm$ SEM) effects obtained with CPDD 0067. No animal self-administered this compound at rates greater than those engendered by saline.
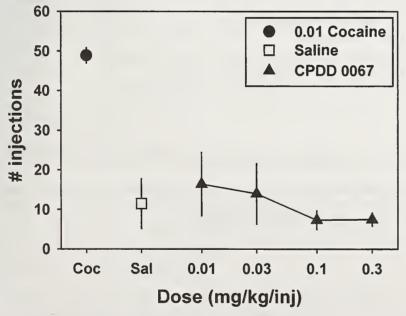

Figure 3. Self-administration studies with CPDD 0067.

No behavioral changes were noted following CPDD 0067 test sessions, although 2 of 3 animals failed to emit a single response in afternoon sessions following morning exposure to 0.1 and 0.3 mg/kg/injection of CPDD 0067.

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations)

Flumazenil Discrimination. In monkeys receiving 5.6 mg/kg/day of diazepam and discriminating between 0.1 mg/kg (JI) or 0.178 mg/kg (JE) of flumazenil and vehicle, flumazenil dose-dependently increased responding on the drug (flumazenil)-associated lever with a dose of 0.1 mg/kg occasioning greater than 80% drug-lever responding in

each monkey (Table 10). Over the doses studied, flumazenil decreased response rate in JI and increased response rate in JE.

Subject	TABLE 10 Flumazenil Dose (mg/kg)			
	Veh	0.01	0.032	0.1
JI	0 / 1.76	0 / 1.79	27 / 1.46	82 / 0.83
JE	0 / 0.46	0 / 0.38	74 / 0.90	88 / 1.04

Data represent percent drug-appropriate responding / response rate (responses / second)
Veh, vehicle

CPDD 0067 did not substitute for the flumazenil discriminative stimulus (Table 11) up to doses (1.0 mg/kg in JE and 3.2 mg/kg in JI) that suppressed responding. Data shown are an average of responding at 30 minutes after administration of CPDD 0067.

Subject	TABLE 11 CPDD 0067 (mg/kg)				
	Veh	0.1	0.32	1.0	3.2
JI	0 /1.36	NT	0 / 1.59	0 / 0.85	* / 0
JE	0 / 0.45	0 / 0.70	0 / 0.13	* / 0	NT

Data represent percent drug-appropriate responding / response rate (responses / second)
*Discrimination data are not presented when response rate was <20% of control response rate
Veh, vehicle
NT, not tested

At the largest doses studied (3.2 mg/kg in JI and 1.0 mg/kg in JE), the onset of action for CPDD 0067 to suppress responding was 15 minutes and the duration of action was 90-120 minutes (Table 12).

Subject (mg/kg of CPDD 0067)	TABLE 12 Min after CPDD 0067							
	15	30	45	60	75	90	105	120
JI (3.2)	* / 0.10	* / 0	* / 0	0 / 0.54	4 / 0.19	2 / 0.16	0 / 0.43	0 / 0.49
JE (1.0)	* / 0	* / 0	* / 0	* / 0.05	0 / 0.20	0 / 0.55	0 / 0.63	0 / 0.75

See Table 11 for details

Midazolam Discrimination. In monkeys discriminating between 0.32 mg/kg of midazolam and vehicle, midazolam dose-dependently increased responding on the drug (midazolam)-associated lever with a dose of 0.32 mg/kg occasioning greater than 80% drug-lever responding in each monkey (Table 13). Over the doses studied, midazolam increased response rate in RO and decreased response rate in GI. CPDD 0067 did not substitute for the midazolam discriminative stimulus (Table 14) up to a dose (10.0 mg/kg) that decreased responding. Data shown are from responding at 120 minutes after administration of CPDD 0067. At the largest dose (10.0 mg/kg) of CPDD 0067, the largest decrease in responding was observed in the last cycle of the 2-hr session (Table 15).

Subject	TABLE 13 Midazolam Dose (mg/kg)				
	Veh	0.01	0.032	0.1	0.32
RO	0 /2.38	0 / 2.65	0 / 2.49	0 / 2.64	100 / 3.09
GI	0 / 1.94	0 / 1.60	0 / 1.22	1 / 0.99	100 / 0.95

See Table 11 for details

Subject	TABLE 14 CPDD 0067 Dose (mg/kg)			
	Veh	3.2	5.6	10.0
RO	0 /2.24	0 / 1.72	0 / 2.37	0 / 1.26
GI	0 / 1.35	NT	0 / 1.89	0 / 0.70

See Table 11 for details

Subject (mg/kg of CPDD 0067)	TABLE 15 Min after CPDD 0067							
	15	30	45	60	75	90	105	120
RO (10.0)	0 / 2.05	0 / 1.69	0 / 1.76	0 / 1.47	0 / 1.47	0 / 1.33	0 / 1.35	0 / 1.26
GI (10.0)	0 / 1.34	0 / 1.34	0 / 1.80	0 / 1.60	0 / 1.30	0 / 1.99	0 / 1.72	0 / 0.70

See Table 11 for details

Discriminative Stimulus Effects in Rats (LSD discrimination)

Up to a dose that eliminated responding (3 mg/kg), CPDD 0067 failed to substitute for the LSD discriminative stimulus in rats (Figure 4). The largest dose of CPDD 0067 that did not eliminate responding (1.0 mg/kg) also was studied for its effects over a broader range of pretreatment times (Figure 5) and, under those conditions, failed to substitute for LSD.

Competition Binding in Rat Brain

Although CPDD 0067 displaced binding in all three assays, indicating some binding affinity for $5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, and $5\text{-}HT_{2C}$ receptors in rat brain (Table 9), overall its affinity for all three receptors was comparatively low.
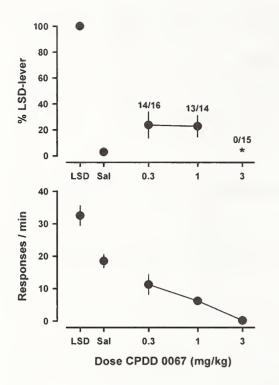
Figure 4. Discriminative stimulus effects of CPDD 0067 in rats discriminating between 0.1 mg/kg of LSD (triangles) and saline (inverted triangles). CPDD 0067 was administered 30 minutes before testing. See Figure 2 for other details.
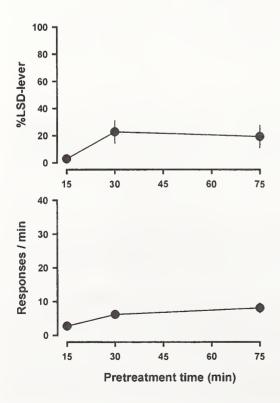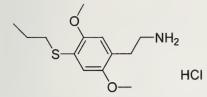

Figure 5. Time course of effects for 1.0 mg/kg of CPDD 0066 in rats discriminating LSD. See Figures 2 and 4 for other details.

CPDD 0068: 2,5-Dimethoxy-4-(n)-propyl-thiophenethylamine HCL

Reinforcing Effects in Rhesus Monkeys

Four doses of CPDD 0068 were evaluated in three rhesus monkeys. Figure 6 shows the mean (± SEM) effects obtained with CPDD 0068. No animal self-administered this compound at rates greater than those engendered by saline. Following sessions when large unit doses of CPDD 0068 were available, animals appeared sluggish and tended to display stereotyped jaw opening and head movements, especially after 0.01 and 0.03 mg/kg/injection. In addition, animals obtained fewer injections of cocaine in afternoon sessions following morning test sessions with CPDD 0068 as compared to sessions following morning sessions with cocaine (Figure 7).
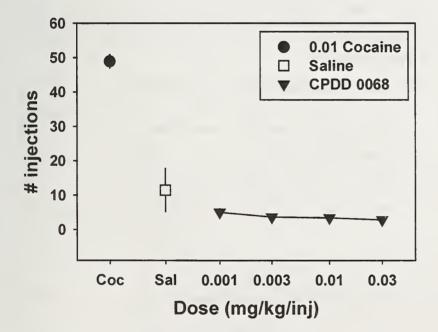

Figure 6. Self-administration studied with CPDD 0068

Discriminative Stimulus Effects in Rhesus Monkeys (amphetamine discrimination)

When administered 60 minutes before the session, CPDD 0068 lacked amphetamine-like discriminative stimulus effects and did not systematically alter response rate up to a dose of 3.0 mg/kg (Table 16). Following 3.0 mg/kg of CPDD 0068, monkeys were visibly affected (e.g., appeared more calm than usual and staring). All ate monkey chow offered after the session.

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations)

Flumazenil Discrimination. In monkeys receiving 5.6 mg/kg/day of diazepam and discriminating between 0.1 mg/kg of flumazenil and vehicle, flumazenil dose-dependently increased responding on the drug-associated lever with a dose of 0.1 mg/kg occasioning greater than 80% drug-lever responding in each monkey (Table 17). Flumazenil dose-dependently decreased response rate.
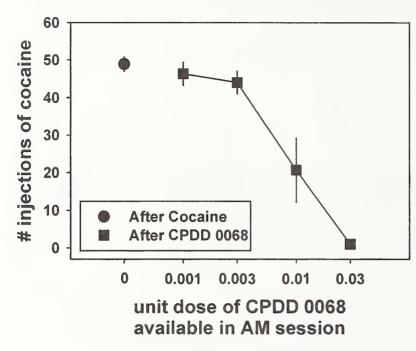
215

Figure 7. Cocaine self-administration in sessions following morning sessions with CPDD 0068.

Subject	TABLE 16 CPDD 0068 (D0SE) MG/KG				
	AMPH	SALINE	0.3	1.0	3.0
8515	100 / 1.4	1.5 / 1.8	0 / 1.1	0 / 1.0	0 / 1.0
M163	100 / 1.8	5 / 1.4	0 / 2.0	0 / 2.3	0 / 1.9
Ou3	100 / 2.3	0 / 2.7	0 / 2.1	0 / 2.0	0 / 2.4

See Table 1 for other details.

Subject	TABLE 17 Flumazenil Dose (mg/kg)			
	Veh	0.01	0.032	0.1
JI	0 / 1.41*	11 / 1.65	53 / 1.29	98 / 0.79
NA	0 / 1.00	13 / 0.95	51 / 0.40	84 / 0.17

*Data represent percent drug-appropriate responding / response rate (responses / second)
Veh = vehicle

CPDD 0068 did not substitute for the flumazenil discriminative stimulus (Table 18) up to a dose (0.32 mg/kg) that suppressed responding. Data shown are from 30 minutes after administration of CPDD 0068 (peak onset for rate-decreasing effects).

| Subject | TABLE 18 CPDD 0068 Dose (mg/kg) | | | | |
	Veh	0.01	0.032	0.1	0.32
JI	9 / 1.59	NS	0 / 1.60	0 / 0.87	* / 0
NA	2 / 0.83	10 / 0.13	* / 0	NS	* / 0

*Discrimination data are not presented when food was not delivered
NS = not studied
See Table 17 for other details

Midazolam Discrimination. In monkeys discriminating between 0.32 mg/kg of midazolam and vehicle, midazolam dose-dependently increased responding on the drug-associated lever with a dose of 0.32 mg/kg occasioning greater than 80% drug-lever responding in each monkey (Table 19). The largest dose of midazolam (0.32 mg/kg) slightly decreased response rate.

CPDD 0068 did not substitute for the midazolam discriminative stimulus (Table 20) up to a dose (0.32 mg/kg) that significantly decreased response rate (GI) and that produced emesis and salivation. Data shown are from 30 minutes after administration of CPDD 0068 (peak onset for rate-decreasing effects).

| Subject | TABLE 19 Midazolam Dose (mg/kg) | | | | |
	Veh	0.01	0.032	0.1	0.32
SA	0 /3.25	0 / 3.01	0 / 2.69	33/ 1.68	100 / 1.63
GI	0 / 1.71	0 / 1.54	0 / 1.76	63/ 1.00	98 / 0.53

See Table 17 for other details

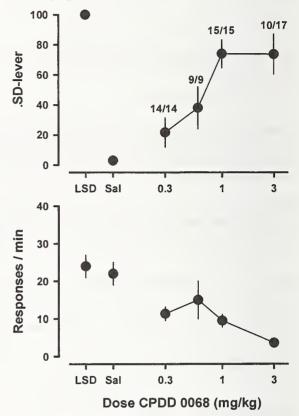| Subject | TABLE 20 CPDD 0068 Dose (mg/kg) | | | |
	Veh	0.032	0.1	0.32
SA	0 /2.77	0 / 2.89	0 / 2.89	0 / 2.82
GI	0 / 1.75	NS	0 / 0.74	0 / 0.14

See Tables 17 and 18 for other details

Discriminative Stimulus Effects in Rats (LSD discrimination)

Increasing doses of CPDD 0068 occasioned increased responding on the LSD-associated lever with an average of more than 70% responding on the LSD lever occurring at doses of 1 and 3 mg/kg (Figure 8). A dose of 3 mg/kg of CPDD 0068 markedly decreased rates of responding. Figure 9 shows a comparison of the time course of 0.3 mg/kg of DOM and 1 mg/kg of CPDD 0068. The most LSD-lever responding occurred with DOM 75 minutes after administration of CPDD 0068 45 minutes after administration.

CPDD 0068 induced the head-twitch response in mice (Table 8) at doses of 0.3-3.0 mg/kg. Similar to effects obtained with DOM, the dose-response function for CPDD 0068-induced head-twitching was biphasic, with a maximum of 15.6 twitches per 10 minutes occurring at a dose of 1.0 mg/kg.

Figure 8. Discrimination stimulus effects of CPDD 0068 (circles) in rats discriminating between 0.1 mg/kg LSD (triangles) and saline (inverted triangles) 45 minutes prior to testing. See Figure2
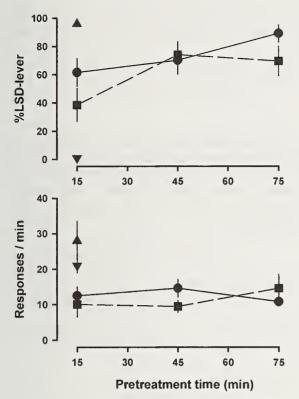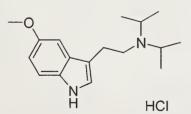
Figure 9. Time course of effects for 0.3 mg/kg of [-]-DOM (circles) and 1.0 mg/kg of CPDD 0068 (squares) in rats discriminating between 0.1 mg/kg of LSD (triangles) and saline (inverted triangles). See Figures 2 and 8 for other details.

Competition Binding in Rat Brain

CPDD 0068 displaced binding in all three assays indicating binding affinity for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors in rat brain (Table 9); however, CPDD 0068 had highest affinity for 5-HT_{2A}, and 5-HT_{2C} receptors.
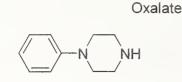
CONCLUSIONS

CPDD 0066   **HCl**
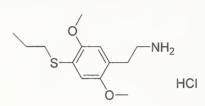
5-Methoxy-N,N-diisopropyltryptamine HCl

CPDD 0066 did not maintain self administration responding in monkeys and, up to doses that decreased rats of responding, did not substitute for amphetamine, midazolam or flumazenil in monkeys. However, like DOM, CPDD 0066 induced head-twitching in mice and substituted partially for an LSD discriminative stimulus in rats; like other tryptamines, CPDD 0066 had highest affinity for 5-HT_{1A} receptors. Moreover, the LSD-like effects of CPDD 0066 were attenuated by the 5-HT_{2A} receptor antagonist, pirenpirone. Collectively, these data are consistent with the view that this compound exerts LSD-like behavioral effects and, therefore, that its abuse could be due to LSD-like hallucinogenic activity at 5-HT receptors. The much greater potency of CPDD 0066 in altering responding in the midazolam and flumazenil discrimination procedures (s.c.), as compared to the amphetamine discrimination procedure (i.g.), indicates that the bioavailability of CPDD 0066 is greater after s.c. as compared to i.g. administration.

Oxalate

CPDD 0067

1-Phenylpiperazine Oxalate

CPDD 0067 was not self administered by rhesus monkeys and, up to doses that decreased rates of responding, did not substitute for midazolam or flumazenil in monkeys or for LSD in rats. CPDD 0067 had very low affinity for 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors and did not share behavioral actions with LSD. CPDD 0067 is structurally similar to benzylpiperazine (BZP; CPDD 0063); however, unlike BZP (Fantegrossi et al., 2004b) it was not self administered by monkeys. Ongoing studies are assessing whether this compound, like BZP (Fantegrossi et al., 2004b), shares discriminative stimulus effects with amphetamine in monkeys.

CPDD 0068

2,5-Dimethoxy-4-(n)-propyl-thiophenethylamine HCl

CPDD 0068, like CPDD 0066, has a profile of effects that is similar to well characterized hallucinogens (e.g., LSD, DOM). Specifically, CPDD 0068 wais not self administered by monkeys, did not substitute for amphetamine, and, up to doses that decrease rates of responding, did not substitute for midazolam or flumazenil. However, as might be expected of an analog of DOM, this compound had relatively high affinity for 5-HT_{2A} and 5-HT_{2C} receptors, it induced head-twitching in mice, and it substituted partially for an LSD discriminative stimulus in rats. Collectively, these data are consistent with the view that this compound exerts LSD-like behavioral effects and, therefore, that its abuse could be due to LSD-like hallucinogenic activity at 5-HT receptors. The much greater potency of CPDD 0068 in altering responding in the midazolam and flumazenil discrimination procedures (s.c.), as compared to the amphetamine discrimination procedure (i.g.), suggesting that the bioavailability of CPDD 0068 is greater after s.c. as compared to i.g. administration.

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