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The College on Problems of Drug Dependence, Inc.

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Virginia Commonwealth University

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QUEBEC, CANADA

Sunday, June 17, 2007

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Suicidality and SSRI treatment in depressed, substance-abusing adolescents

P. Riggs1,2, S.K. Mikulich-Gilbertson1,2 and S.K. Stover1,2, 1Psychiatry, and 2Division of Substance Dependence, University of Colorado at Denver Health Science Campus, Denver, CO

White matter organization and substance use disorders: A preliminary study in adolescents and young adults

D. Thatcher1, J.L. Weston1, S. Chickering1, R.A. Terwilliger2 and D.B. Clark1, 1Psychiatry, University of Pittsburgh, and 2Carnegie Mellon University, Pittsburgh, PA

OPIOID TREATMENT I

The standing heel-rise test and injection drug use: Relations to chronic venous disorders, balance, gait, and walk time

B.A. Pieper1, T. Templin1, T. Birk1 and R. Kirsner2, 1Wayne State University, Detroit, MI and 2University of Miami, Miami, FL

Neurocognitive characterizations of Russian heroin addicts without a significant history of other drug use

D.H. Fishbein1, E. Krupitsky2, B. Flannery1, D. Langevin3, G. Bobashev1, K. Bolla4, E. Zvartau2, 1RTI Intl, Baltimore, MD, 2St. Petersburg State Pavlov Med. U., St. Petersburg, Russian Federation 3Pacific Inst. for Research & Evaluation, Calverton, MD & 4Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Psychomotor and cognitive performance in methadone maintenance patients before vs. after daily methadone dosing

M.Z. Mintzer, R.G. Vandrey, G.E. Bigelow, M.L. Stitzer and E.C. Strain, Johns Hopkins University, Baltimore, MD

Methadone dosage and cognitive impairment in methadone-maintained patients

V. Swingedouw1, S. Auriacombe2, E. Reviriego1, M. Fatseas1 and M. Auriacombe1, 1Addiction Psychiatry JE2358/INSERM-IFR99, Universite Victor Segalen Bordeaux 2, and 2Cognitive Neurology, University Hospital, Bordeaux, France

A randomized controlled pilot trial of methylphenidate and cognitive-behavioral group therapy for cocaine dependence in heroin prescription

K.M. Dürsteler-MacFarland1, C. Bürki2, J. Strasser1, S. Petitjean1, D. Ladewig1 and G.A. Wiesbeck1, 1Psychiatry, University, Basle, and 2Psychiatry, University, Berne, Switzerland

Individual differences to naloxone vs. placebo in opioid-dependent humans responding under a naloxone discrimination procedure: Influence of sex and methadone maintenance dose

M.P. Chopra, M. Mancino, Z. Feldman, J. McGaugh and A. Oliveto, Psychiatry and Human Behavior, University of Arkansas for Medical Sciences, Little Rock, AR

Low-dose naloxone challenge for quantitative opioid dependence measurement

S.M. Stine, M. Greenwald, M. Ebenbichler, D. Tansil and C. Schuster, Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI

Buprenorphine/naloxone maintenance for opioid dependence in primary care

E.W. Gunderson1,2, D.A. Fiellin3, A.R. Nelson1, S.K. Vosburg1 and F.R. Levin1,2, 1Columbia University, and 2NYS Psychiatric Institute, New York, NY, and 3Yale University, New Haven, CT

Buprenorphine vs. naltrexone maintenance treatment for opium- or heroin-dependent individuals in Iran: Preliminary findings of a pilot randomized clinical trial

R.S. Schottenfeld1, A. Mokri2, H. Taheri Nakhost2 and M.C. Chawarski1, 1Yale University School of Medicine, New Haven, CT and 2INCAS, Tehran, Iran

A placebo-controlled trial of naltrexone and fluoxetine for opioid addiction: Analysis of medication responders

E. Krupitsky2, G.E. Woody1, E. Zvartau2, D. Mazalov2, M. Tsoi2, V. Egorova2, A. Burakov2, T. Didenko2, T. Romanova2, E. Verbitskaya2, A. Bespalov2, N. Neznanov2, T. Slavina2, A. Grinenko2 and C. O'Brien1, 1U. Penn., Philadelphia, PA and 2Clinical Pharm. of Addictions, St. Petersburg State Pavlov Medical University, St. Petersburg, Russian Federation

Patient satisfaction with opioid substitution therapy: More than withdrawal

A. Elkader1,2, B.A. Sproule1,2, B. Brands1,2,3, M. Zack1,2 and R. Callaghan1,2, 1Centre for Addiction and Mental Health, and 2University of Toronto, Toronto, and 3Office of Research and Surveillance, DCSC, Health Canada, Ottawa, ON, Canada

First Republic of Georgia randomized controlled trial (RCT) for drug abuse treatment: The process and initial results of developing a couple's treatment for drug abuse

D. Otiashvili1, H. Jones2, M. Chavchanidze1, I. Kirtadze1 and M. Tuten2, 1Addiction Research Center, Union Alternative Georgia, Tbilisi, Georgia and 2Johns Hopkins University, Baltimore, MD

Quality of life among methadone or buprenorphine maintenance treatments outpatients

P. Courty1, D. Alexeï1, C. Auclair2, L. Gerbaud2 and P.M. Llorca1, 1CMP B, CSST SATIS, and 2Department of Public Health, CHU G.MONTPIED, Clermont Ferrand cedex 1, France

Change in social network injecting and drug use behaviors among injecting drug users who enter treatment

J.J. Lloyd1, C.A. Latkin2, M. Pu3, L.J. Cornelius4, D. Bishai2, S. Huettner2, J.R. Havens5 and S.A. Strathdee3,2, 1Temple U., Philadelphia, PA 2Johns Hopkins, and 4U. of Maryland, Baltimore, MD, 3UCSD Sch. of Med., San Diego, CA and 5U. of Kentucky, Lexington, KY

Differences in characteristics between in- and out-of-treatment heroin addicts

R. Schwartz1, S. Kelly1, K.E. O'Grady2, J.A. Peterson1, S. Gwin Mitchell1 and B.S. Brown3, 1Friends Research Institute, Balto, and 2University of Maryland, College Park, MD, and 3University of North Carolina, Wilmington, NC

Clustering of methadone patients reveals the association between their desire to use heroin, to reduce methadone dose and self-efficacy

H. Hunziker, L. Boesch and R. Stohler, Research Group on Substance Use Disorders, Psychiatric University Hospital of Zürich, Zürich, Switzerland

Desire for heroin use without taking the "hard" way of methadone maintenance: A hierarchical factor model on the hidden dimension in patients' attitudes to methadone

L. Boesch, H. Hunziker, R. Leisinger and R. Stohler, Research Group on Substance Use Disorders, Psychiatric University Hospital of Zürich, Zürich, Switzerland

Attitudes toward buprenorphine and methadone among opioid-dependent individuals

B.S. Brown1,2, S.M. Kelly1, R.P. Schwartz1, E.A. Sears1 and K.E. O'Grady3, 1Friends Research Institute, Baltimore, MD, 2University of North Carolina, Wilmington, NC and 3University of Maryland, College Park, MD

Self-schema with drug addict patients

A. Gauchet2, P. Melin1 and C. Tarquinio3, 1General Hospital, Saint Dizier, 2University of Psychology, Grenoble, France and 3University of Psychology, Metz, France

The effect of eliminating a harm reduction component of an opioid agonist treatment program

A. Cotton1,3, R. Guerra1, B. Hartzler2, N. Gignoux1 and D. Calsyn2,3, 1VA Puget Sound HCS, 2Alcohol and Drug Abuse Institute, and 3Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA

Prognostic factors of opioid withdrawal following high dose buprenorphine maintenance therapy: A retrospective case-control study

B. Lebeau1, L. Cattan2 and E. Brunelle3, 1Addictologist, Paris 11, 2Addictologist, Paris 16, and 3Addictologist, Loos en Gohelle, France

Predictors of buprenorphine treatment outcome

C.P. Domier, M.P. Hillhouse, G. Doraimani and W. Ling, Integrated Substance Abuse Programs, University of California, Los Angeles, Los Angeles, CA

The impact of cocaine use on outcomes in office-based buprenorphine treatment

D. Fiellin, L. Sullivan, B. Moore, P. O'Connor, M. Chawarski, D. Barry, M. Pantalon and R. Schottenfeld, Internal Medicine, Yale University School of Medicine, New Haven, CT

Buprenorphine stabilization: Does dose matter?

W. Ling, M.P. Hillhouse, C.P. Domier, C. Thomas, J. Jenkins, G. Doraimani, J. Annon and J. Hunter, Integrated Substance Abuse Programs, University of California, Los Angeles, Los Angeles, CA

Retention and early treatment outcomes associated with 5- and 30-day buprenorphine detoxification
> S. King1, B. Brown3,1, R. Schwartz1, D. Gandhi2, W. Barksdale2, E. Weintraub2, E.C. Katz1, 1Friends Research Institute, Inc., and 2Psychiatry, University of Maryland Medical School, Baltimore, MD and 3Psychology, University of North Carolina, Wilmington, NC

Outcomes for patients in office-based methadone maintenance
> S. Petitjean, K.M. Dürsteler-MacFarland, J. Strasser, D. Ladewig and G.A. Wiesbeck, Psychiatry, University of Basel, Basel, Switzerland

GENDER, WOMEN

Estradiol modulation of d-amphetamine in premenopausal women: A dose-response study
> S. Babalonis1,3, J.A. Lile1, C.S. Emurian1, C.A. Martin2,1 and T.H. Kelly1,2,3, 1Behavioral Science, 2Psychiatry, and 3Psychology, University of Kentucky, Lexington, KY

Changes in mood, performance, food craving and food intake across the menstrual cycle in women with premenstrual dysphoric disorder
> S. Shakibaie Smith, S. Collins, F.R. Levin and S.M. Evans, Psychiatry, Division of Substance Abuse, New York State Psychiatric Institute, New York, NY

Polydrug use models among women in the autonomous region of Valencia, Spain
> S. Tomás1, A. Vidal-Infer2, T. Samper2 and J. Perez3, 1Dirección General de Drogodependencias, Conselleria de Sanitat, Generalitat Valenciana, and 2FEPAD, Valencia, and 3Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Frequency and type of adverse events associated with treating women with trauma in community substance abuse treatment programs
> T. Killeen1, C. Brown2, A. Campbell3, H. Jiang3, R. Sampson1, E. Nunes3 and D. Hien3, 1Medical University of South Carolina, and 2Charleston Center, Charleston, SC, and 3Columbia University, New York, NY

Parenting stress, sense of competence and self-efficacy in mothers receiving outpatient drug treatment
> M. Kerwin, C. Arabia and C. Williams, Psychology, Rowan University, Glassboro, NJ

Gender differences in depression symptoms among substance users: Relationship with depression diagnosis
> P.J. Seignourel, C. Green and J. Schmitz, Psychiatry and Behavioral Sciences, University of Texas - Houston, Houston, TX

Gender differences in the effects of alcohol on emotional regulation in social drinkers
> T. Udo1,2, M.E. Bates1, E. Vaschillo1, B. Vaschillo1, S. Ray1 and E.Y. Mun1, 1Center of Alcohol Studies, Rutgers, State University of New Jersey, and 2School of Public Health, University of Medicine and Dentistry of New Jersey, Piscataway, NJ

Gender differences in alcohol use among university students in Lebanon: The role of religion and religiosity
> L.A. Ghandour1,2, E.G. Karam2 and W.E. Maalouf1,2, 1Johns Hopkins School of Public Health, Baltimore, MD and 2Institute for Development, Research, Advocacy and Applied Care, Beirut, Lebanon

Stability in religious coping among methadone maintenance treatment patients, and gender differences
> I. Cohen1, E. Peles1, Y. Benyamini2 and M. Adelson1, 1Adelson Clinic for Drug Abuse Treatment and Research, Tel Aviv Medical Center, and 2Tel Aviv University, Tel Aviv, Israel

Gender differences among opiate users in a 25-year longitudinal follow-up study
> C. Grella, Integrated Substance Abuse Programs, UCLA, Los Angeles, CA

Gender differences among in- and out-of-treatment opioid-dependent individuals
> S.M. Kelly1, R.P. Schwartz1, K.E. O'Grady2, J.A. Peterson1, S. Gwin-Mitchell1 and B.S. Brown1,3, 1Friends Research Institute, Baltimore, and 2University of Maryland, College Park, MD and 3University of North Carolina, Wilmington, NC

Alternative approaches to contolling drug use: An examination of gender differences
> M.A. Davey-Rothwell, C.A. Latkin and K.E. Tobin, Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Gender differences in motivation to abstain from methamphetamine use
> C.S. Culbertson, M.R. Costello, C.A. Kenny, D. Tziortzis, E. O'Laco, R. De La Garza and T.F. Newton, Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA

Gender differences in self-reported reasons for cocaine use
> T.M. Wright, P. Mardikian, S. LaRowe, K. Cochran and R. Malcolm, Psychiatry, MUSC, Charleston, SC

On the rocks: Barriers to treatment-seeking among African-American women who are chronic crack users
> R.S. Karg, W.M. Wechsberg, K.M. Sawyer and F. Browne, Substance Abuse Treatment Evaluations and Interventions, RTI International, Research Triangle Park, NC

Effect of gender, age, and race on buprenorphine treatment outcome
> D.A. Gorelick1, I.D. Montoya2, J.R. Schroeder1, C. Contoreggi1, R.E. Johnson3,4, P.J. Fudala4 and K.L. Preston1, 1NIDA/NIH, IRP, and 3Johns Hopkins Univ., Baltimore, 2NIDA/NIH, Rockville, MD, and 4Reckitt Benckiser Pharmaceuticals, Inc., Richmond, VA

Differential risks and expectations: A comparison of male and female cocaine-dependent outpatients entering treatment
> K.M. Lester1, L.M. Najavits1 and R.D. Weiss2, 1National Center for PTSD, Women's Health Sciences Division, VA Boston Healthcare System, Boston, MA and 2Alcohol and Drug Abuse Treatment Program, McLean Hospital, Belmont, MA

Gender differences in a cocaine vaccine trial of TA-CD/08
> T. Gardner1,2, B. Martell3, J. Poling4,5, E. Mitchell4,5 and T. Kosten1,2, 1Baylor College of Med., and 2Michael E. DeBakey VA Medical Center, Houston, TX, 3Med. and 4Psychiatry, Yale University Sch. of Med., New Haven, and 5West Haven VAMC, West Haven, CT

Gender differences in sleep and sleep-dependent learning in abstinent cocaine users
> P.T. Morgan, P. Paliwal, R.T. Malison and R. Sinha, Psychiatry, Yale University, New Haven, CT

Factor analysis of the Allen Barriers to Treatment Instrument with a clinical sample of female outpatient substance abusers
> J. Lindsay, University of Texas Health Science Center at Houston, Houston, TX

The role of locus-of-control in female crack/cocaine users
> S. Bradford, A. Ben Abdallah, C. Callahan and L. Cottler, School of Medicine, Washington University in St. Louis, Saint Louis, MO

HIV/HCV, IMMUNE FUNCTION

NK cell activity and infections in non-parenteral heroin dependence: A pilot study from India
> M. Vaswani and N.G. Desai, National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, India

Effect of withdrawal from opioids on immune function in addicts
> T.K. Eisenstein, J.J. Meissler, J. Shack, J. Moore, N. Thingalaya, J. Breslow and R. Spiga, Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA

Modeling the synergistic relationship between cocaine and HIV in the huPBL-NOD-SCID/IL-2rgamma-null mouse
> G.C. Baldwin, S.M. Kiertscher, K.M. Whittaker, D.P. Tashkin and M.D. Roth, Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA

Depression and QoL in direct observed therapy as compared with self-administration of PegIFN- α2a in chronic hepatitis C patients on methadone maintenance
> M. Sulkowski1, A. Tice2, R. Yapp3, H. Bodenheimer4, A. Monto5, S. Rossi6 and H. Bonkovsky7, 1Johns Hopkins U., Baltimore, MD. 2U. of Hawaii, Honolulu, HI. 3Good Samaritan Hosp., Downers Grove, IL. 4Beth Israel Med. Ctr, NY, NY, 5SF VAMC, San Francisco, CA, 6Roche Lab., Nutley, NJ and 7CT Health Center, Farmington, CT

Predictors of bacterial infections among hepatitis-C-negative injection drug users in Rhode Island
> K.T. Phillips1,2 and M.D. Stein1,2, 1Brown University Medical School, and 2Rhode Island Hospital, Providence, RI

Prevalence and correlates of previous hepatitis B vaccination and infection among young drugusers in New York City
> S. Amesty1,2, D. Ompad2, S. Galea2,3, C. Fuller2,4, Y. Wu2, B. Koblin5, D. Vlahov2,4, 1Columbia U., 2NY Academy of Med., NY, NY, 3U. Michigan School of Public Health, Ann Arbor, MI 4Columbia U. Mailman School of Public Health, and 5Infectious Disease Prevention, NY Blood Center, NY, NY

Effects of a motivational intervention to reduce alcohol use among injecting drug users at risk of HCV
> W. Zule, E.C. Costenbader and C. Coomes, Behavioral Health Criminal Justice, RTI International, Research Triangle Park, NC

Knowledge about hepatitis C among clients and staff in methadone clinics in Israel
> R. Cohen-Moreno and Y. Neumark, School of Public Health, Hebrew University-Hadassah, Jerusalem, Israel

Effectiveness of an HCV drug treatment program staff training in changing attitudes toward HCV patients
> S.M. Strauss1, C. Munoz-Plaza1, J. Astone-Twerell1, D. Des Jarlais2, M. Gwadz1, H. Hagan1, A. Osborne1 and A. Rosenblum1, 1NDRI, and 2Beth Israel Medical Center, New York, NY

Disparities in health services for addiction-related infections in substance abuse treatment programs
> L.S. Brown, Jr.1,2, S.A. Kritz1, E.J. Bini3, J. Robinson4, D. Alderson5 and J. Rotrosen6, 1ARTC, Brooklyn, 2Weill Cornell Med. Col., 3Gastroenterology and 6Psychiatry, VA NY Harbor Healthcare Sys. and NYU Sch. of Med., NY, 4Nathan Kline Inst., Orangeburg, 5NYS Psychiatric Inst., NY Presbyterian Hosp., New York, NY

HIV risk behavior among patients with co-occurring bipolar and substance use disorders: Associations with mania and drug abuse

    C.S. Meade, F.S. Graff, M.L. Griffin and R.D. Weiss, Psychiatry, McLean Hospital/Harvard Medical School, Belmont, MA

Severity of substance use, treatment involvement and HIV risk behavior among adult substance users in treatment

    Y.F. Chan, M.L. Dennis, R. Funk and C. Scott, Lighthouse Institute, Chestnut Health Systems, Bloomington, IL

Behavioral drug and HIV risk reduction counseling with abstinence-contingent take-home buprenorphine: A pilot randomized clinical trial

    M.C. Chawarski[1], M. Mazlan[2] and R.S. Schottenfeld[1], [1]Yale University School of Medicine, New Haven, CT and [2]SAC, Muar, Malaysia

Study on drug use, sex behaviors, use of condoms and HIV risk among IDUs in Teku

    M.B. Chhetri, Planning, CIAA, Kathmandu, Nepal

Sex on drugs among high-risk groups

    E.C. Costenbader, W.A. Zule and C. Coomes, Behavioral Health Criminal Justice, RTI, International, Research Triangle Park, NC

Drug use, sexual risks and STIs among a sample of MSM in Los Angeles

    S. Larkins, S. Shoptaw, J. Wang, P. Gorbach and C. Hucks-Ortiz, Family Medicine, University of California, Los Angeles, Los Angeles, CA

Drug-using women who inaccurately perceive sex risk are more likely to improve sex risk behaviors at 4 months

    E.C. Garvin, A. Ben Abdallah and L.B. Cottler, Epidemiology and Prevention Research Group, Washington University School of Medicine, St. Louis, MO

HIV/AIDS risk perception, sexual partnerships and condom use among African-American substance users

    L.J. Floyd, A. Lawson and W. Latimer, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

Gender differences in perceived vulnerability to HIV infection

    M.M. Mitchell, S.G. Severtson, B.E. Mancha, C.M. Graham, W.W. Latimer, Mental Health, Johns Hopkins University, Baltimore, MD

The feasibility of delivering a brief HIV risk reduction intervention targeting HIV-infected IDUs in a community-based setting

    M. Copenhaver[1], R. Bruce[2], I.C. Lee[3] and F. Altice[2], [1]University of Connecticut, Storrs, and [2]Yale AIDS Program, New Haven, CT and [3]National Chengchi University, Taipei, Taiwan

Interim methadone maintenance reduces HIV-risk behaviors

    M. Wilson[1], R.P. Schwartz[1], K.O. O'Grady[2], D. Highfield[1] and J.H. Jaffe[1,3], [1]Friends Research Institute, Baltimore, [2]University of Maryland College Park, College Park and [3]University of Maryland School of Medicine, Baltimore, MD

Results from a controlled trial of a motivational intervention for improving treatment enrollment among needle-exchange participants

    V.L. King, M. Kidorf, J. Peirce and R. Brooner, Psychiatry, Johns Hopkins School of Medicine, Baltimore, MD

Gender differences in sex risks among Ukraine injection drug users

    R.E. Booth, J.T. Brewster, W. Lehman, S. Dvoryak and L. Sinitsyna, Psychiatry, University of Colorado School of Medicine, Denver, CO

Correlates of unsafe injecting among Russian injecting drug users

    V. Gyarmathy[1,2], N. Li[1], C.A. Latkin[1], K.E. Tobin[1], A.P. Kozlov[3], H.D. Chilcoat[4] and I.F. Hoffman[5], [1]Johns Hopkins Bloomberg Sch. of Public Health, Baltimore, MD, [2]NDRI, Inc., NY, NY [3]Biomedical Ctr., St. Petersburg, Russian Fed., [4]GlaxoSmithKline, RTI, and [5]U. of North Carolina at Chapel Hill, Chapel Hill, NC

Correlates of injection drug use among female sex workers in two Mexican-U.S. border cities

    T.L. Patterson[1], R. Lozada[2], S. Semple[1], M. Fraga[3], J. Salazar[4], H. Staines[5], A. DelaTorre[6], M. Philbin[1] and S. Strathdee[1], [1]UCSD, La Jolla, CA, [2]Pro-COMUSIDA, and [3]Aut. de Baja Calif., Tijuana, [4]Aut. de Tamaulipas, Matamoros, [5]Aut. de Cd. Juarez, Cd. Juarez, Mexico and [6]University of California, Davis, Davis, CA

"The rush": Narratives of crystal methamphetamine use among HIV+ gay, bisexual, and MSM injectors

    R.L. de Guzman[1,4], S. Eyre[2] and G. Galloway[3], [1]Anthropology, Graduate Center, CUNY, New York, NY, [2]University of California, and [3]St. Luke's Hospital, San Francisco, CA and [4]BST Predoctoral Fellow Program, NDRI/MHRA, New York, NY

WHO collaborative study on substitution therapy of opioid dependence and HIV/AIDS

    R. Ali[1], A. Buavirat[2], S. Chiamwongpaet[2], S. Dvoryak[3], B. Habrat[4], S. Jie[7], R. Mardiati[5], A. Mokri[6], J. Moskalewicz[4], D. Newcombe[1], V. Poznyak[8], A. Uchtenhagen[9], D.S. Utami[5] and C. Zhao[7], [1]Australia, [2]Thailand, [3]Ukraine, [4]Poland, [5]Indonesia, [6]Iran, [7]China

Implementation fidelity of the Adolescent-Community Reinforcement Approach (A-CRA): Impact on adolescent substance use and HIV risk

B. Garner, M. Godley, S. Godley, R. Funk and M. Dennis, Chestnut Health Systems, Bloomington, IL

Characteristics of syringe sharing among young injection drug users: Results from a study of ketamine injectors

S.E. Lankenau[1,2], B. Sanders[1,2], J. Jackson-Bloom[2] and D. Hathazi[2], [1]University of Southern California, and [2]Division of Research on Children, Youth, and Families, Children Hospital Los Angeles, Los Angeles, CA

HIV risk reduction among substance-abusing homeless youth

N. Slesnick and M. Kang, Ohio State University, Columbus, OH

Temporal trends in HIV suggest higher prevalence in non-injection vs. injection drug users in Harlem and the Bronx, 2001-2006

D.C. Ompad[1], S. Galea[1,2], C.M. Fuller[1,3], C.A. Chan[1] and D. Vlahov[1,3], [1]NY Academy of Medicine, [2]University of Michigan, Ann Arbor, MI and [3]Columbia University New York, NY

Drug use, hepatitis and HIV in homeless in Guadalajara

A. Gutierrez-Padilla[1,2], O.Campollo[1,2], M. Mendoza-Garcia[1,2], S. Plasencia Perez[1,2], M. Lebrao[1,2], R. Vargas-Lopez[1,2], A. Gonzalez-Garrido[1,2] and M.I. Hernandez-Rivas[2], [1]Centro de Estud. de Alcoholismo y Adicciones, and [2]University of Guadalajara, Guadalajara, Jalisco, Mexico

Spatial distribution and correlates of HIV infection in injection drug users in St. Petersburg, Russia, 2002-2003

R. Heimer[1], R. Barbour[1], A.V. Shaboltas[2], I.F. Hoffman[3], S.V. Verevochkin[2], A.A. Kozlov[2] and A.P. Kozlov[2], [1]Yale University School of Medicine, New Haven, CT [2]Biomedical Center, St. Petersburg, Russian Federation and [3]University of North Carolina, Chapel Hill, NC

SYMPOSIUM V - COGNITIVE AND EMOTIONAL PROCESSING BIASES IN ADDICTION: COGNITIVE, BEHAVIORAL, AND PSYCHOPHARMACOLOGICAL MECHANISMS
Chairs: Matt Field and Theodora Duka

General introduction and symposium overview

Matt Field, University of Liverpool, Liverpool, UK

The role of attention in human goal-directed drug-seeking behavior

Lee Hogarth, University of Sussex, Falmer, Brighton, UK

Reciprocal relationships between cognitive biases, craving, and inhibitory control

Matt Field, University of Liverpool, Liverpool, UK

Brain mechanisms underlying cognitive biases and craving in substance abuse

Ingmar Franken, Erasmus University Rotterdam, The Netherlands

Pharmacological challenge studies of attentional processes in addictive behaviors

Marcus Munafo, University of Bristol, Bristol, UK

Discussant: Emotional sensitivity and cognitive impairments in alcoholism

Theodora Duka, University of Sussex, Falmer, Brighton, UK

General discussion

Theodora Duka, University of Sussex, Falmer, Brighton, UK

ORAL COMMUNICATIONS 5 - SOCIAL AND ENVIRONMENTAL FACTORS IN DRUG ABUSE
Chairs: Sari Izenwasser and Jennifer Newman

Cocaine discrimination in maternally separated and handled pups as adults

S.J. Kohut and A.L. Riley, Psychology, American University, Washington, DC

The effects of social and environmental enrichment on cocaine self-administration in female rats

M.A. Smith and J.C. Iordanou, Psychology, Davidson College, Davidson, NC

Social and environmental factors alter cocaine conditioned place preference in adolescent rats

S. Izenwasser, C. Rios and D. Wade, Psychiatry and Behavioral Sciences, University of Miami Miller School Medicine, Miami, FL

Role of environmental context in the ontogeny of cocaine-induced behavioral sensitization

C.A. Crawford, S.A. Baella, N.M. Stuebner, L.R. Halladay and S.A. McDougall, Psychology, California State University, San Bernardino, San Bernardino, CA

Further investigation into the interactions between social rank and cocaine reinforcement in male monkeys

M.A. Nader[1,2], P.W. Czoty[1], R. Gould[1], S. Nader[1], H.D. Gage[2] and J.R. Kaplan[3], [1]Physiology and Pharmacology, [2]Radiology, and [3]Pathology, Wake Forest University School of Medicine, Winston-Salem, NC

Effects of social stimuli on phencyclidine self-administration in rhesus monkeys
  J. Newman, J. Perry and M. Carroll, Psychiatry, University of Minnesota, Minneapolis, MN
Neuronal activation associated with cue reinstatement of extinguished cocaine-seeking behavior as measured by c-fos mRNA
  P.R. Kufahl[1], A.R. Zavala[1], A. Singh[1], T. Osredkar[2], J.N. Joyce[2] and J.L. Neisewander[1], [1]Psychology, Arizona State University, Tempe, and [2]Sun Health Research Institute, Sun City, AZ
Heroin purchasing is income- and price-sensitive
  J.K. Roddy[1], C.L. Steinmiller[2] and M.K. Greenwald[2], [1]University of Michigan Dearborn, Dearborn, and [2]Wayne State University, Detroit, MI

ORAL COMMUNICATIONS 6 – ALCOHOL RESEARCH: WHAT'S THE PROOF?
Chairs: Timothy Wilens and George Kenna

Atomoxetine treatment of adults with ADHD and comorbid alcohol abuse
  T.E. Wilens[2], L.A. Adler[3], M.D. Weiss[4], J.L. Ramsey[1], R.J. Moore[1], D. Renard[5] and L.R. Levine[1], [1]Lilly Research, Indianapolis, IN, [2]Massachusetts General Hosp., Boston, MA, [3]New York University School of Medicine, New York, NY, [4]U. of British Columbia, Vancouver, BC, Canada and [5]Lilly Research, Brussels, Belgium
Stress, coping, and well-being among family members of women with substance use and psychiatric disorders
  B.C. Moore[1], D.E. Biegel[2] and T.J. McMahon[1], [1]Psychiatry, Yale University School of Medicine, West Haven, CT and [2]Case Western Reserve University, Cleveland, OH
Motivation to change alcohol use and treatment engagement in incarcerated youth
  M. Clair[1,2], L. Stein[1,2,3], S.M. Colby[1], N.P. Barnett[1], P.M. Monti[1,4], C. Golembeske, Jr.[1,2] and R. Lebeau[3], [1]Brown University, Providence, [2]Rhode Island Training School, Cranston, [3]University of Rhode Island, Kingston, and [4]VAMC, Providence, RI
Remission from alcohol dependence and sex differences in a community sample
  N. Dasgupta[1,2] and H.D. Chilcoat[2], [1]Epidemiology, University of North Carolina School of Public Health at Chapel Hill, Chapel Hill, NC and [2]Worldwide Epidemiology, GlaxoSmithKline, Research Triangle Park, NC
Persons entering residential substance abuse treatment in Los Angeles: How gender, depression and alcohol disorders are related to substance abuse retention
  S.B. Hunter[1], K. Watkins[1], S. Wenzel[1] and J. Gilmore[2], [1]RAND Health, Santa Monica, and [2]Behavioral Health Services, Gardena, CA
Substance abuse problem severity among female DUI offenders as a function of rurality
  M. Webster[1,2], D.B. Clark[2], D. Saman[2] and J. Pimentel[2], [1]Behavioral Science, and [2]Center on Drug and Alcohol Research, University of Kentucky, Lexington, KY
Adolescent alcohol abuse treatment: Outcomes and change mechanisms
  H.B. Waldron, T.J. Ozechowski and H. Hops, CFAR, Oregon Research Institute, Eugene, OR
The safety and tolerability of combining aripiprazole and topiramate with alcohol
  G.A. Kenna, D. Nielsen, S. DeCuBellis, R.M. Swift, and D.J. Rohsenow, Center for Alcohol and Addiction Studies, Brown University, Providence, RI

ORAL COMMUNICATIONS 7 – COMORBIDITY: DOUBLE TROUBLE
Chairs: Jennifer Tidey and Silvia Martins

Depression relief from smoking in smokers with schizophrenia compared to non-psychiatric heavy-smoking controls
  J.W. Tidey[1,2], D. Rohsenow[2,1], G. Kaplan[3] and R. Swift[2,1], [1]Brown University, and [2]Providence VAMC, Providence, RI and [3]VA Boston Healthcare, Brockton, MA
Personality and psychiatric co-morbidity discriminates pathological gamblers among same sex sib-pairs
  D.S. Lobo[1,2], S. Martins[3,2], H. Tavares[2], J. Kennedy[1], H. Vallada[2] and V. Gentil[2], [1]CAMH, University of Toronto, Toronto, ON, Canada [2]Institute of Psychiatry, University of São Paulo, São Paulo, Brazil and [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Perceived unmet need for mental health care among Canadians with co-occurring substance dependence and mental illness
  K.A. Urbanoski[1], B. Rush[1,2] and J. Cairney[1,3], [1]Centre for Addiction and Mental Health, [2]Psychiatry, and [3]Public Health Sciences, University of Toronto, Toronto, ON, Canada
Socio-demographic correlates of co-occurring mental disorders and substance use problems in Canada
  D.G. Bassani, B.R. Rush, K. Urbanoski and S. Castel, Psychiatry, University of Toronto, Toronto, ON, Canada

Substance use and mental health problems in returning Iraqi veterans
A. Kline1 and M. Falca-Dodson2, 1University of Medicine and Dentistry, New Brunswick, and 2New Jersey Department of Military and Veterans Affairs, Trenton, NJ
A twin-family study of suicidality and illicit drug use in young people
Q. Fu1,2, A.C. Heath2 and K.K. Bucholz2, Community Health, Saint Louis University School of Public Health, Psychiatry, Washington University School of Medicine, St. Louis, MO
Gender differences in HIV risk behavior, traumatic event exposure, and PTSD in syringe exchange enrollees
J. Peirce, C.K. Burke, K.J. Neufeld, K.B. Stoller, M.S. Kidorf and R.K. Brooner, Johns Hopkins University School of Medicine, Baltimore, MD
Gender differences in conditional substance dependence by psychiatric diagnosis in the U.S. population
S.S. Martins1 and D.A. Gorelick2, 1Mental Health, Johns Hopkins Bloomberg School of Public Health, and 2NIDA/NIH, Intramural Research Program, Baltimore, MD

PUBLIC POLICY FORUM
Chair: Martin Y. Iguchi

A new approach to peace in the war on drugs
Kurt L. Schmoke, Howard University School of Law

REPORT FROM ONDCP
DRUG POLICY: PREVENTION, INTERVENTION, TREATMENT PROGRAMS
Presented by Bertha K. Madras, Deputy Director, Demand Reduction
Office of National Drug Control Policy

SYMPOSIUM VI - AFFECTIVE DYSFUNCTION IN SUBSTANCE ABUSE: NEUROIMAGING
Chairs: Thomas R. Kosten and Staci Gruber

Reduced visual and auditory brain activation during affect responses in cocaine abusers
Thomas R. Kosten, Baylor College of Medicine, Michael E. DeBakey VA Medical Center, Houston, TX
Altered affective response in chronic marijuana smokers
Staci Gruber, McLean Hospital, Harvard Medical School, Belmont, MA
Exploring the inverse relationship between resting perfusion in frontal limbic regions and affective symptoms in substance use disorders
Jesse Jong-Shik Suh, University of Pennsylvania, Treatment Research Center on Studies of Addiction, Philadelphia, PA
Imaging alterations in affective processing of cocaine users: From chronic use to long-term abstinence
Colleen A. Hanlon, Wake Forest University School of Medicine, Winston-Salem, NC
Discussant
Linda J. Porrino, Wake Forest University School of Medicine, Winston-Salem, NC

ORAL COMMUNICATIONS 8 - BRINGING UP BABY: DEVELOPMENTAL EFFECTS OF DRUG ABUSE
Chairs: Lisa Schrott and Veronica Accornero

Abnormal brain myelination occurs following perinatal opioid exposure in the rat
S.E. Robinson1, E.S. Sanchez2, J.W. Bigbee3 and C. Sato-Bigbee2, 1Pharmacology and Toxicology, 2Biochemistry, and 3Anatomy and Neurobiology, Virginia Commonwealth University, Richmond, VA
Sex differences in motivation to self-administer cocaine during the transition from adolescence to adulthood in rats
W.J. Lynch, Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, VA
Lobeline-induced sex differences in adolescent rats: Females exhibit increased sensitivity to the hypoactive effects of lobeline
S.B. Harrod, Psychology, University of South Carolina, Columbia, SC
Estimated effects of prenatal cocaine exposure on initial drug opportunity and use during early adolescence
V.H. Accornero1, E.S. Bandstra1, G.R. Simpson1, M.K. Glavach1, L. Xue1, C.E. Morrow1, C.B. McCoy1 and J.C. Anthony2, 1University of Miami Miller School of Medicine, Miami, FL and 2Michigan State University School of Human Medicine, East Lansing, MI

The effects of prenatal cocaine and lead exposure on substance use risk in 11-year-old children using the ALEXSA
 S. Minnes1, L.T. Singer1,2, S. Satayathum2, A. Aguirre1,2 and T. Ridenour3, 1General Medical Sciences, and 2Pediatrics, Case Western Reserve University, Cleveland, OH and 3Center for Education and Drug Abuse Research, University of Pittsburgh, Pittsburgh, PA

Effects of prenatal toluene exposure on performance under a progressive-ratio reinforcement schedule
 P. Cooper1, J.H. Hannigan2,1 and S. Bowen1,2, 1Psychology and 2Obstetrics and Gynecology, Wayne State University, Detroit, MI

Adolescent ethanol-induced deficits in spatial learning and memory: Role of CB1 cannabinoid receptor
 R. Sircar1,2, V.K. Yaragudri3, L. Wu1 and B.L. Hungund3,4, 1Zucker Hillside Hosp., Glen Oaks, 2Albert Einstein College of Medicine, Bronx, 3Nathan Kline Inst. for Psychiatric Research, Orangeburg, and 4College of Physicians & Surgeons, Columbia U., NY, NY

Role of sex and developmental history on the antinociceptive response to acute oxycodone in adult rats
 L.M. Schrott, G.S. Johnson, L.M. Franklin and J.B. Tatom, Pharmacology, LSU Health Sciences Center-Shreveport, Shreveport, LA

ORAL COMMUNICATIONS 9 - CLEARING THE SMOKE: ELUCIDATING NICOTINE MECHANISMS OF ACTION
Chairs: Robert Pechnick and Bernard LeFoll

Increased nicotine self-administration after prenatal exposure to nicotine in the rat
 R.N. Pechnick1,2, H. Nobuta1, X. Liu1, C. Bresee1, R. Poland1, J. Xu1 and C. Wang1, 1Cedars-Sinai Medical Center, and 2Brain Research Institute, Los Angeles, CA

Rimonabant, a cannabinoid CB1 receptor antagonist, reduces nicotine self-administration by squirrel monkeys: Influence of behavioral history
 B. Le Foll1,2, C. Wertheim2 and S.R. Goldberg2, 1Translational Addiction Research Laboratory, CAMH, Toronto, ON, Canada and 2Preclinical Pharmacology, NIH/NIDA, Baltimore, MD

Beta2 nicotinic acetylcholine receptor availability in living tobacco smokers during early and prolonged abstinence: A [123I] 5-IA-85380 SPECT imaging study
 K. Cosgrove1,2, I. Esterlis1,2, S. Stiklus1,2, T. Kloczynski1,2, S. Krishnan-Sarin1, S. O'Malley1, F. Bois1,2, G. Tamagnan3, J. Seibyl3 and J. Staley1,2, 1Psychiatry, Yale University, New Haven, 2VACHS, West Haven, and 3Institute for Neurodegenerative Disorders, New Haven, CT

Smoking alters cerebellar vermis glutathione
 C.M. Anderson, A. Prescot and P.F. Renshaw, Psychiatry, McLean Hospital/Harvard Medical School, Belmont, MA

Brain regional cerebral metabolic rates of glucose in response to cigarette-smoking cues are reduced in successfully compared to unsuccessfully treated heavy smokers with bupropion
 A. Weinstein1,2,3, J. Greif2, Z. Yemini2, M. Greemland3, H. Lerman3, A. Weizman4, R. Chisin1 and E. Even-Sapir3, 1Hadassah Hosp., Jerusalem, 2Lung Institute, and 3Nuclear Medicine, Sourasky Med. Ctr., Tel Aviv, and 4Geha Hosp., Petach Tikvah, Israel

Molecular targets of nicotine withdrawal are differentially expressed in adolescent and adult rats
 D.M. Byers2, L.A. Natividad1, L.N. Irwin2 and L.E. O'Dell1, 1Psychology, and 2Biology, University of Texas El Paso, El Paso, TX

Effects of NPY and [D-His26]-NPY on the negative affective aspects of nicotine withdrawal
 A.W. Bruijnzeel, M.S. Gold, M. Prado and D. Rylkova, Psychiatry, University of Florida, Gainesville, FL

Nicotine withdrawal-associated deficits in working memory: A role for the β2 nicotinic acetylcholine receptor subunit
 J.D. Raybuck1,2 and T.J. Gould1, 1Psychology, and 2Center for Substance Abuse Research, Temple University, Philadelphia, PA

ORAL COMMUNICATIONS 10 - CHRONIC DRUGS AND CHRONIC PAIN
Chairs: Sudie Back and Peggy Compton

Chronic fentanyl administration and withdrawal in aging rats: Effects on nociception, operant behavior, and physical performance
 D. Morgan1, J. DuPree1, C.C. Howell1 and C.S. Carter2,3, 1Division of Addiction Medicine, University of Florida College of Medicine, 2Geriatric Research, Education, Clinical Center, and 3The University of Florida Institute on Aging, Gainesville, FL

Analgesic actions of fentanyl and hydrocodone in rats treated with extended-release naltrexone
    R.L. Dean, M.S. Todtenkopf, D.R. Deaver, M. Arastu, N. Dong, K. Reitano, K. O'Driscoll, K. Kriksciukaite and
    D.R. Gastfriend, Alkermes, Cambridge, MA
Hyperalgesia induced by methadone in an animal model
    J.L. Hay, R.J. Irvine and J.M. White, Pharmacology, University of Adelaide, Adelaide, SA, Australia
Chronic pain in patients with opioid dependence: Prevalence, severity, treatment, characteristics of substance abuse
treatment, and pain-related disability
    M. Clark and R. Brooner, Johns Hopkins University, Baltimore, MD
Prevalence rates of chronic pain and interest in pain management among patients seeking MMT
    D.T. Barry1, M. Beitel1, D. Joshi2, J. Falcioni2 and R.S. Schottenfeld1, 1Yale University School of Medicine,
    and 2APT Foundation, Inc., New Haven, CT
Correlates and gender differences of chronic pain patients using prescription opiates: A pilot study
    S.E. Back1, A.E. Waldrop1, A.R. Smith2, S. Reeves2, B. Hicks1, R. Payne1 and K.T. Brady1, 1Psychiatry,
    Medical University of South Carolina, and 2Anesthesia and Perioperative Medical University of South Carolina,
    Charleston, SC
Chronic dextromethorphan does not improve hyperalgesia in methadone patients
    P. Compton1,2, M. Torrington2 and W. Ling2, 1School of Nursing, and 2Integrated Substance Abuse Programs,
    UCLA, Los Angleles, CA
PTSD and substance use disorders in patients with chronic pain in primary care
    J. Liebschutz1, R. Saitz1, T. Averbuch1, R. Weiss2, T. Keane1 and J.H. Samet1, 1Boston University Schools of
    Medicine and Public Health, and 2Harvard Medical School, Boston, MA

MARIAN W. FISCHMAN MEMORIAL AWARD LECTURE
Presentation of the Marian W. Fischman Memorial Award to Dorothy K. Hatsukami, University of Minnesota
Medical School
Introduction by Jack Henningfield

WORKSHOP VI - COMPUTATIONAL MODELING OF COMPLEX SYSTEMS IN PROBLEMS OF DRUG
DEPENDENCE: A NEW RESEARCH SOLUTION
Chair: Mark Froimowitz

The complexities of the physiology of drug dependence: Why we might need computational models
    Jane Acri, NIDA, Bethesda, MD
Computational modeling of complex systems in problems of drug dependence: A new research solution
    Tandy Herren, Computational Biology, DNA Print Pharmaceuticals, Sarasota, FL

WORKSHOP VII - PHARMACOTHERAPIES FOR STIMULANTS ADDICTION
Chairs: Frank Vocci and Ahmed Elkashef

Aripiprazole, methylphenidate and placebo in the treatment of amphetamine dependence
    Kimmo Kuoppasalmi, National Public Health Institute, Helsinki, Finland
Randomized controlled trial of d-amphetamine maintenance for treatment of methamphetamine dependence
    Jason White, University of Adelaide, Adelaide SA, Australia
Modafinil for cocaine dependence, results from NIDA/DPMC multisite trial
    Ahmed Elkashef, NIDA, Bethesda, MD
Discussant: Targets for stimulants dependence
    Frank Vocci, NIDA, Bethesda, MD

WORKSHOP VIII - REDUCING OPIOID ANALGESIC ABUSE: MODELS FOR SUCCESSFUL
COLLABORATION AMONG GOVERNMENT, INDUSTRY AND OTHER KEY STAKEHOLDERS
Chairs: Herbert Kleber and Meredith Smith

The epidemiology of prescription drug abuse in the United States: National, state and local data
    Wilson Compton, NIDA, Bethesda, MD
The roles of the FDA and the pharmaceutical industry in addressing prescription drug abuse: The FDA's perspective
    Scott Gottlieb, FDA, Rockville, MD

Efforts to date by the pharmaceutical industry to address the problem of prescription drug abuse and diversion: What's been done, what's been successful?
    John Gilbert, Hymen, Phelps, McNamara, Washington, DC
A model, community-wide initiative to assure effective pain management and decrease drug misuse and diversion through state, county and local partnerships
    Donald Burt, Berkshire Healthcare System, Pittsfield, MA
Moving forward: Best practices for promoting partnerships among government, pharmaceutical industry and local community stakeholders to combat prescription drug abuse and diversion
    Nathaniel Katz, Tufts Medical School, Analgesic Research, Needham, MA

WORKSHOP IX - INDUSTRY OBJECTIVES FOR ABUSE LIABILITY TESTING
Chairs: Beatriz Rocha and S. Steven Negus

Overall challenges of abuse liability during drug development and approval of new compounds
    Mark Amman, Pfizer
Worldwide regulatory environment
    Beatriz Rocha, Merck
Major hurdles faced by industry in the preclinical, clinical, regulatory and risk management areas
    Mary Jeanne Kallman, Eli Lilly
Challenges for approval of a new compound. Case study I: Rozarem
    Gloria Harris, Takeda
Challenges for approval of a new compound. Case study II: Varencline
    Hans Rollema, Pfizer

TUESDAY, JUNE 19, 2007

POSTER SESSION II - AMPHETAMINE/METHAMPHETAMINE
The rise in treatment admissions for methamphetamine use in Los Angeles County from 2001through 2005
    D.A. Crevecoeur, C. Snow, B. Rutkowski and R. Rawson, Integrated Substance Abuse Programs, University of California, Los Angeles, Los Angeles, CA
Characteristics of female methamphetamine addicts entering residential drug treatment: Program implications
    B. Crowell1, C.F. Tirado2 and R. Dorst1, 1Nexus Recovery Center Inc., and 2University of Texas Southwestern Medical Center, Dallas, TX
Methamphetamine and sex: Qualitative perspectives of women users
    A. Hamilton, Psychiatry, University of California, Los Angeles, Los Angeles, CA
The color of meth: Is it related to adverse health outcomes? An exploratory study in Tijuana, Mexico
    S. Strathdee1, P. Case2, R. Lozada3, A. Mantsios1, M. Pu1, K.C. Brouwer1 and T.L. Patterson1, 1University of California San Diego, San Diego, CA, 2Fenway Health, Boston, MA and 3Pro-COMUSIDA, Tijuana, Mexico
Methamphetamine dependence: Assessing participants in the Methamphetamine Treatment Project 4 years after treatment
    P. Marinelli-Casey, M.P. Hillhouse, R. Gonzales, A. Ang, F. Cosmineanu, J. Hunter and R.A. Rawson, ISAP, University of California, Los Angeles, Los Angeles, CA
Psychiatric illness as a predictor of post-treatment methamphetamine use
    S. Glasner-Edwards, M.P. Hillhouse, P. Marinelli-Casey, R. Gonzales, A. Ang, F. Cosmineanu and R.A. Rawson, Integrated Substance Abuse Programs, University of California, Los Angeles, Los Angeles, CA
Drug court treatment for methamphetamine dependence: Treatment response and posttreatment outcomes
    R. Gonzales1, P. Marinelli-Casey1, M.P. Hillhouse1, A. Ang1, J. Zweben2, J. Cohen2, P. Fulton Hora2 and R.A. Rawson1, 1Integrated Substance Abuse Programs, University of California, Los Angeles, Los Angeles, and 2East Bay Community Recovery Project, Hayward, CA
Methamphetamine-dependent treatment participants as parents
    M.P. Hillhouse, P. Marinelli-Casey, J. Hunter, F. Cosmineanu, R. Gonzales and R.A. Rawson, Integrated Substance Abuse Programs, University of California, LA, Los Angeles, CA
Treatment utilization and barriers to treatment among dependent methamphetamine users: Results from a survey of dependent users and service providers
    P. Kenny, A. Pennay, A. Harney and N. Lee, Clinical Research, Turning Point Alcohol and Drug Centre, Fitzroy, Victoria, Australia

Comparison of self-report, urinalysis and segmental hair analysis of drugs in amphetamine users enrolled in a clinical trial

J.J. Strandberg1, F.C. Kugelberg2, K. Alkass1, L. Bredberg1, R. Kronstrand2, J. Franck3 and H. Druid1, 1Forensic Medicine, Karolinska Institutet, Stockholm, 2Forensic Genetics and Forensic Toxicology, National Board of Forensic Medicine, Linkoping, and 3Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Effects of naltrexone on the subjective response to amphetamine in amphetamine-dependent individuals

N. Jayaram-Lindstrom and J. Franck, Neuroscience, Karolinska Institutet, Stockhom, Sweden

Perindopril attenuates methamphetamine-induced subjective effects, implicating angiotensin II in mediating effects of stimulants

T.F. Newton1, R. De La Garza1, K. Grasing2,3, R. Donovick1 and Z. Franco1, 1David Geffen School of Medicine at UCLA, Los Angeles, CA, 2Kansas City VA Medical Center, and 3University of Kansas School of Medicine, Kansas City, MO

Determinants of cardiovascular response to methamphetamine

G. Fleury, R. De La Garza, J.J. Mahoney, III and T.F. Newton, Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

Increased heart rate and motor activity with illicit methamphetamine use in a naturalistic setting compared to controlled settings

P.B. Yang, R. De La Garza and T.F. Newton, Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

Acute administration of methamphetamine does not alter cognitive function in abstinent methamphetamine-dependent individuals

A.D. Kalechstein, B. Jackson, R. De La Garza and T.F. Newton, Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

Methamphetamine enhances metacognition of agency in humans

M.G. Kirkpatrick, J.A. Metcalfe and C.L. Hart, Columbia University, New York, NY

Sleep disturbances and excessive daytime sleepiness in methamphetamine-dependent individuals: Implications for cognitive function

B. Jackson, R. De La Garza and T.F. Newton, Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

How long does craving predict use of methamphetamine? Assessment of use one to seven weeks after the assessment of craving

G.P. Galloway1 and E. Singleton2, 1Addiction Pharmacology Research Laboratory, California Pacific Medical Center, San Francisco, CA and 2MayaTech Corporation, Silver Spring, MD

Self-perceived explanations for drug use and relapse among methamphetamine-addicted volunteers

C.A. Kenny, S.E. Evans, R. De La Garza, K. Gunnia, A.D. Kalechstein and T.F. Newton, Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

Unrestricted access to methamphetamine in the past is associated with increased use of methamphetamine in the present

M.R. Costello, R. De La Garza, C. Hurley, R.E. Fintzy, A.D. Kalechstein and T.F. Newton, Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

A novel rat model of methamphetamine-seeking during withdrawal

R.G. Fox1, K.A. Cunningham1, S.E. Specio2 and T.C. Napier2, 1Center for Addiction Research, University of Texas Medical Branch, Galveston, TX and 2Pharmacology, Rush University Medical Center, Chicago, IL

Bupropion attenuates methamphetamine self-administration and sucrose-seeking in adult male rats

C.M. Reichel, J.L. Linkugel and R.A. Bevins, Psychology, University of Nebraska-Lincoln, Lincoln, NE

The putative dopamine D3 receptor antagonists SB-277011A, NGB2904, or BP897 attenuate methamphetamine-enhanced brain stimulation reward in rat

E. Gardner1, K. Spiller1, Z. Xi1, X. Peng1, X. Li1, C. Dillon1, C. Ashby, Jr.2 and C. Heidbreder3, 1NIDA, Baltimore, MD, 2Saint John's University, New York, NY and 3GlaxoSmithKline Pharmaceuticals, Verona, Italy

GENES

Histone modifications associated with the promoters of neuropeptide genes involved in the effects of drugs of abuse in the rat striatum and hypothalamus

B. Reed, R. Picetti, V. Yuferov and M.J. Kreek, Laboratory of the Biology of Addictive Diseases, The Rockefeller University, New York, NY

Incubation of heroin-seeking behavior and accompanying molecular changes

K.L. Kuntz, R.C. Twining, K.M. Patel, A.E. Baldwin, W.M. Freeman, P.S. Grigson and K.E. Vrana, Penn State University, Hershey, PA

Morphine effects on striatal transcriptome in mice

M. Korostynski, M. Piechota, D. Kaminska and R. Przewlocki, Molecular Neuropharmacology, Institute of Pharmacology PAS, Krakow, Poland

Estimating genetic effects from ostensibly genetically uninformative data prior to collecting DNA

R.K. Price, N.K. Risk, J.D. Grant, A. Agrawal and K.K. Bucholz, Psychiatry, Washington University School of Medicine, St. Louis, MO

Analysis of prodynorphin promoter polymorphisms

M. Rouault, D. Nielsen, V. Yuferov, A. Ho and M.J. Kreek, The Rockefeller University, New York, NY

Human prodynorphin gene polymorphisms and cocaine dependence

V. Yuferov, F. Ji, M. Johncilla, J. Ott and M.J. Kreek, The Rockefeller University, New York, NY

Preliminary study on the relationship between 5-HTR2A-102C/T, Iowa Gambling Task scores, and abstinence in cocaine users treated with citalopram and contingency management

N. Moukaddam, F.G. Moeller, J.M. Schmitz, S. Lane, J.L. Steinberg and A. Swann, Psychiatry, University of Texas Health Science Center at Houston, Houston, TX

Ontogeny-dependent contribution of the nNOS gene to cocaine psychomotor sensitization

M.A. Balda[1], K.L. Anderson[2] and Y. Itzhak[1,2], [1]Neuroscience Program, and [2]Psychiatry, University of Miami, Miami, FL

Is the DAT 9/9 genotype protective against the development of methamphetamine dependence? 32

R. De La Garza, G. Fleury, E.M. Wagreich, J.T. McCracken and T.F. Newton, Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

Test for association between GABRA2 and conduct/alcohol use disorders in adolescent patients and controls

J.T. Sakai[1], M.C. Stallings[2], T.J. Crowley[1] and M.A. Ehringer[2,3], [1]Psychiatry, University of Colorado School of Medicine, Denver, [2]Institute for Behavioral Genetics, and [3]Integrative Physiology, University of Colorado, Boulder, CO

Protective effect against alcohol dependence of the thermolabile variant of MTHFR

A. Benyamina[1], R. Saffroy[2], P. Pham[2], L. Karila[1], B. Debuire[2], A. Lemoine[2] and M. Reynaud[1], [1]Psychiatry, and [2]Biochemistry and Molecular Biology, Hôpital Paul Brousse, Villejuif, France

Development of a pathway-focused oligoarray for neurobiology research on drug addiction

J. Wang, D. Zhang, R. Gutala and M.D. Li, Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, VA

ALCOHOL: HUMAN STUDIES

Application of the Relapse Risk Scale to alcoholics in Japan: Comparison with stimulant abusers

Y. Ogai[1], M. Yamashita[2], K. Endo[3], A. Haraguchi[1], Y. Ishibashi[1], T. Kurokawa[4], T. Muratake[5], R. Suga[2], T. Hori[6], M. Umeno[7], N. Asukai[1], E. Senoo[1] K. Ikeda[1], [1]Tokyo Inst. of Psych., [3]Urabe Hosp., [7]Tokyo Metro. Matsuzawa Hosp., [2]Nakajo Daini Hosp., Tokamachi,[4]Hirakawa Hosp., Hachioji, [5]Niigata U., Niigata, [6]Musashi Hosp., Kodaira, Japan

A Chilean validation of the alcohol use disorder identification test

G. Acuna[1], R. Santis[1], M. Garmendia[2], M. Alvarado[2] and O. Arteaga[2], [1]Psychiatry, Universidad Catolica, and [2]Escuela Salud Publica, Universidad de Chile, Santiago, Chile

HIV risk behaviors among female IDUs in developing and transitional countries

C.M. Cleland[1], D.C. Des Jarlais[2], T.E. Perlis[2] and G.V. Stimson[3], [1]NDRI Inc., and [2]Beth Israel Medical Center, New York, NY and [3]Imperial College of Science, Technology, and Medicine, London, UK

Male-female differences in alcohol-related attitudes: Data from purposive sample surveys of adults in Slovenia: 2001-2005

M. Radovanovic[1] and Z. Cebasek-Travnik[2], [1]Epidemiology, Michigan State University, East Lansing, MI and [2]University Psychiatric Hospital, Ljubljana, Slovenia

Drinking contexts, gender, and culture in Peru

M. Piazza, I. Bustamante, G. Alvarado, D. Pedersen and P. Asenjo, School of Public Health, Universidad Peruana Cayetano Heredia, Barranco, Peru

Latino immigrant population and alcohol use in Spain

S. Tortajada[1], S. Tomas[2], M. Castellano[2], R. Aleixandre[1], J.C. Valderrama[1], P. Needle[3] and J.C. Perez de los Cobos[4], [1]IHCD Lopez Piñero, CSIC-U. de Valencia, [2]Direccion General de Drogodepen, Valencia, and [4]Hosp. Sant Pau, Barcelona, Spain [3]NIDA, Atlanta, GA

Adult transition from at-risk drinking to alcohol dependence: The relationship of family history and drinking motives

C. Beseler[1], E. Aharonovich[2], K. Keyes[2] and D. Hasin[2], [1]Biostatistics, and [2]College of Physicians and Surgeons, Columbia University, New York, NY

Risk associated with exceeding recommended daily drinking limits among adults reporting varying degrees of family history of alcoholism

M. Steinley-Bumgarner, L. Mangrum and R. Spence, Addiction Research Institute, University of Texas, Austin, TX

Higher levels of gamma glutamyl transpeptidase as indicator of alcohol use in patients diagnosed with liver disease

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Domestic violence and dependence: A study on the association of both phenomena

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Correlates of recent alcohol use in heroin-dependent research volunteers

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Exploratory factor analysis suggests that the relative reinforcing efficacy of alcohol is binary

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Smoking explains much, but not all, of the relationship between MAO activity and behavioral/psychological characteristics associated with alcohol dependence

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Extended-release naltrexone (XR-NTX) reduces holiday drinking in alcohol-dependent patients

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Cognitive impairment change in alcohol-dependent subjects at 3 months post-detoxification

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Social support networks for mothers with problem drinking

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NEUROIMAGING

Metabolic signature of place preference to methamphetamine (METH) in rodents

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Development of an apparatus and methodology for conducting functional magnetic resonance imaging in conscious rhesus monkeys

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Neurobiological and behavioral predictors of social rank in female monkeys

P.W. Czoty[1], N.V. Riddick[1], H.D. Gage[2], M. Icenhower[1], M.C. Bounds[2], J.R. Kaplan[3], A.J. Bennett[1,3], P.J. Pierre[1,3] and M.A. Nader[1,2], [1]Physiology and Pharmacology, [2]Radiology, and [3]Pathology-Comparative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC

Dopamine effects on ventral striatal and orbitofrontal activation during a reward-conflict task in adult volunteers

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Response inhibition in cocaine-dependent individuals and controls under a Go/No-Go task with different levels of difficulty

S.D. Lane[1], F.G. Moeller[1], J.L. Steinberg[1], M. Buzby[1], P.A. Narayana[1], L.A. Kramer[1] and T.R. Kosten[2], [1]University of Texas Health Science Center and [2]Baylor College of Medicine, Houston, TX

Decreased frontal and temporal cortical thickness in cocaine dependence: Preliminary results

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Resting amygdalar connectivity is impaired in cocaine patients as compared to matched controls

Y. Li, Z. Wang, T. Franklin, D. Langleben, C.P. O'Brien, J. Detre and A.R. Childress, Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA

Striatal activation in a cocaine-craving paradigm using perfusion fMRI at 3T
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Altered dorsal striatum functioning in chronic cocaine users during internally and externally guided motor control
    C.A. Hanlon, L.B. Livengood, M.D. Miller and L.J. Porrino, Physiology and Pharmacology, Wake Forest University, Winston-Salem, NC

Emotional intelligence in abstinent cocaine patents: Difficulties understanding and managing emotions
    S.M. Hyman, H. Fox, K.I. Hong and R. Sinha, Psychiatry, Yale University, New Haven, CT

Cocaine vs. placebo infusions yield increased BOLD fMRI response to visual stimulation in healthy brains
    S.B. Lowen, L.D. Nickerson and J.M. Levin, Brain Imaging Center, McLean Hospital, Belmont, MA

Sleep homeostasis and restorative process in cocaine users following sleep deprivation
    G.H. Trksak[1,5], J.E. Jensen[3,5], W.B. Tartarini[2], M.A. Maywalt[2], M. Brendel[2], M.J. Kaufman[3,5], P.F. Renshaw[3,5], C. Dorsey[4] and S.E. Lukas[1,2,5], [1]BPRL, [2]Sleep Research Program, and [3]Brain Imaging Center, McLean Hosp., Belmont, [4]Sleep Health Centers, Newton, and [5]Harvard Medical School, Boston, MA

Low resting perfusion in the ventrolateral prefrontal cortex predicts increased depressive symptoms in methadone-maintained opiate patients
    J.J. Suh[1], R. Ehrman[1,2], S. Busch[1], M. Holloway[1], Z. Wang[1], Y. Li[1], J.G. Hakun[1], M. Goldman[1], M. MacDougall[1,2], C.P. O'Brien[1,2], J. Detre[1], D. Langleben[1,2] and A.R. Childress[1,2], [1]University of Pennsylvania, and [2]VAMC, Philadelphia, PA

Changes in quantitative electroencephalography during a Virtual Reality Treatment Program in alcohol-dependent males
    S. Lee[1], D. Han[2], S. Kim[1], S. Oh[1], P. Renshaw[2] and S. Lukas[2], [1]Psychiatry, Incheon Eun Hye Hospital, Seoul, South Korea and [2]BPRL/BIC, McLean Hospital, Belmont, MA

Task-specific interactive effects of HIV/AIDS and alcohol dependence on brain electrophysiology and behavior
    L.O. Bauer, Psychiatry, University of Connecticut School of Medicine, Farmington, CT

FMRI of intravenous nicotine administration: A two-predictor analysis
    D.P. Olson, M. Rohan, N. Goletiani, P. Renshaw, J. Mendelson and N. Mello, Brain Imaging Center and Alcohol and Drug Abuse Research Center, McLean Hospital - Harvard Medical School, Belmont, MA

Decreases in gray matter in select brain regions associated with cocaine dependence are unrelated to cigarette smoking
    T. Franklin, J. Hakun and A.R. Childress, Psychiatry, University of Pennsylvania, Philadelphia, PA

Comparison of the sensitivity of three morphometric measures in polydrug abusers
    J.G. Hakun, T.R. Franklin, M. Holloway and A.R. Childress, Psychiatry, University of Pennsylvania, Philadelphia, PA

NICOTINE: HUMAN STUDIES

Self-administration of intravenous nicotine in male and female smokers
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Subjective and hormonal effects of cigarette smoking for four and 12 minutes
    J.H. Mendelson, N.V. Goletiani, M.B. Sholar, A.J. Siegel and N.K. Mello, Alcohol and Drug Abuse Research Center, McLean Hospital-Harvard Medical School, Belmont, MA

Effect of D-cycloserine on smoking behavior in nicotine-dependent smokers
    E.J. Santa Ana, H. Corona, T. Babuscio, K. Carroll and B. Rounsaville, Psychiatry, Yale University School of Medicine/VA CT Healthcare System, West Haven, CT

Human abuse liability of varenicline, a nicotinic receptor partial agonist, in smokers and nonsmokers
    S.L. McColl[1], E.M. Sellers[1,3], A. Burstein[2] and K. Reeves[2], [1]Administration, Ventana Clinical Research Corporation, Toronto, ON, Canada, [2]Pfizer Inc., Groton, CT and [3]University of Toronto, Toronto, QC, Canada

Influence of the duration of abstinence on the relative reinforcing effects of cigarette smoking: A new methodology
    J.H. Yoon[1], S.T. Higgins[1,2] and M.P. Bradstreet[1], [1]Psychiatry, and [2]Psychology, University of Vermont, Burlington, VT

Tolerance for smoking discomfort: A new questionnaire of ability to handle nicotine withdrawal and cravings
    A. Sirota[1,2], D.J. Rohsenow[1,3], S.M. MacKinnon[2], R.A. Martin[2], G. Kaplan[5], P.M. Monti[2,3], A. Almeida[4], J. Tidey[1] R. Swift[1,3], [1]VAMC, & [2]Ctr for Alcohol & Addiction Studies, [3]Psych. & Human Behavior, Brown U., Providence, RI, [4]Boston U. School of Public Health, & [5]VA Boston Health Care System, Boston, MA

Sex difference in smoking and abstinence on self-reports of mood, cigarette craving, and withdrawal symptoms
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Barriers to quitting smoking among substance-dependent patients in treatment
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Greater nicotine use is not associated with less smoking compensation during smoking reduction
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Breath carbon monoxide levels and urine cotinine in methadone-maintained smokers
K.E. Dunn, S.C. Sigmon and S.T. Higgins, University of Vermont, Burlington, VT

Marijuana use and nicotine dependence among adolescent smokers: Does the first smoked substance matter?
E.T. Moolchan, L. Garver, C.C. Collins, D.H. Epstein, S.J. Heishman and M.J. Gasior, NIDA/NIH Intramural Research Program, Baltimore, MD

The relationship between cannabis and nicotine use in adolescent substance use disorder treatment
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Problem behavior profiles in subgroups of drug users
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Prevalence of Attention Deficit Hyperactivity Disorder in young smokers presenting for a smoking cessation study
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Safety and feasibility of atomoxetine for smoking cessation in young smokers with and without Attention Deficit Hyperactivity Disorder: A pilot study
H.P. Upadhyaya, W. Hiott, K. Gray, M. Carpenter, A. Simpson and G. Frattaroli, Medical University of South Carolina, Charleston, SC

Effects of atomoxetine on nicotine abstinence symptoms
R. Ray, C. Jepson, A.A. Strasser, F. Patterson, M. Rukstalis, S. Seigel and C. Lerman, Psychiatry, University of Pennsylvania, Philadelphia, PA

Impulsivity and early trajectory among adolescent tobacco smokers
C.E. Wieczorek, M. Jaszyna-Gasior, C.C. Collins, L.A. Garver, C.S. Parzynski, K.M. Lee and E.T. Moolchan, NIDA/NIH Intramural Research Program, Baltimore, MD

Impulsivity and treatment outcome in adolescent smokers in tobacco cessation trial - Preliminary findings
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Delay-discounting is related to treatment outcomes for adolescent cigarette smoking
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Adolescent smokers rate delay-discounting rewards as less certain than adolescent nonsmokers
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Cigarette smokers discount the past more than controls
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Temporal horizons in smokers
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Smoking cessation treatment at community-based substance abuse rehabilitation programs: Impact on cigarette smoking
M. Reid1, B. Fallon2, S. Sonne3, F. Flammino1, E. Nunes4, E. Kourniotis4, R. Brady4, H. Jiang7, C. Arfken5, E. Pihlgren5, L. Giordano6, J. Robinson7 J. Rotrosen1, 1NYU, NY 2Mt. Sinai Med. Ctr, NY 4Columbia U. Col. of Physicians & Surgeons, NY 7Nathan Kline Inst., NY 3MUSC, SC 5Wayne State U. Sch. of Med., MI 6Duke U., NC

Knowledge, attitudes and practices regarding nicotine dependence in various service settings
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Gender differences in cessation support by partners of health-compromised smokers
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Male-female and between-country differences in tobacco dependence diagnostic assessments: Colombia and United States
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Smoking patterns and problems among male and female youth in Palestine
M.S. AlAfifi1, M. Kariri2 and S. ElSousi1, 1Substance Abuse Research Center, and 2Ministry of Health, Gaza, Israel

A national survey of smoking-cessation services in adolescent residential substance-abuse treatment facilities in Canada, 2006
R. Callaghan1,3, J. Brewster2,1, J. Tavares3,1 and L. Taylor1,3, 1Centre for Addiction and Mental Health, 2Ontario Tobacco Research Unit, and 3University of Toronto, Toronto, ON, Canada

A child's intentions to smoke tobacco and later onset of smoking: A longitudinal study of male female differences
Y.G. Flores-Ortega and J.C. Anthony, Epidemiology, Michigan State University, East Lansing, MI

COMORBIDITY I

Discriminative stimulus effects of methylphenidate in adults with and without Attention Deficit Hyperactivity Disorder
S.H. Kollins, J.S. English, H. Ravi and A.K. Chrisman, Psychiatry, Duke University Medical Center, Durham, NC

Meta-analysis of associations of depression and substance use and impairment in intravenous drug users
K.R. Conner1, M. Pinquart2 and P.R. Duberstein1, 1University of Rochester Medical Center, Rochester, NY and 2Friedrich Schiller University, Jena, Germany

Effect of PTSD diagnosis and contingency management procedures on cocaine use in opioid-dependent cocaine abusers maintained on low- vs. high-dose LAAM
J. McGaugh, M.J. Mancino, Z. Feldman and A. Oliveto, University of Arkansas for Medical Sciences, Little Rock, AR

Feasibility testing of Mentorship for Substance Abuse and Trauma
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Psychiatric symptom improvement in women following group substance abuse treatment: Results from the Women's Recovery Group study
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An analysis of the prevalence and persistence of psychotic behaviors in cocaine- vs.methamphetamine-dependent participants
J.J. Mahoney, III, R. De La Garza, P. Yurovsky, A.R. Dillon, A.D. Kalechstein and T.F. Newton, Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA

A comparison of the efficacy of aripiprazole on psychiatric and substance use outcomes in bipolar and schizophrenic patients
B.K. Tolliver, A.L. McRae, M.L. Verduin, S.J. Anderson, A. Herrin, R. Carter and K.T. Brady, Medical University of South Carolina, Charleston, SC

Schizophrenic patients who smoke appear to have fewer psychotic symptoms and decreased lipid peroxidation in the context of significantly elevated anti-oxidant enzyme activities
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Outcomes of mutual aid for co-occurring disorders: A controlled trial
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Substance use, psychiatric, and service characteristics of clients with co-occurring disorders completing substance abuse treatment
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Social networks of individuals with co-occurring substance abuse and mental disorders: Preliminary findings and directions for future research
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The interaction of co-occurring mental disorders and recovery management checkups on substance abuse treatment participation and recovery

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Development of ASI psychiatric severity cut-off scores to identify co-occurring axis-1 psychiatric disorders

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Single-gender group treatment for substance use disorders improves outcomes for women with high psychiatric severity

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Characteristics of alcoholics with comorbid anxiety or depression in an ongoing, placebo-controlled trial of acamprosate

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Oral d-amphetamine effect on alcohol craving in alcohol-dependent and co-morbid alcohol dependent/major depressive disorder participants

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Psychiatric disorders in cannabis abusers vs. cannabis-dependent subjects requesting treatment

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Childhood trauma and health outcomes in adults with comorbid substance abuse and mental health disorders

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A comparison of psychosocial functioning and cognitive functioning between depressed and non-depressed patients with marijuana dependence

B.E. Smith1, A. Fletcher1, D.J. Brooks1, J. Mariani1,2 and F.R. Levin1,2, 1Substance Abuse, New York State Psychiatric Institute, and 2Psychiatry, Columbia University, New York, NY

The epidemiology of ecstasy: Comparing risk factors for amphetamine and ecstasy use in the general population

K. Keyes and D.S. Hasin, New York State Psychiatric Institute, New York, NY

Patterns of prescription drug misuse, illicit drug use, and mental health problems in the Miami club culture

H.L. Surratt, J.A. Inciardi and S.P. Kurtz, University of Delaware, Coral Gables, FL

Symptoms of anxiety and depression in childhood precede ecstasy use

A. Huizink, R.F. Ferdinand, J. Van der Ende and F.C. Verhulst, Child and Adolescent Psychiatry, Erasmus MC, Rotterdam, Netherlands

Psychopathology and personality among young polysubstance users: Specific correlates of regular tobacco use

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Substance abuse counselor certification: How is nicotine addiction addressed?

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Effect of depression on smoking cessation outcomes

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Preliminary investigation of a behavioral group treatment for depressed smokers

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Depressive symptoms and smoking behavior among adolescent smokers

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OPIOID TREATMENT II

No influence of antisocial personality disorder on methadone treatment retention
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Conflict tactics of opiate-dependent men and women
A. Alvanzo and E. McCance-Katz, Virginia Commonwealth University, Richmond, VA

Predictors of witnessing and experiencing violence among current and former out-of-treatment cocaine and opiate abusers in Baltimore, Maryland
C.A. Latkin and W. Hua, Health Behavior and Society, Johns Hopkins School of Public Health, Baltimore, MD

The subculture of drug-related violence in New Orleans before and after Hurricane Katrina
E. Dunlap and B.D. Johnson, Special Populations Research, National Development and Research Institutes, New York, NY

Distance to needle exchange and needle sharing among injection drug users in Baltimore
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Increased risk among traveling young injection drug users
P. Lum, J. Ford, A. Paciorek, K. Shafer and J. Hahn, University of California at San Francisco, San Francisco, CA

Early injection initiation in Tijuana, Mexico: Family influences and associated harms
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Parental drug use, living situation, and time to injection among heroin users in Baltimore, MD
B.E. Mancha, S.G. Severtson and M.M. Mitchell, Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Opioid-dependent persons in two integrated health plans
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Dispensing of methadone and buprenorphine by pharmacists. Cross-sectional survey, Bayonne, France
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PRESCRIPTION DRUG ABUSE

Demographic differences in sources of prescription opioids for abuse: Data from the NAVIPPRO system
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Prescription opioid abuse in urban versus rural areas using RADARS System data
E.J. Campagna1, E. Bailey1 and R. Dart1,2, 1Rocky Mountain Poison and Drug Center, and 2University of Colorado Health Sciences Center, Denver, CO

Characterizing the nonmedical use/abuse and diversion of opioid analgesics in 2006: Findings from ethnographic field research
J.D. Haddox, J.P. Fitzgerald, A.T. Kline and M.Y. Smith, Purdue Pharma LP, Stamford, CT

Age at onset of nonmedical use of prescription drugs and its association with prescription drug use disorders: Results from a national study
S.E. McCabe, B.T. West, M. Morales, J.A. Cranford and C.J. Boyd, University of Michigan, Ann Arbor, MI

The association between "gateway" substances and abuse of prescription opioids in young adults
L. Sullivan, J. Tetrault, W. Becker, R. Desai and D. Fiellin, Internal Medicine, Yale University School of Medicine, New Haven, CT

First exposures in prescription opioid abusers
B. Sproule1,2 and A. Elkader2,1, 1Centre for Addiction and Mental Health, and 2University of Toronto, Toronto, ON, Canada

Regular prescription drug misuse signals greater health problems among Miami club drug users
S.P. Kurtz, J.A. Inciardi and H.L. Surratt, Center for Drug and Alcohol Studies, University of Delaware, Coral Gables, FL

Expectancies for prescription stimulants in recreational and medical users
A. Looby and M. Earleywine, Psychology, University at Albany, State University of New York, Albany, NY

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Difficulties encountered contacting certified buprenorphine providers listed on the SAMHSA Website physician locator
> G. Caraballo and C.E. Albizu-García, Graduate School of Public Health, University of Puerto Rico, San Juan, Puerto Rico

Physician compliance with methadone treatment guidelines
> C. Strike1,3, W. Hillier2, E. Wenghofer2,3, W. Gnam1,3 and M. Millson3, 1Centre for Addiction and Mental Health, 2College of Physicians and Surgeons of Ontario, and 3University of Toronto, Toronto, ON, Canada

An evaluation of state priorities, guidelines and funding for infectious disease services in substance abuse treatment programs
> S.A. Kritz1, L.S. Brown, Jr.1, R.J. Goldsmith2, E.J. Bini3, J. Robinson4, D. Alderson5 and J. Rotrosen6, 1ARTC, Brooklyn, NY, 2Cin. VAMC, U. of Cin., Cincinnati, OH, 3VA NY Harbor Hlth Syst. & NYU Sch. of Med., 4Nathan Kline Inst., Orangeburg, 5NYSPI, NY Presbyterian Hosp., and 6VA NY Harbor Hlth Sys. and NYU Sch. Med., NY, NY

Therapeutic mistrust and therapeutic pessimism in drug addiction research
> C.B. Fisher1, M. Oransky1, M. Mahadevan1, M. Singer2, G. Mirhej2 and D. Hodge2, 1Fordham University, Bronx, NY and 2Hispanic Health Council, Hartford, CT

Drug abuse and criminality in juveniles in New Delhi: Public health issues
> S. Sharma, N.G. Desai and G. Sharma, Psychiatry, IHBAS, Delhi, India

Recruitment and retention implications from the 2005- 06 NFATTC Workforce Survey
> J.R. Knudsen1 and S. Gallon2, 1RMC Research Corporation, and 2Oregon Health and Science University, Portland, OR

How states use workforce needs assessment data to improve addiction treatment services
> A.M. Williams1, J.R. Knudsen2 and T.G. Durham1, 1The Danya Institute, Inc., Silver Spring, MD and 2RMC Research Corporation, Portland, OR

Research on psychoactive substance use in Latin America and the Caribbean: Priorities, capacities and impact
> C. Gallo1, F. Fiestas1, G. Poletti1, D. Razzouk2, J. Mari2, I. Bustamante1, S. Sarabia1, S. Sagastegui1 and G. Mazzotti1, 1University Peruana Cayetano Heredia, Lima, Peru and 2University Federal de São Paulo, Sao Paulo, Brazil

Analysis of oral communications accepted to the CPDD and subsequent publication
> R. Aleixandre1, J.C. Valderrama1, M. Bolaños1, F. Bueno2, S. Tortajada1, P. Needle3 and J.C. Perez de los Cobos4, 1IHCD Lopez Piñero [CSIC-Univ. de Valencia], 2Plan Muni. De Drogodepend. del Ayunta. de Valencia, Spain, 3NIDA External Consulant, Atlanta, GA and 4Hosp. Sant Pau, Barcelona, Spain

A bibliometric study of two drug addiction research specialty journals
> S.W. Gust1 and E.L. Winstanley2, 1International Program, NIDA, Bethesda, and 2Behavioral Pharmacology Research Unit, Johns Hopkins School of Medicine, Baltimore, MD

SYMPOSIUM VII - HOW ARE GENES AFFECTING RISK OF ALCOHOL DEPENDENCE RELEVANT TO DRUG DEPENDENCE?
Chairs: Henry Kranzler and Joel Gelernter

Serotonergic genes, gene X environment interaction, and risk of alcohol and drug dependence
> Henry Kranzler, University of Connecticut School of Medicine, Farmington, CT

New findings on genes close to DRD2 and risk of alcohol, nicotine, and cocaine dependence
> Joel Gelernter, Yale University School of Medicine, West Haven, CT

GABA-A subunit genes, risk of alcohol dependence, and correlations with the subjective effects of alcohol
> Jonathan Covault, University of Connecticut School of Medicine, Farmington, CT

ADH genes and risk of alcohol and drug dependence
> Xingguang Luo, Yale University School of Medicine, West Haven, CT

Discussant
> Charles O'Brien, University of Pennsylvania School of Medicine, Philadelphia, PA

ORAL COMMUNICATIONS 11 - HIV/AIDS
Chairs: Clyde McCoy and Lisa Metsch

Clustering of high-risk sex behaviors among men and women drug users
> C.B. McCoy1, V. DeGruttola2 and M. Comerford1, 1University of Miami, Miami, FL and 2Harvard University, Cambridge, MA

Sexual-risk behavior among female crack users in São Paulo, Brazil
S.A. Nappo1,2, L.G. Oliveira1,2 and Z.M. Sanchez1,2, 1Federal University of São Paulo, and 2CEBRID, São Paulo, Brazil

Use of crack cocaine among HIV-infected persons is associated with high risk sexual activity and failure to receive outpatient HIV care
L. Metsch1, C. del Rio2, A. Rodriguez1, T. Sullivan2, G. Cardenas1, L. Gooden1, M. Pereyra1, C. Bell2, T. Brewer1, T. Kuper1, S. Lewis3 and R. Rothenberg2, 1U. of Miami School of Medicine, Miami, FL, 2Emory U. School of Medicine, Atlanta, GA and 3Barry U., Miami, FL

Injection stimulant use and HIV risk in central Ukraine
O. Zezyulin1, K. Dumchev1, J. Schumacher2, R. Soldyshev3, L. Moroz3 and P. Slobodyanyuk1, 1Vinnitsya Regional Narcological Dispensary, Vinnitsya, Ukraine, 2U. of Alabama at Birmingham, Birmingham, AL and 3Vinnitsya Pirogov National Medical U., Vinnitsya, Ukraine

Correlates of meth use among men who attend an STD clinic that primarily serves gay men
E.T. Rudy1, S. Shoptaw2,3, P. Kerndt1, J. Hall4, T. Horton4 and S. Tilekar4, 1LA County Department of Public Health, 2Department of Family Medicine, and 3Integrated Substance Abuse Programs, UCLA, and 4LA Gay and Lesbian Center, Los Angeles, CA

10 years of universal access to HIV treatment: Learning from the Brazilian experience
M. Malta1, F.I. Bastos1, S.A. Strathdee2 and M. Monteiro3, 1FIOCRUZ, Rio de Janeiro, Brazil, 2University of California, San Diego, CA and 3PAHO/WHO, Washington, DC

Medication adherence and viral load in HIV-positive, methamphetamine-using MSM
J. Arnsten2, D.A. Bux1, J. Morgenstern1, J.T. Parsons3 and J. Severino1, 1Columbia University, New York, 2Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, and 3Hunter College and Graduate Center, City University of New York, New York, NY

Pilot study of directly administered antiretroviral therapy as a structural intervention in methadone maintenance
J. Alexander1,2, N. Haug1, Y. Song1 and J. Sorensen1, 1University of California San Francisco School of Medicine, San Francisco, CA and 2Touro College of Osteopathic Medicine, Mare Island, CA

ORAL COMMUNICATIONS 12 - Y GENDER XPLAINS THE DIFFERENCE
Chairs: Kathleen Brady and Andrea Stone

Gender differences in response to stress and cues in cocaine-dependent individuals
K.T. Brady, A.L. McRae, S.E. Back, A.E. Waldrop, M.E. Saladin and S.D. Yeatts, Psychiatry, Medical University of South Carolina, Charleston, SC

Changing gender trends in adolescent drug use
A.L. Stone, Psychosocial and Community Health, University of Washington, Seattle, WA

Who starts then stops cocaine use? United States, 2003
G.F. Alvarado1,2 and J.C. Anthony2,1, 1Public Health, Cayetano Heredia Peruvian University, Lima, Peru and 2Epidemiology, Michigan State University, East Lansing, MI

A gender-specific investigation of long-term drug use among an urban African-American cohort
E.E. Doherty1, K.M. Green2 and M.E. Ensminger2, 1Mental Health, and 2Health, Behavior, and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Gender differences in methamphetamine use in youth and young adults treated for substance dependence
M.E. Roth, C. Walker and V. Slaymaker, Butler Center for Research at Hazelden, Center City, MN

Factors associated with substance abuse treatment utilization among male and female incarcerated substance users
M. Staton-Tindall1, J. Havens1, C. Oser1, M. Prendergast2 and C. Leukefeld1, 1Behavioral Science, University of Kentucky, Lexington, KY and 2Integrated Substance Abuse Programs, University of California, Los Angeles, Los Angeles, CA

Role of individual, treatment, and post-treatment factors on sustained remission: Examining gender differences
V. Stanick1, A. Laudet1 and B. Sands2, 1National Development Research Institute, and 2Woodhull Medical Center, New York City, NY

Gender as a moderator in the relationship between behavioral measures of risk-taking and impulsivity in a sample of inner-city, African-American substance users
B. Baker1, C.W. Lejuez1, M. Bornovalova1, M.T. Tull1 and B. Reynolds2, 1University of Maryland, College Park, MD and 2Ohio State University, Columbus, OH

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ORAL COMMUNICATIONS 13 - STIMULANTS: PRECLINICAL STUDIES
Chairs: Kathleen Kantak and John Mantsch

Regulation of the serine/threonine protein kinase Akt in the nucleus accumbens following amphetamine in mice
J. Miller[1,2] and E. Unterwald[1,2], [1]Pharmacology, and [2]Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA
Subregional analysis of basolateral amygdala regulation of cocaine-seeking behavior in rats: Differential effects of SKF81297 during maintenance and reinstatement conditions
Y. Mashhoon, L. Yager and K.M. Kantak, Psychology, Boston University, Boston, MA

Systemic injections of VPA leads to enhanced reinstatement of conditioned-cued reinstatement of cocaine-seeking in rats: Role of HDAC in appetitive reinforcement
T.E. Kippin and K.A. Kerstetter, Psychology and Neuroscience Research Institute, University of California, Santa Barbara, CA

Effect of footshock-stress intensity on methamphetamine reinstatement in rats
K.L. Shelton and P.M. Beardsley, Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA

Levo-tetrahydropalmatine attenuates cocaine self-administration and cocaine-induced reinstatement in rats
J. Mantsch[1], S.J. Li[3], R. Risinger[4], E. Katz[1], S. Awad[1], D. Baker[1] and Z. Yang[1], [1]Biomedical Sciences, [4]Psychiatry, Marquette University, and [3]Biophysics, Medical College of Wisconsin, Milwaukee, WI and [2]Beijing Institute of Basic Medical Sciences, Beijing, China

Long-term memory of cocaine-associated context: Disruption of reconsolidation, extinction, renewal and reinstatement
Y. Itzhak[1,2], J.B. Kelley[2] and K.L. Anderson[1], [1]Psychiatry, and [2]Neuroscience Program, University of Miami, Miami, FL

Alpha synuclein protein levels are increased in cocaine abusers
N. Adi[1], J. Pablo[1], L. Duque[1], F.R. Ervin[2] and D.C. Mash[1], [1]Neurology, Miller School of Medicine, Miami, FL and [2]McGill University, Montreal, ON, Canada

Central probes of cholinergic receptor systems and associated cognitive functioning in cocaine-ddicted subjects
B. Adinoff[1,2], M.J. Williams[1], S.E. Best[1,2], T. Zielinski[1], T.S. Harris[3], E.R. Schreffler[1] and M.D. Devous[3], [1]Psychiatry, University of Texas Southwestern, [2]VA North Texas Health Care System, and [3]University of Texas Southwestern Medical Center, Dallas, TX

Early Career Investigator Awards Luncheon

ANIMALS IN RESEARCH FORUM
ADVOCATING AND EXPLAINING
CONTROVERSIAL SCIENCE
Presented by Richard Bianco
Office of Regulatory Affairs, University of Minnesota

WORKSHOP X - OPIOID USE DISORDER IN ADOLESCENTS: EPIDEMIOLOGY, PATIENT CHARACTERISTICS, EVIDENCE-BASED TREATMENTS AND COSTEFFECTIVENESS OF BUPRENORPHINE TREATMENT
Chairs: Geetha Subramaniam and Michael Dennis

Adolescents with opioid use disorders: Prevalence, problems and patient characteristics
Geetha Subramaniam, Johns Hopkins University, Baltimore, MD
Evidence-based behavioral and pharmacological treatment of opioid-dependent adolescents
Lisa Marsch, NDRI, New York, NY
Cost-effectiveness of Bup/Nal treatment for opioid-addicted youth
Daniel Polsky, University of Pennsylvania, Philadelphia, PA
Findings from a NIDA-CTN clinical trial of Bup/Nal-facilitated rehabilitation for opioid-ependent adolescents/youth adults
George Woody, Treatment Research Institute, Philadelphia, PA
Society for Adolescent Substance Abuse Treatment Effectiveness (SASATE) business meeting
Michael L. Dennis, Chestnut Health Systems, Bloomington, IL

WORKSHOP XI - 13TH ANNUAL CONTINGENCY MANAGEMENT WORKING GROUP
Chair: Stacey Sigmon

WORKSHOP XII - ISSUES IN MEDICATIONS DEVELOPMENT FOR RELAPSE PREVENTION
Chairs: David McCann and Ahmed Elkashef

The importance of relapse prevention in drug addiction treatment
   Charles O'Brien, University of Pennsylvania School of Medicine, Philadelphia VA Medical Center, Philadelphia, PA
Animal models of relapse: An overview
   Jane B. Acri, NIDA, NIH, HHS, Bethesda, MD
Use of extinction/reinstatement rat models of relapse in medications discovery
   David McCann, NIDA, NIH, HHS, Bethesda, MD
Human laboratory models of relapse: Approaches, pitfalls and a view of the future
   Anna Rose Childress, University of Pennsylvania, Philadelphia VA Medical Center, Philadelphia, PA
Considerations in the design of clinical trials for assessing the efficacy of relapse prevention medications
   Ahmed Elkashef, NIDA, NIH, HHS, Bethesda, MD
   Discussant
   Frank Vocci, NIDA, Bethesda, MD

WORKSHOP XIII - NIDA DRUG SUPPLY AND ANALYTICAL SERVICES PROGRAM: AN OVERVIEW
Chairs: Hari H. Singh and David Shurtleff

An overview of the NIDA drug supply & analytical services program
   Hari H. Singh, Division of Basic Neuroscience and Behavioral Research, NIDA, Bethesda, MD
NIDA drug supply inventory and acquisition of drugs of abuse and new chemical compounds by synthesis
   F. Ivy Carroll, Research Triangle Institute, Research Triangle Park, NC
Acquisition, storage and distribution of drugs of abuse and other chemical compounds
   Kenneth H. Davis, Jr., Research Triangle Institute, Research Triangle Park, NC
Quantitative analysis of drugs of abuse in biological samples
   David E. Moody, University of Utah, Salt Lake City, UT
X-ray crystallography of chemical compounds and biological substrates
   Jeffrey R. Deschamps, Naval Research Laboratory, Department of Navy, Washington, DC
Guidance on acquiring DEA registration for using controlled substances in research
   Christine A. Sannerud, U.S. Drug Enforcement Agency, Washington, DC

Wednesday, June 20, 2007

POSTER SESSION III - ALCOHOL: ANIMAL STUDIES
Attenuation of stress-induced ethanol consumption in male Lewis rats by the CCK-B antagonist L-365, 260
   J.M. Mitchell[1,2,3], K.S. Chen[3] and H.L. Fields[1,2,3], [1]Neurology, UCSF, Emeryville, [2]Wheeler Center for the Neurobiology of Addiction, UCSF, San Francisco, and [3]Ernest Gallo Clinic and Research Center, UCSF, San Francisco, CA
Dissociation between physiological and motivational effects of alcohol in female Fischer & Lewis rats
   P.G. Roma[1], S.A. Chen[2], C.S. Barr[2] and A.L. Riley[1], [1]Psychopharmacology Laboratory, Department of Psychology, American University, Washington, DC and [2]Laboratory of Clinical and Translational Studies, Section on Primate Studies, NIAAA, Poolesville, MD
GABA-A/alpha5 receptor mechanisms in the discriminative stimulus effects of GABA-A modulators
   D. Platt[1], M. Van Linn[2], T. Clayton[2], J. Cook[2] and J. Rowlett[1], [1]Harvard Medical School/NEPRC, Southborough, MA and [2]University of Wisconsin, Milwaukee, WI
The effect of ethanol on working memory and repeated learning in Wistar rats
   G.R. Wenger, Pharmacology & Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR
Ethanol and LiCl induced-suppression of schedule-induced polydipsia
   S.L. Handler, S.J. Kohut, R.L. Hertzbach and A.L. Riley, Psychology, American University, Washington, DC

Addition of concurrently available food decreases the sensitivity of ethanol self-administration to disruption by fluvoxamine

B.C. Ginsburg1 and R.J. Lamb1,2, 1Psychiatry, and 2Pharmacology, University of Texas Health Science Center at San Antonio, San Antonio, TX

SEDATIVE-HYPNOTICS

Comparison of bretazenil and midazolam self-administration under a progressive-ratio schedule: Labor supply analysis

J.K. Rowlett, NEPRC, Harvard Medical School, Southborough, MA

Differential antagonism of the sedative and motor effects of zolpidem and alprazolam by BCCT

A.N. Duke1,2, D.M. Platt1, J.M. Cook3, M.L. Van Linn3 and J.K. Rowlett1,2, 1HMS/New England Primate Research Center, Southborough, MA, 2Neuroscience & Behavior, University of Massachusetts, Amherst, MA and 3Chemistry, University of Wisconsin, Milwaukee, WI

The reinforcing effects of an acute oral dose of zolpidem in drug-naïve and drug-experienced human volunteers

S.C. Licata, D. Penetar, S. Dunlap and S.E. Lukas, Psychiatry, McLean Hospital/Harvard Medical School, Belmont, MA

Non-medical use, abuse and dependence on sedatives and tranquilizers among U.S. adults: Correlation with anxiety

R.A. Desai, W. Becker and D.A. Fiellin, Yale University School of Med., New Haven, CT

Effect of task difficulty on a Morris water maze reversal task in rats prenatally exposed to toluene

J. Batis1, S.E. Bowen1,2 and J.H. Hannigan1,2, 1Psychology, Wayne State University, Detroit, MI and 2Obstetrics & Gynecology, Wayne State University, Detroit, MI

Repeated toluene exposure hampers behavioral performance as measured by a waiting-forreward operant task

S. Bowen and P. McDonald, Psychology, Wayne State University, Detroit, MI

HALLUCINOGENS

PCP-treatment-dependent differential regulation of the NMDAR is dependent on PSD-95 expression and mediated by calpain

N.C. Anastasio, Y. Xia and K.M. Johnson, University of Texas, Galveston, Galveston, TX

Human trace amine associated receptor 1: A neuromodulator of hallucinogens?

A.H. Lewin, S.W. Mascarella, M.A. Porter and H.A. Navarro, Research Triangle Institute International, Research Triangle Park, NC

5-Methoxydiethyltryptamine shares stimulus effects with abused hallucinogens

M.B. Gatch, M. Rutledge, C.M. Taylor and M.J. Forster, Pharmacology & Neuroscience, University of Texas Health Science Center, Fort Worth, TX

Discriminative stimulus effects of DOM in rhesus monkeys: Pharmacologic selectivity and receptor mechanisms

J. Li1, K.C. Rice2 and C.P. France1, 1Pharmacology, University of Texas Health Science Center, San Antonio, TX and 2Laboratory of Medicinal Chemistry, Bethesda, MD

Comparison of the discriminative stimulus effects of DOM, MDL100907 and ketanserin in rats: Inverse agonism?

A. Unzeitig1, J. Li1, K.C. Rice2 and C.P. France1, 1Pharmacology, University of Texas Health Science Center at San Antonio, San Antonio, TX and 2Laboratory of Medicinal Chemistry, NIDDK, Bethesda, MD

Characterizing emerging drugs using quantitative semantic analysis of Internet trip reports

M.J. Baggott1,2, J.R. Coyle2, J.C. Lopez2 and D.E. Presti3, 1Helen Wills Neuroscience Institute, and 3Molecular and Cell Biology, UC Berkeley, Berkeley, CA 2Addiction Pharm. Res. Laboratory, California Pacific Medical Center Research Institute, San Francisco, CA

Reported pharmacological effects after the ingestion of research chemicals and smart drugs in a naturalistic setting

M. Farre1,3, R. de La Torre1,2, M. Pujadas1, E. Marchei4, M. Pellegrini4, J. Fiz1,3, R. Pacifici4, P. Zuccaro4 and S. Pichini4, 1Pharmacology, IMIM, 2Universitat Pompeu Fabra, 3Universitat Autonoma, Barcelona, Spain and 4Istituto Superiore di Sanità, Rome, Italy

PAIN/ANALGESIA

The effect of the chemokines MCP-1 and MIP-1beta on antinociception induced by opioid agonists in rats

X. Chen1, E.B. Geller1, T.J. Rogers1,2,3 and M.W. Adler1, 1Center for Substance Abuse Research, 2Department of Pharmacology, and 3Fels Institute for Cancer and Molecular Biology, Temple University School of Medicine, Philadelphia, PA

A new role for MCP-1: Mediation of kappa opioid receptor antinociceptive and hypothermic effects in mice

K. Benamar, E.B. Geller and M.W. Adler, Center for Substance Abuse Research, Temple University, Philadelphia, PA

Decrease in the efficiency of GABAergic neurotransmission associated with an increase in GABA transporter located on astrocytes under the neuropathic pain-like state
> K. Nanjo, M. Narita, M. Narita, N. Kuzumaki, K. Niikura, K. Miyoshi, Y. Funada and T. Suzuki, Department of Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences, Tokyo, Japan

Estrous cycle effects on behavioral and physiological responses to inflammatory pain
> N.J. Amador1,2, K.Y. Shivers1,2, D. Hunter1,2, G. Barr1,2, S. Jenab1,2 and V. Quinones-Jenab1,2, 1Psychology, Hunter College of CUNY, and 2Biopsychology and Behavioral Neuroscience Doctoral Subprogram, Graduate Center of CUNY, New York, NY

Developmental and hormonal effects on inflammatory responses to pain in female rats
> K.Y. Shivers1,2, N. Amador1,2, D. Hunter1,2, S. Jenab1,2 and V. Quinones-Jenab1,2, 1Psychology, Hunter College of CUNY, New York, NY and 2Biopsychology and Behavioral Neuroscience, Graduate School and University Center, CUNY, New York, NY

Decrease in NMDAR-NR2B subunit levels by intrathecal shRNA blocks group I mGluRmediated hyperalgesia
> B.H. Gabra, F.L. Smith, F.K. Kessler, J.K. Ritter and W.L. Dewey, Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA

Prescription opioid-abusing chronic pain patients: Clinical characteristics associated with relapse
> J. Manubay1,2, S.D. Comer1,2, S.K. Vosburg1,2, J. Lee1,2, S. Stephens1,2 and M.A. Sullivan1,2, 1Psychiatry, Columbia University, and 2Substance Abuse, New York State Psychiatric Institute, New York, NY

Effects of sublingual buprenorphine/naloxone and oral oxycodone on pain perception in prescription opioid-abusing chronic pain patients
> M.A. Sullivan, J. Lee, W.J. Kowalczyk, S.K. Vosburg and S.D. Comer, Columbia University/NYSPI, New York, NY

Post-surgical analgesia predicted by pre-surgical self-reported sleep
> T. Roehrs1,2, M. Hyde1, M. Greenwald2 and T. Roth1,2, 1Sleep Disorders and Research Center, Henry Ford Hospital, and 2Psychiatry and Behavioral Neuroscience, Wayne State University School of Medicine, Detroit, MI

COCAINE BEHAVIOR: ANIMALS STUDIES
Novel approach to the analyses of conditioned place preference
> A.M. Sandler dela Cruz, D.V. Herin and K.A. Cunningham, Center for Addiction Research, University of Texas Medical Branch, Galveston, TX

Incentive salience of cocaine is remarkably similar across the postpartum period
> M. Pereira, K.M. Seip, E.I. Dziopa and J.I. Morrell, Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, NJ

Cocaine-induced locomotor sensitization during conditioning and locomotor rates during test may predict resulant place preference in lactating dams
> K. Seip, M. Pereira, E. Dziopa and J. Morrell, Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, NJ

Conditioned place preference as a model for investigating social and drug rewards in adolescent rats
> K.J. Thiel and J.L. Neisewander, Psychology, Arizona State University, Tempe, AZ

The reinstatement of cocaine-induced place aversions and preferences with priming injections of cocaine
> G.D. Busse1, F.S. Hall2 and A.L. Riley1, 1Department of Psychology, American University, Washington, DC and 2Molecular Neurobiology Branch, NIDA, Baltimore, MD

Estrogen enhances conditioned place preference to cocaine
> Y.M. Torres, Y. Arroyo and A.C. Segarra, Physiology, University of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico

Acute effects of progesterone and testosterone on cocaine self-administration by female nonhuman primates
> N.K. Mello, J.H. Mendelson, I.M. Knudson, S.S. Negus and M. Kelly, Alcohol and Drug Abuse Research Center, McLean Hospital-Harvard Medical School, Belmont, MA

Progesterone pretreatment attenuates reinstatement of cocaine-seeking in freely cycling female rats
> M.W. Feltenstein, A.R. Henderson and R.E. See, Neurosciences, MUSC, Charleston, SC

Allopregnanolone attenuates the reinstatement of cocaine-seeking behavior in female rats
> J.J. Anker1, E.B. Larson2, N.A. Holtz1, L.A. Gliddon1 and M.E. Carroll1, 1Psychiatry, University of Minnesota, Minneapolis, MN and 2Psychiatry, UT Southwestern, Dallas, TX

Estrous cycle effects on DARPP-32 activity after acute cocaine
> J. Weiner1, W. Sun1,2, L. Zhou2, V. Quinones-Jenab1,2 and S. Jenab1,2, 1Psychology, Hunter College of CUNY, and 2Biopsychology and Behavioral Neuroscience Doctoral Subprogram, Graduate Center of CUNY, New York, NY

Sex differences in the development of cocaine-induced behavioral sensitization and tolerance

L. Zhou2,3, W. Sun4, K. Weierstall4, A.C. Minerley4, S. Jenab1,4 and V. Quinones-Jenab1,3,4, 1Psychology and 2Biology, Hunter College, and 3Grad. Ctr. of CUNY, 4Biopsychology and Behavioral Neuroscience Doctoral Subprogram, Grad. Ctr. of CUNY, New York, NY

Isoflurane anesthesia dampens cocaine-induced sensitization in the rat

D. Dow-Edwards, Physiology and Pharmacology, SUNY-Downstate, Brooklyn, NY

Incubation of cocaine-seeking behavior is enhanced and more enduring in female relative to male rats

K.A. Kerstetter, V. Aguilar, M. Jachimowicz, R. Choy, C. Kaspar and T.E. Kippin, Psychology and Neuroscience Research Institute, University of California, Santa Barbara, CA

Does response-contingent access to cocaine reinstate cocaine-seeking behavior in C57BL/6J mice?

P.J. Kruzich, Physiology, Medical College of Georgia, Augusta, GA

Selective role for basolateral amygdala in reconsolidation of cocaine-context associations that guide context-induced cocaine-seeking behavior

D.R. Ramirez, J.L. Eaddy and R.A. Fuchs, Psychology, University of North Carolina, Chapel Hill, NC

Time-limited role of the hippocampus in regulating context-induced cocaine-seeking behavior

A.L. Atkins, J.J. Szalay and K.M. Kantak, Psychology, Boston University, Boston, MA

Accumbal extracellular glutamate levels during cocaine self-administration and its extinction: A time-course microdialysis study

M. Miguéns, N. del Olmo, I. Torres, A. Higuera-Matas, C. García-Lecumberri and E. Ambrosio, Psicobiología, Universidad Nacional de Educación a Distancia, Madrid, Spain

Role of mGluR5 in the behavioral-stimulant effects of cocaine in squirrel monkeys

R.M. Bauzo1,2, M. Zhou2, H.L. Kimmel1,2 and L.L. Howell1,2,3, 1Neuroscience, Emory University, 2Division of Neuroscience, Yerkes National Primate Research Center, and 3Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA

Neurotensin response to psychostimulant self-administration

P. Frankel, A.J. Hoonakker and G.R. Hanson, Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, UT

Effects of chronic administration of the D1 receptor partial agonist SKF 83959 on eye blinking in squirrel monkeys

R.I. Desai, C.A. Paronis, J. Connolly, N. Shaller and J. Bergman, Preclinical Pharmacology Laboratory, McLean Hospital/Harvard Medical School, Belmont, MA

Effects of dopamine D2 agonists on injection/food choice behavior in cocaine-trained monkeys

J. Bergman and C.A. Paronis, ADARC-MRC, Harvard Medical School/McLean Hospital, Belmont, MA

Novel D3 receptor antagonists and partial agonists attenuate the discriminative stimulus effects of cocaine and reinstatement of cocaine-seeking in squirrel monkeys

C. Achat-Mendes1, D.M. Platt1, P. Grundt2, S. Langer1, K. Bano1, A.H. Newman2 and R.D. Spealman1, 1NEPRC, Harvard Medical School, Southboro, MA and 2Medicinal Chemistry, NIDA, Baltimore, MD

IMPULSIVITY AND ATTENTION

Are lapses of attention a form of impulsive behavior?

H. de Wit1 and J.B. Richards2, 1Psychiatry, University of Chicago, Chicago, IL and 2Research Institute on Addiction, Buffalo, NY

Measuring lapses of attention in rodents

J.B. Richards1 and H. de Wit2, 1Research Institute on Addictions, University of Buffalo, Buffalo, NY and 2Psychiatry, University of Chicago, Chicago, IL

Methylphenidate effects on attentional set-shifting in a rodent model of ADHD

R.C. Harvey and K.M. Kantak, Psychology, Boston University, Boston, MA

Multi-method assessment of impulsive behaviors

A.E. Waldrop1, K.T. Brady1 and C.W. Lejuez2, 1Medical University of South Carolina, Charleston, SC and 2University of Maryland, College Park, MD

Impulsivity and decision making: Relationship to treatment outcome in cocaine dependence

M.E. Mooney1, C. Green2, J. Schmitz2, J. Steinberg2, A. Swann2, S. Lane2 and F.G. Moeller2, 1Psychiatry, University of Minnesota, Minneapolis, MN and 2Psychiatry and Behavioral Sciences, University of Texas Houston Medical School, Houston, TX

Time-limited role of the hippocampus in regulating context-induced cocaine-seeking behavior

A.L. Atkins, J.J. Szalay and K.M. Kantak, Psychology, Boston University, Boston, MA

Accumbal extracellular glutamate levels during cocaine self-administration and its extinction: A time-course microdialysis study
> M. Miguéns, N. del Olmo, I. Torres, A. Higuera-Matas, C. García-Lecumberri and E. Ambrosio, Psicobiología, Universidad Nacional de Educación a Distancia, Madrid, Spain

Role of mGluR5 in the behavioral-stimulant effects of cocaine in squirrel monkeys
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Neurotensin response to psychostimulant self-administration
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Effects of chronic administration of the D1 receptor partial agonist SKF 83959 on eye blinking in squirrel monkeys
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Effects of dopamine D2 agonists on injection/food choice behavior in cocaine-trained monkeys
> J. Bergman and C.A. Paronis, ADARC-MRC, Harvard Medical School/McLean Hospital, Belmont, MA

Novel D3 receptor antagonists and partial agonists attenuate the discriminative stimulus effects of cocaine and reinstatement of cocaine-seeking in squirrel monkeys
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IMPULSIVITY AND ATTENTION

Are lapses of attention a form of impulsive behavior?
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Measuring lapses of attention in rodents
> J.B. Richards1 and H. deWit2, 1Research Institute on Addictions, University of Buffalo, Buffalo, NY and 2Psychiatry, University of Chicago, Chicago, IL

Methylphenidate effects on attentional set-shifting in a rodent model of ADHD 53
> R.C. Harvey and K.M. Kantak, Psychology, Boston University, Boston, MA

Multi-method assessment of impulsive behaviors
> A.E. Waldrop1, K.T. Brady1 and C.W. Lejuez2, 1Medical University of South Carolina, Charleston, SC and 2University of Maryland, College Park, MD

Impulsivity and decision making: Relationship to treatment outcome in cocaine dependence
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Delay discounting of money, cocaine, cigarettes, and health in cocaine-dependent outpatients
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Delay discounting and sensitization to the locomotor-activating effects of d-amphetamine
> J.L. Perry and M.T. Bardo, University of Kentucky, Lexington, KY

COCAINE BEHAVIOR: HUMAN STUDIES

A randomized, double-blind, placebo-controlled multi-center trial of baclofen for the treatment of cocaine dependence
> R. Kahn2, S. Shoptaw1, A. Elkashef2, A. Childress3, P. Fudala4, L. Gorgon2, S. Kilby4, K. Biswas4 and K.G. Heinzerling1, 1UCLA, Los Angeles, CA, 2NIDA, Bethesda, MD, 3University of Pennsylvania and 4Veteran Affairs, Philadelphia, PA

Dopamine beta-hydroxylase levels influence response to disulfiram in cocaine-dependent methadone patients
> A. Oliveto1, J. Poling2, M. Mancino1, R. Pruzinsky2, K. Gonsai2, J. Cubells3, G. Anderson2, M. Chopra1, K. Carroll2, T.R. Kosten4 and C. Cargile1, 1UAMS, Little Rock, AR, 2Yale School of Medicine, New Haven, CT, 3Emory University, Atlanta, GA and 4Baylor, Houston, TX

Disulfiram enhances paranoia during "binge" cocaine self-administration
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The measurement of craving in cocaine pharmacotherapy trials: What do we learn from it?
> K.M. Kampman, K. Lynch, H.M. Pettinati, C. Dackis, W. Dundon, K. Varillo, C. Fairbairn, M. Yama and C.P. O'Brien, Psychiatry, University of Pennsylvania, Philadelphia, PA

Exposure techniques versus topiramate treatment on cocaine addiction
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Patterns of cigarette use during treatment for cocaine dependence
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Behavioral patterns of cocaine use: Treatment implications
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Assessing cocaine reinforcement: A comparison of the Multiple-Choice Procedure, selfadministration behavior, and subjective responses
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Effects of reinforcement magnitude on cocaine use and retention in an outpatient treatment for cocaine addicts
> O. Garcia-Rodriguez, R. Secades-Villa and J.R. Fernandez-Hermida, Psychology, University of Oviedo, Oviedo, Spain

Cocaine use and depressive symptoms following participation in laboratory studies of cocaine
> C. Saldana, C.L. Hart, M. Zawodna, S. Vosburg, M. Haney, B.J. Fay, A. Couraud, E. Rubin and R.W. Foltin, Psychiatry, Columbia University, New York, NY

EEG absolute power during extended cocaine abstinence
> K.H. Levin, R.I. Herning, W.E. Better, D.H. Epstein, J.L. Cadet and D.A. Gorelick, NIDA, Intramural Research Program, Baltimore, MD

Comparison of three set-shifting measures in cocaine-dependent males
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Features of Spanish adult patients with Attention Deficit Hyperactivity Disorder who ask forcocaine use treatment
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The outcome of treatment in a psychoactive substance-related mental disorder ward
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Cognitive performance of cocaine-dependent subjects: Effects of psychiatric symptoms on Frontal Assessment Battery
> S. Nicastri[1,2] and P.J. Cunha[1,2], [1]Alcohol and Drug Abuse Treatment Program, Hospital Israelita Albert Einstein, and [2]Interdisciplinary Group of Studies on Alcohol and Drugs, University of São Paulo, São Paulo, Brazil

Neurocognitive deficits and retention to treatment in cocaine-dependent patients: A 6-month follow-up study
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Cognitive measures as predictors of treatment outcome for cocaine dependence
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Relationship between cocaine use and psychological predictors of treatment outcome depends on type of urine-testing method
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Assessing mechanisms of change in cocaine/alcohol continuing care
> K.G. Lynch[1], J.R. McKay[1], S.A. Maisto[2], T.R. TenHave[1] and M.S. Cary[1], [1]University of Pennsylvania, Philadelphia, PA and [2]Syracuse University, Syracuse, NY

Treatment compliance, not severity at treatment entry, predicts 12-month abstinence among homeless
> J.E. Schumacher[1], J.B. Milby[2], D. Wallace[3], R.E. Vuchinich[2], S.G. Kertesz[1], S. Sieweke[2] and R.E. Cusimano[4], [1]Division of Preventive Medicine, [4]Mathematics, and [2]Psychology, U. of Alabama, Birmingham, AL and [3]Rho Federal Systems Division, Inc., Chapel Hill, NC

Adapting contingency management to homeless, out-of-treatment MSM substance users

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How hidden are hidden populations? The case of out-of-treatment cocaine users in Chile

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Development of user-driven control strategies on high risk crack-cocaine use in the city of São Paulo, Brazil

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Predicting medical care access among out-of-treatment drug-using women

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Predictors of adult victimization among high risk, cocaine-using women

K. Vaddiparti, C. Callahan, A. Ben Abdallah and L.B. Cottler, Psychiatry, Washington University School of Medicine, St. Louis, MO

Characterization of treatment-seeking substance abusers at the UT-Houston Substance Abuse Research Center from 1990-2006

D.V. Herin, N. Moukaddam, C. Green, S.L. Sayre and J. Grabowski, Psychiatry, University of Texas Health Science Center at Houston, Houston, TX

Crack cocaine trajectories among a community sample of users in Dayton, Ohio

R. Falck, J. Wang and R.G. Carlson, Community Health, Wright State University School of Medicine, Dayton, OH

Drug use patterns and drug-related disorders of cocaine users. Results from the Epidemiological Survey on Substance Abuse in Germany

L. Kraus, R. Augustin, B. Orth and G. Bühringer, IFT Institut für Therapieforschung, Munich, Germany

POLYDRUG TREATMENT I

Naltrexone and disulfiram are effective addiction pharmacotherapies in impaired healthcare practitioners

E.F. McCance-Katz, P.A. Pade and J.S. Knisely, Psychiatry, Virginia Commonwealth University, Richmond, VA

Contracting and contingency management is an effective treatment component in impaired health professionals

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Efficacy of aripiprazole in patients with substance use disorders

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Transcutaneous electroacupuncture decreases drug use and craving in drug-dependent individuals

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Transcutaneous electroacupuncture decreases cue-induced EEG physiological responses in drug-dependent individuals

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Reinforcement density in prize-based reinforcement of simultaneous abstinence from cocaine and heroin

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Experiment to improve the validity of self-report utilizing feedback from prior assessments and on-site urine testing

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Comparison of Addiction Severity Index drug use self-reports and urinalysis results among dependent patients undergoing treatment

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A comparison of behavioral and self-report measures of distress tolerance among urban minority drug users

R.M. Schuster, S.B. Daughters, M.N. Sargeant, P. Proano and C.W. Lejuez, University of Maryland, College Park, MD

PERINATAL EFFECTS OF DRUGS

Role of breast cancer resistant protein on transplacental transfer of methadone
    T.N. Nanovskaya, S. Patrikeeva, S. Hemauer, G. Hankins and M.S. Ahmed, OB/GYN Maternal Fetal Medicine, University of Texas Medical Branch, Galveston, TX
Effects of buprenorphine, methadone, L-acetyl methadole and their metabolites on pregnenolone formation by human placenta
    O. Zharikova, S. Deshmukh, T.N. Nanovskaya, G. Hankins and M.S. Ahmed, OB/GYN Maternal Fetal Medicine, University of Texas Medical Branch, Galveston, TX
Cocaine impairs neocortical development by causing oxidative ER stress and down-regulation of cyclin A in neural progenitor cells
    C. Lee[1], J. Chen[1], T. Hayashi[1], S.Y. Tsai[1], J.F. Sanchez[1], S.L. Errico[1], R. Amable[1], T.P. Su[1], J. Shen[2], K.G. Becker[3], H.M. Geller[4] and W.J. Freed[1], [1]IRP, NIDA, NIH, [2]ScienCell Research Lab., San Diego, CA, [3] IRP, NIA, NIH, DHHS, Baltimore, MD and [4]NHLBI, NIH, Bethesda, MD
Dosing pre to postpartum with either buprenorphine or methadone
    H.E. Jones[1], R.E. Johnson[1,2], D.R. Jasinski[3], M. Tuten[1] and L. Milio[4], [1]Psychiatry, Johns Hopkins University, Baltimore, MD, [2]Reckitt Benckiser Pharmaceuticals Inc, Richmond, VA, [3]Medicine, and [4]OB/GYN, Johns Hopkins University, Baltimore, MD
Methadone in pregnancy: Treatment retention and neonatal outcomes
    L. Burns[1], R.P. Mattick[1], C. Wallace[2] and K. Lim[2], [1]National Drug and Alcohol Research Centre, University of New South Wales, and [2]Centre for Epidemiology and Research, New South Wales Health Department, Sydney, NSW, Australia
Substance use, psychological distress and violence among pregnant and breastfeeding Australian women
    C. Wallace[1], L. Burns[2], S. Gilmour[2] and D. Hutchinson[2], [1]Public Health Training & Development Branch, NSW Health Department, and [2]National Drug and Alcohol Research Centre, Sydney, NSW, Australia
Comparison of characteristics of opioid-dependent pregnant women in rural and urban settings
    S.H. Heil[1,2], L.C. Trifiletti[1] and H.E. Jones[3], [1]Psychiatry, and [2]Psychology, University of Vermont, Burlington, VT, and [3]Psychiatry, Johns Hopkins University, Baltimore, MD
A description of pregnant women seeking substance use treatment in Baltimore, MD
    W.W. Latimer[1], S.G. Severtson[1], H. Jones[2], L. Jansson[1], V. Walters[1] and M. Tuten[1], [1]Mental Health, Johns Hopkins Bloomberg School of Public Health, and [2]Center for Addiction and Pregnancy, Johns Hopkins University, Baltimore, MD
Correspondence between changes in cigarette smoking and caffeine use among pregnant women
    R. Rogers, S.T. Higgins, S.H. Heil, C.S. Thomas and R.M. Vitale, University of Vermont, Burlington, VT
Maternal nicotine exposure and characteristics of adolescent smoking behaviors: Preliminary findings
    E.D. Thorner, M. Jaszyna-Gasior, C.C. Collins, M.K. Leff and E.T. Moolchan, NIDA, NIH, Baltimore, MD
Self-report of psychopathology in a sample of pregnant smokers and pregnant quitters
    T. Linares Scott, S.H. Heil and S.T. Higgins, Psychiatry, University of Vermont, Burlington, VT
The association between drug use and intimate partner violence among pregnant women: The importance of the recipient-perpetrator distinction
    G.K. Tzilos, S.J. Ondersma, J.R. Beatty and S. Chase, Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI
Prevalence and correlates of mood disorders among substance-dependent pregnant women in treatment
    T. Mendelson, S.G. Severtson, C.H. Salama and W.W. Latimer, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Screening for comorbid mood disorder among pregnant substance-dependent patients: Characteristics of the Addiction Severity Index and Beck Depression Inventory
    M. Chisolm, M. Tuten, H. Jones and E. Strain, Johns Hopkins University School of Medicine, Baltimore, MD
Drug use in pregnant women with mood disorders
    M.B. Kelly, K.L. Wisner and M.D. Cornelius, Psychiatry, University of Pittsburgh, Pittsburgh, PA
Prenatal marijuana exposure and PTSD among adolescents
    C. Larkby, L. Goldschmidt, M.D. Cornelius and N.L. Day, Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA
Maternal trauma exposure, PTSD, mental representations and caregiving behavior: Implications for the mother-toddler attachment system
    N. Schmitt, C. DeCoste and N. Suchman, Psychiatry, Yale University, New Haven, CT
Maternal representations, reflective functioning, and caregiving behavior: Implications for intervention development
    N. Suchman[1], C. DeCoste[1], N. Schmitt[1] and L. Mayes[2], [1]Psychiatry, Yale University School of Medicine, and [2]Yale Child Study Center, New Haven, CT

Gender differences in provider's screening for perinatal substance use

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COMORBIDITY II

College-aged cigarette smokers: Personality, mood, and substance use

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Mental health and substance abuse problems among homeless veterans seeking residential services

B. Sussner, D. Smelson, A. Kline, M. Losonczy and J. Kuhn, Mental Health and Behavioral Sciences, U.S. Department of Veterans Affairs, Lyons, NJ

Adult antisocial behavior in cocaine and cannabis dependence

J.J. Mariani, J. Horey, A. Bisaga, E. Nunes, E. Aharonovich, W. Raby and F.R. Levin, Division on Substance Abuse, Columbia University, New York State Psychiatric Institute, New York, NY

Social phobia and AOD dependence in the NESARC: Prevalence, onset, and comorbidity

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Rate of pathological gambling in methadone maintenance treatment patients–a cross-sectional study

E. Peles, S. Schreiber, A. Sason and M. Adelson, Adelson Clinic for Drug Abuse Treatment & Research, Tel Aviv Medical Center, Tel Aviv, Israel

Gender differences in the comorbidity of smoking behavior and major depression

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The prevalence of depression symptoms in a population attending a tobacco treatment program in Brazil

E.C. Moreira, Medicine, CETAD/UFBA, Salvador, Brazil

Integrated group therapy vs. group drug counseling for bipolar disorder and substance dependence: A replication study using front-line drug counselors

R.D. Weiss, M.L. Griffin, W.B. Jaffee, R.E. Bender and F.S. Graff, McLean Hospital/HMS, Belmont, MA

A brief treatment engagement intervention for individuals with a mental health and substance abuse problem

D.A. Smelson, A. Kline and D. Ziedonis, Psychiatry, VA-New Jersey/UMDNJ-RWJ Medical School, Lyons, NJ

Increasing treatment adherence in individuals with co-occurring disorders

M.V. Pantalon, M.E. Lavery, R.S. Schottenfeld and B.J. Rounsaville, Psychiatry, Yale University School of Medicine, New Haven, CT

Patterns of impulsivity in normal controls and pathological gamblers with and without a history of substance use disorder: Preliminary analysis

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Dually diagnosed patients in a psychiatric emergency service

G. Stahler, J. Mennis, D. Nemiroff, T. Manik-Perlman and R. Spiga, Temple University, Philadelphia, PA

Longitudinal predictors of substance abuse among a cohort of adults with severe mental illness enrolled in Maryland Medicaid

K. Dowling, P.K. Alexandre and D.M. Steinwachs, Johns Hopkins University, Baltimore, MD

TREATMENT AND TRAINING

Organizational structure and functioning as predictors of staff turnover and director change in outpatient substance abuse treatment

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Education, certification and licensure among counselors and supervisors within the clinical trials network

T. Rieckmann, B. Fuller, E. Edmundson and D. McCarty, Oregon Health & Science University, Portland, OR

Substance abuse counselors' self-reported training needs vary with certification type and years of experience in the field

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Substance abuse treatment workforce in the upper midwest

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Improving TC resident emotional competency using a targeted training program

W. Mandell and J. Dahl, Phoenix House Foundation, New York, NY

Patient commitment language improves during motivational interviewing with therapist supervision via tele-conferencing

P.C. Amrhein[1,2], J.L. Smith[1], K.M. Carpenter[1], A.C. Brooks[1], D. Levin[1], E.A. Schreiber[1], T. Blackmer[1], L.A. Travaglini[1] and E.V. Nunes[1], [1]Division on Substance Abuse, NY State Psychiatric Insti., New York, NY and [2]Psychology, Montclair State University, Montclair, NJ

Modeling longitudinal turnover in therapy groups with rolling admissions

A.A. Morgan-Lopez[1] and W. Fals-Stewart[2], [1]RTI, Research Triangle Park, NC and [2]University of Rochester, Rochester, NY

Initial findings from International Treatment Effectiveness Project

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

THEORETICAL/COMMENTARY

Teaching effectively online: New challenges and opportunities for addiction educators

W.L. Woods[1], N. Roget[1] and A.H. Skinstad[2], [1]University of Nevada, Reno, Reno, NV and [2]University of Iowa, Iowa City, IA

What if we really believed addiction was a chronic illness? A shift from an acute care to a sustained care recovery management model

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Listening for the voices of families: A qualitative process for systems change in Nebraska children's mental health and substance abuse system

K.J. Speck and A.H. Skinstad, Master of Arts in Counseling, Doane College, Lincoln, NE

Strange bedfellows? How use reduction and harm reduction can co-exist

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A framework for a population level analysis of substance-related harms on the basis of acuity and chronicity

D. Brown[1] and B. Rush[2], [1]BC Provincial Health Services Authority, Vancouver, BC and [2]Centre for Addiction and Mental Health, Toronto, ON, Canada

A systems approach to understanding the nonmedical use/abuse and diversion of opioid analgesics: Implications for risk management

J.P. Fitzgerald, M.Y. Smith and J.D. Haddox, Purdue Pharma L.P., Stamford, CT

Respondent-driven sampling: Comments on the process of coupon distribution for recruiting young noninjecting heroin users in Chicago

L. Ouellet[1], D. Broz[1] and E. Ward[2], [1]Epidemiology & Biostatistics, and [2]Health Policy Administration, University of Illinois at Chicago, Chicago, IL

A role for cognitive assessments as a predictor of clinical outcomes

B.N. Sullivan[2], G.W. Hanson[2], N.A. Roget[1] and W.L. Woods[1], [1]Mountain West ATTC, Univ of Nevada, Reno, NV and [2]Utah Addiction Center, University of Utah, Salt Lake City, UT

Choice implies cognitive-based individual differences in impulsivity and drug use

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Towards a consensus on terminology for psychoactive pharmaceutical products abuse

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Motivations for use of addictive substances: Interactions with psychopathology. Proposal for an integrated descriptive model

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Criteria for residual neuropsychological impairment from drug exposure: Commentary

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A comparison of NSDUH results and RADARS® System Poison Center Network results for the non-medical use of opioid analgesics 2003-2004

A.T. Kline[1], M.Y. Smith[1], J.P. Fitzgerald[1], J.D. Haddox[1] and J.E. Bailey[2], [1]Purdue Pharma LP, Stamford, CT and [2]Rocky Mountain Poison and Drug Center, Denver Health, Denver, CO

Human hallucinogen research: Guidelines for safety

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The impact of missing data on substance abuse clinical trials

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A model for dropout during screening phase for two cocaine clinical trials

R.J. Malcolm1, S.L. Hedden1,2 and P. Mardikian1, 1Psychiatry, and 2Biostatistics, Bioinformatics and Epidemiology, Medical University of South Carolina, Charleston, SC

LITERATURE REVIEWS

Epidemiology of drug abuse treatment in South Africa

M.N. Phaswana-Mafuya1, K.F. Peltzer1 and B. Johnson2, 1Social Aspects of HIV/AIDS and Health, Human Sciences Research Council, Port Elizabeth, South Africa and 2NDRI, NY, NY

Epidemiology of acohol and drug use in South Africa: A review

K. Peltzer1, N. Phaswana-Mafuya2 and B. Johnson3, 1HSRC, Pretoria, and 2HSRC, Port Elizabeth, South Africa and 3NDRI, New York, NY

Illicit drug markets in South Africa: A Review

B.D. Johnson1, G. Mohlala2, K. Peltzer2 and N. Phaswana-Mafuya2, 1Special Populations Research, National Development and Research Institutes, New York, NY and 2Human Sciences Research Council, Pretoria, South Africa

A review of behavioral counseling content for optimizing the use of buprenorphine for treating opioid dependence in U.S. drug-treatment CBOs

F. Altice2, M. Copenhaver1 and R. Bruce2, 1University of Connecticut, Storrs, and 2Yale AIDS Program, New Haven, CT

Cost-effectiveness of buprenorphine, methadone and levo-alpha-acetylmethadol for opioid dependence

E.O. Akerele1,2, B. Kaufman2, U. Lee2, A. Safron2, E.O. Okao1 and N.S. Nahar1, 1Psychiatry, Columbia University College of Physician and Surgeons, Harlem Hospital Center, and 2Public Health, Mailman School of Public Health/Columbia University, New York, NY

To what extent does gender identity, peer relationships, and parental relationships play a part in adolescent female substance use?

S. Renes, Olympic Educational Service District #114, Port Angeles, WA

Prescription drug abuse: Looking beyond the hyperbole

S.H. Schnoll, M.D. Ertischek, J.E. Henningfield, R.V. Fant and J.M. Rohay, Pinney Associates, Bethesda, MD

What do we know about substance abuse following disaster?

S.D. Noursi1 and C.S. North2, 1Division of Epidemiology, Services and Prevention Research, Bethesda, MD and 2Psychiatry, UT Southwestern Medical Center and VAMC, Dallas, TX

A qualitative review of serotonin syndrome, ecstasy (MDMA) and the use of other serotonergic substances: A clinically relevant hierarchy of risk

J. Copeland, E. Silins and P. Dillon, National Drug and Alcohol Research Centre Sydney, NSW, Australia

SYMPOSIUM VIII - WHERE THERE'S SMOKE THERE'S FIRE: UNDERSTANDING VULNERABILITY TO TOBACCO AND MARIJUANA USE IN SCHIZOPHRENIA
Chairs: Ivan D. Montoya and Frank Vocci

The endocannabinoid system in schizophrenia

Daniel Piomelli, Center for Drug Discovery, University of California, Irvine, CA

Nicotinic receptor dysregulation in schizophrenia

Sherry Leonard, University of Colorado at Denver and Health Sciences Center, Aurora, CO

Effects of nicotine and cannabis on cognitive and clinical outcomes in schizophrenia

Deepak Cyril D'Souza, Yale School of Medicine, VA Connecticut Healthcare, West Haven, CT

Towards the development of pharmacotherapies for nicotine and cannabis addiction in schizophrenia

Ivan D. Montoya, NIDA, Bethesda, MD

Discussant: Up in smoke: What do the co-morbidities of nicotine and cannabis misuse tell us about schizophrenia and addiction vulnerability?

Tony P. George, University of Toronto, Center for Addiction and Mental Health, Toronto, Ontario, Canada

SYMPOSIUM IX - PROGESTERONE EFFECTS ON STRESS AND COCAINE INTAKE: TRANSLATION FROM THE LABORATORY TO THE CLINIC
Chairs: Rajita Sinha and Nancy Mello

Progesterone inhibits the escalation and reinstatement (relapse) of cocaine-seeking behavior
    Marilyn Carroll, University of Minnesota, Minneapolis, MN
Altered progesterone levels, stress response, craving and relapse susceptibility in cocainedependent women
    Rajita Sinha, Yale University, Connecticut Mental Health Center, New Haven, CT
The modulatory role of oral micronized progesterone on the effects of smoked cocaine in humans
    Suzette M. Evans, Columbia University, New York, NY
Progesterone effects on cocaine responses and cocaine intake: Laboratory and clinical trial findings
    Mehmet Sofuoglu, Yale University, West Haven, CT
Discussant
    Nancy K. Mello, McLean Hospital, Alcohol and Drug Abuse Research Center, Belmont, MA

ORAL COMMUNICATIONS 14 - OPIOID NOVEL MECHANISMS: THINKING OUTSIDE THE BOX
Chairs: Mark Greenwald and Jason Rogers

Dopamine D1 receptor antagonism of the prefrontal cortex attenuates heroin-seeking in a reinstatement model in rats
    J. Rogers, S. Ghee, A. Carnell and R. See, Neurosciences, Medical University of South Carolina, Charleston, SC
Activation of muscarinic and nicotinic acetylcholine receptors in the nucleus accumbens core is necessary for the acquisition of drug reinforcement
    G. Zernig, J.A. Crespo, K. Sturm, P. Stöckl and A. Saria, Psychiatry, Medical University Innsbruck, Innsbruck, Austria
Identification of GABAA receptor subunit alpha 3 gene and confirmation of the μ *opioid receptor gene in determining genetic vulnerability to develop heroin addiction*
    D.A. Nielsen[1], F. Ji[2], V. Yuferov[1], A. Ho[1], A. Chen[2], O. Levran[1], J. Ott[2] and M.J. Kreek[1], [1]Laboratory of the Biology of Addictive Diseases, and [2]Laboratory of Statistical Genetics, The Rockefeller University, New York, NY
Baclofen blocks the development, expression and reinstatement of opiate conditioned place preference
    G.B. Kaplan[1,2], S.C. Heinrichs[1], K.A. Leite-Morris[2,1] and W. Fan[2,1], [1]Mental Health & Research Services, VA Boston Healthcare System, and [2]Psychiatry and Pharmacology, Boston University School of Medicine, Boston, MA
AMPA receptor surface expression in limbic brain regions following acute and repeated administration of morphine or methamphetamine
    A.L. Mickiewicz[1,2] and T.C. Napier[2], [1]Pharmacology, Loyola University Medical Center, Maywood, and [2]Pharmacology, Rush University Medical Center, Chicago, IL
ABCB1 genetic variants influence methadone dose requirement
    K. O'Hara[1], E. Peles[2], S. Barral[1], B. Ray[1], L. Borg[1], J. Ott[1], M. Adelson[2], M.J. Kreek[1] and O. Levran[1], [1]The Rockefeller University, New York, NY and [2]Adelson Clinic for Drug Abuse, Treatment & Research, Sourasky Medical Center, Tel Aviv, Israel
Effects of candidate anti-relapse medications on withdrawal-associated increases in opiate reinforcement
    S. Negus[1] and K.C. Rice[2], [1]Alcohol & Drug Abuse Research Center, McLean Hospital-Harvard Medical School, Belmont, MA and [2]Laboratory of Medicinal Chemistry, NIDDK/NIH, Bethesda, MD
Opioid-seeking behavior is related to recent cocaine use and serotonin transporter promoter(5HTTLPR) genetic polymorphism
    M. Greenwald[1] and M. Burmeister[2], [1]Wayne State University, Detroit, MI and [2]University of Michigan, Ann Arbor, MI

ORAL COMMUNICATIONS 15 - IMAGING: PICTURES AT AN EXCITATION/INHIBITION
Chairs: Anna Rose Childress and Marc Kaufman

BOLD fMRI studies of μ *&* κ *opioid agonists in awake macaques: Pharmacological specificity & dose-effect relationships*
    M.J. Kaufman[1], B.B. Frederick[1], M. Brimson[1], S.B. McWilliams[2], A. Bear[2], D. Meltzer[1], P.F. Renshaw[1] and S.S. Negus[2], [1]Brain Imaging Center, and [2]Alcohol & Drug Abuse Research Center, McLean Hospital, Belmont, MA

Neural activation differences in young adults with and without a family history of alcoholism during the Iowa Gambling Task
> A. Acheson1, J. Robinson1, P.T. Fox1, D.C. Glahn2 and W.R. Lovallo3, 1Research Imaging Center, and 2Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX and 3Behavioral Sciences Laboratories, VAMC, Oklahoma City, OK

Diffusion tensor imaging in MDMA users and controls: Association with Iowa Gambling Task Performance
> F. Moeller1, J.L. Steinberg1, K.M. Hasan2, S.D. Lane1, L.A. Kramer2, M. Buzby1, A.C. Swann1 and P.A. Narayana2, 1Psychiatry, and 2Diagnostic and Interventional Imaging, University of Texas Health Science Center at Houston, Houston, TX

BOLD fMRI of the effects of smoked tobacco and placebo tobacco
> K. Lindsey1, B.B. Frederick2, E.T. Ryan1, L.D. Nickerson2 and S.E. Lukas1, 1BPRL/Psychiatry, and 2Brain Imaging Center, McLean Hospital, Belmont, MA

[I-123]Iomazenil SPECT imaging of GABA-A-benzodiazepine receptor in smokers and nonsmokers
> I. Esterlis1, K. Cosgrove1, F. Bouis1, T. Kloczynski1, S. Stiklus1, E. Perry1, G. Tamagnan1,2, J. Seibyl1,2, S. Krishnan-Sarin1, S. O'Malley1, G. Mason1 and J. Staley1, 1Psychiatry, Yale University, West Haven, and 2Institute for Neurodegenerative Disorders, New Haven, CT

Treating inhalant abuse with gamma vinyl-GABA
> S.L. Dewey, D.E. Lee, A. Gifford and W.K. Schiffer, Brookhaven National Laboratory, Upton, NY

Brain substrates for cue-induced cocaine craving ("GO!") and its inhibition ("STOP!") as revealed by machine classifier learning
> A.R. Childress, Z. Wang, Y. Li, R. Ehrman, A.V. Hole, M.R. MacDougall, T. Franklin, D. Langleben, J. Detre and C.P. O'Brien, Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA

Neural mechanisms underlying drug-related attentional bias in active cocaine users
> R. Hester1 and H. Garavan2,3, 1University of Queensland, St Lucia, QLD, Australia 2Trinity College Dublin, Dublin, Ireland and 3Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, WI

SYMPOSIUM X - IMPROVING CORRECTIONAL AND RE-ENTRY RESOURCE USE AND PLANNING THROUGH SCREENING AND ASSESSMENT: FINDINGS FROM THE CJ-DATS COLLABORATIVE
Chair: Carl Leukefeld

Screening and assessment practices in correctional organizations: The impact on re-entry and comprehensive care services
> Faye Taxman, Virginia Commonwealth University, Richmond, VA

Examination of the Inmate Pre-Release Assessment (IPASS) as an Aftercare-Matching Tool
> David Farabee, Integrated Substance Abuse Programs, University of California, Los Angeles, Los Angeles, CA

Using treatment progress indicators to monitor client change
> Kevin Knight, Institute of Behavioral Research, Texas Christian University, Fort Worth, TX

Co-occurring Disorders Screening Instrument (CODSI) for mental disorders: A validation study
> Stanley Sacks, National Development and Research Institutes, Inc., New York, NY

Discussant: The state of the art of prison-based screening and assessment
> Carl Leukefeld, Center on Drug and Alcohol Research, University of Kentucky, Lexington, KY

SYMPOSIUM XI - NEWLY ENGINEERED ANTIBODY AND ENZYME THERAPIES FOR TREATING DRUG ABUSE
Chairs: Michael Owens and C. Nora Chiang

Rational design of high-activity mutants of human butyrylcholinesterase for use as an anticocaine medication
> Chang-Guo Zhan, College of Pharmacy, University of Kentucky, Lexington, KY

Cocaine esterase: A novel enzyme therapy for cocaine abuse
> James Woods, University of Michigan Medical School, Ann Arbor, MI

Humanized anti-cocaine monoclonal antibody as a potential immunotherapy for cocaine abuse
> Andrew B. Norman and William J. Ball, University of Cincinnati, College of Medicine, Cincinnati, OH

Making effective and safe antibody medications for treating phencyclidine and methamphetamine addiction
> Michael Owens, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR

Discussant: Generating safe and effective protein medications for the treatment of stimulant abuse
> Paul Pentel, Hennipen County Medical Center, Minneapolis, MN

ORAL COMMUNICATIONS 16 - GENETICS: CRACKING THE CODE
Chairs: Christian Schutz and Laurie Zawertailo

Association between polymorphisms of the dopamine D2 receptor and "COMT" genes and reward dependence in subjects with excessive Internet video game play
> D. Han1, Y. Lee2, K. Yang1, E. Kim2, I. Lyoo3 and P.F. Renshaw1, 1Brain Imaging Center, Mclean Hospital, Harvard Medical School, Belmont, MA 2Chung-Ang University Medical School, and 3Seoul National University College of Medicine, Seoul, South Korea

Co-morbidity of Attention-Deficit Hyperactivity Disorder with substance use disorder: A genetic analysis
> L.A. Zawertailo1, A. Otting3, J.L. Kennedy2,4 and U.E. Busto1,3, 1Clinical Neuroscience, and 2Neurogenetics, Centre for Addiction and Mental Health, 3Faculty of Pharmaceutical Sciences, and 4Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Beta-arrestins 1 and 2 are associated with nicotine dependence in European-American smokers
> M.D. Li1, D. Sun1, J.Z. Ma2 and T.J. Payne3, 1Psychiatry and Neurobehavioral Sci., and 2Dept. of Public Health Sci., Univ. of Virginia, Charlottesville, VA and 3ACT Center for Tobacco Treatment, Education and Research, Univ. of Mississippi Medical Center, Jackson, MS

The methylenetetrahydrofolate reductase polymorphisms c.677C>T and c.1298A>C influence smoking behavior
> C.G. Schütz1, M. Moskau2, A. Semmler2, H. Köllgen1, T. Klockgether2, W. Maier1, U. Wüllner2 and M. Linnebank2, 1Psychiatry, and 2Neurology, Friedrich-Wilhelms-University, Bonn, Germany

Comorbidity between bipolar disorder and alcohol abuse disorder: A genetic analysis
> B. Yasseen3,1, L.A. Zawertailo1, J.L. Kennedy2,4 and U.E. Busto1,3, 1Clinical Neuroscience, and 2Neurogenetics Research, Centre for Addiction and Mental Health, 3Pharmacology, and 4Psychiatry, University of Toronto, Toronto, ON, Canada

ABCB1 genetic variability and opiate dependence in Caucasians
> O. Levran1, S. Barral1, E. Halperin2, K. O'Hara1, D. Li, J. Ott1 J. Rotrosen, P. Casadonte, S. Linzy, M. Adelson and M.J. Kreek1, 1The Rockefeller University, New York, NY and 2ISCI, Berkeley, CA

Severity of cocaine dependence, craving and early abstinence among allele carriers of DA β hydroxylase polymorphism at 1ST week of treatment with methadone treated patients
> G. Gonzalez1, M. Randall1,2, R. Desai1,2, J. Lappaleinen3 and I. Petrakis1,2, 1Yale University, New Haven and 2VA CT Healthcare System, West Haven, CT, and 3AstraZeneca, Wilmington, DE

Gene expression in human hippocampus from cocaine abusers identifies genes that regulate extracellular matrix remodeling
> D.C. Mash1, J. ffrench-Mullen2, A. Buck1, Y. Qin1 and J. Pablo1, 1Neurology, Miller School of Medicine, Miami, FL and 2Genelogic, Inc, Gaithersburg, MD

ORAL COMMUNICATIONS 17 - HEPATITIS C VIRUS RISK
Chairs: Nina Ebner and Steven Batki

Hepatitis C treatment outcomes in methadone maintenance patients: Preliminary analysis of an on-site treatment trial
> S.L. Batki, K. Canfield, C. Cole, E. Smyth, R. Ploutz-Snyder, R. Levine, K. Amodio, G. Knoeller, K. Strutynski, K. Manser and J.A. Dimmock, SUNY Upstate Medical University, Syracuse, NY

Rate of hepatitis C treatment in opioid-dependent patients is improved by integrating hepatitis treatment and methadone maintenance
> K.A. Harris1,2, J.H. Arnsten2,1 and A.H. Litwin2,1, 1Division of Substance Abuse, Psychiatry & Behavioral Sciences, Albert Einstein College of Medicine, and 2Division of General Internal Medicine, Montefiore Medical Center, Bronx, NY

Outcome of hepatitis C treatment in opioid-dependent, maintained patients
> N. Ebner, C. Aeschbach Jachmann, B. Winklbaur, A. Baewert, K. Thau and G. Fischer, Psychiatry, Medical University Vienna, Vienna, Austria

Former intravenous-drug abusers cured of HCV disease: Are they more vulnerable to reinfection?
> l. Gourarier2, A. Gauchet3 and P. Melin1, 1Internal Medicine, General Hospital, Saint Dizier, 2La Terrasse, Hospital Maison Blanche, Paris, and 3Psychology, University, Grenoble, France

Patterns of opiate use and relation to HIV/HCV in central Ukraine
> K. Dumchev1, O. Zezyulin1, J. Schumacher2, R. Soldyshev3, L. Moroz3 and P. Slobodyanyuk1, 1Vinnitsya Regional Narcological Dispensary, Vinnitsya, Ukraine, 2University of Alabama, Birmingham, AL and 3Vinnitsya Pirogov National Medical University, Vinnitsya, Ukraine

Receptive needle sharing by HCV-negative young IDU depends on relationship factors but not partner HCV status
J. Hahn, J. Evans, P. Davidson, P. Lum and K. Page-Shafer, Medicine, University of California, San Francisco, San Francisco, CA

Hepatitis B and hepatitis C virus services offered by substance abuse treatment programs in the USA
E.J. Bini1, S.A. Kritz2, L.S. Brown2, J. Robinson3, D. Alderson4, P. McAuliffe5, C. Smith6 J. Rotrosen7, 1VA NY Harbor Hlthcare Sys., NYU Sch. Med., NY, 2ARTC, Brooklyn, 3Nathan Kline Inst., Orangeburg, 4NYS, NY Presby. Hosp., NY, 6Med., Mt. Sinai Sch. Med., VA NY Harbor Hlthcare Syst. & NYU Sch. Med., NY, NY, and 5CT Renaissance, Inc., Norwalk, CT

Health care utilization among homeless adults who test positive for hepatitis C
L. Gelberg1, M. Robertson2, L. Arangua1, R.M. Andersen3 and B.D. Leake1, 1David Geffen School of Medicine at UCLA, Los Angeles, 2Public Health Institute, Berkeley, and 3UCLA
School of Public Health, Los Angeles, CA

ORAL COMMUNICATIONS 18 - PRESCRIPTION OPIATE ABUSE: DEVIATING FROM THE SCRIPT
Chairs: Sharon Walsh and Stephen Butler

Relative abuse potential of oral oxycodone, hydrocodone and hydromorphone in non-dependent prescription opioid abusers
S.L. Walsh1,2, P.A. Nuzzo1, M.R. Lofwall2 and J.R. Holtman3, 1Behavioral Science, 2Psychiatry, and 3Anesthesiology, University of Kentucky, Lexington, KY

Description of buprenorphine, methadone, hydrocodone and oxycodone abuse and diversion rates using RADARS® System data
E. Bailey1, L. Cram1 and R. Dart1,2, 1Rocky Mountain Poison and Drug Center, Denver, CO and 2University of Colorado Health Sciences Center, Denver, CO

Effect of tablet mechanical stability on drug preference and relative street value of oxycodone controlled-release (CR) tablets in experienced oxycodone CR abusers
J.B. Ashworth1,2, W.J. Kowalczyk1, S.L. Stephens1, M.A. Sullivan1 and S.D. Comer1, 1NYSPI, Columbia University, New York, NY and 2Grunenthal USA, Inc., Bedminster, NJ

Reinforcing effects of oral oxycodone and morphine: Comparison of drug vs. money and drug vs. drug choice procedures
W.J. Kowalczyk, M.A. Sullivan, S.K. Vosburg and S. Comer, Psychiatry, Columbia University, New York, NY

Risk factors for 30-day and 1-year adult prescription misuse: Effect of gender
T.S. Schepis and S. Krishnan-Sarin, Psychiatry, Yale University, New Haven, CT

Prescription-opioid abuse among patients enrolling in methadone maintenance treatment
A. Rosenblum1, M. Parrino2, S.H. Schnoll4, C. Fong1, C. Maxwell2, C.M. Cleland1, J.D. Haddox3 and S. Magura1, 1NDRI, Inc., and 2American Assoc. for the Treatment of Opioid Dependence NY, NY, and 3Purdue Pharma LP, Stamford, CT and 4Pinney Association, Inc, Bethesda, MD

Relationship between rate of infusion and reinforcing strength of oxycodone in humans
S. Comer1, J.B. Ashworth1,2, M.A. Sullivan1, S.K. Vosburg1, P.A. Saccone1 and R.W. Foltin1, 1Psychiatry, Columbia University, New York, NY and 2Grunenthal USA, Inc., Bedminster, NJ

Integrating quantitative and qualitative data sources for surveillance of product-specific opioid abuse in real-time: The NAVIPPRO System
S.F. Butler1, J.A. Brevard1, J.R. Dickinson1, A. Licari1, S.H. Budman1 and N.P. Katz1,2, 1Inflexxion, Inc, Newton, MA and 2Tufts University School of Medicine, Boston, MA

ORAL COMMUNICATIONS 19 - PSYCHOMETRICS: MEASURE FOR MEASURE
Chairs: Edward Sellers and Kevin Delucchi

Next-day measures may not be reliable for the assessment of subjective effects of alprazolam in recreational users
M. Grigorova1, K. Schoedel1, B. Boris1, D. Thomas2 and E.M. Sellers1, 1Ventana Clinical Research Corporation, Toronto, ON, Canada and 2Schwarz Pharma, Monheim, Germany

Psychometric testing of a self-administered, computerized substance abuse screening instrument for youth
S. Libretto1, Y.H. Wong1, J. Sexton1, S. Nemes2, W.K. Lam3 and C. Williams3, 1Danya International, Silver Spring, and 2Social Solutions International, Olney, MD and 3Research Triangle Institute International, Research Triangle Park, NC

Scale development of smoking cessation knowledge, attitudes and practices
K.L. Delucchi, B. Tajima and J. Guydish, Psychiatry, University of California, San Francisco, San Francisco, CA

Preliminary validity and reliability measures of a new instrument for measuring life history assessment among drug users
    V. Cantillano1, D. Best2 and F. Keaney3,4, 1Pontificia Universidad Católica de Chile, Santiago, Chile, 2King's College, 3Maudsley Hosp., South London & Maudsley NHS Trust, and 4Community Drug and Alcohol Teams for Greenwich District, London, UK

SYMPOSIUM XII - PHENOTYPING RISK-TAKING: QUANTIFYING ADOLESCENT BEHAVIORAL DISINHIBITION FOR GENETIC AND IMAGING STUDIES OF DRUG DEPENDENCE
Chair: Thomas J. Crowley

Phenotyping adolescents' risky and conduct-disordered behaviors
    Thomas J. Crowley, University of Colorado School of Medicine, Denver, CO
Multisystem measures of adolescent risk-taking: What do personality, cognition, and imaging tell us?
    Sandra Brown, University of California, San Diego, La Jolla, CA
In-vivo behavioral assessments of personality and environment for understanding adolescent risk behavior
    Carl Lejuez, University of Maryland, College Park, MD

ORAL COMMUNICATIONS 20 - PHARMACOKINETICS: DATA THAT'S ON THE LEVEL
Chairs: Rinah Yamamoto and Andrew Norman

Flutamide pretreatment alters cocaine pharmacokinetics in men
    R. Yamamoto1,2, C.J. Teter3, T.L. Barros1, T. Juliano2, A. Looby2, M. Maywalt2, J.F. McNeil2, D. Olson1, G. Mallya2, S.E. Lukas2, P.F. Renshaw1 M.J. Kaufman1, 1Brain Imaging Center, and 2Behavioral Psychopharmacology Research Laboratory, and 3Alcohol & Drug Abuse Treatment Program, McLean Hospital, Belmont, MA
A chimeric human anti-cocaine monoclonal antibody antagonizes the cocaine-induced priming of self-administration in rats
    A.B. Norman, M.K. Norman, W.R. Buesing, M.R. Tabet, V.L. Tsibulsky, and W.J. Ball, University of Cincinnati, Cincinnati, OH
Pharmacokinetic and postnatal effects following acute methamphetamine administration in female rats during late-stage pregnancy
    S.J. White1, H.P. Hendrickson2 and S.M. Owens1, 1Pharmacology and Toxicology, and 2Pharmaceutical Sciences, University of Arkansas for Medical Sciences, Little Rock, AR
Methamphetamine and modafinil interactions: Cardiovascular, subjective reports and pharmacokinetics
    R.T. Jones1, E.G. Fernandez1, J.E. Mendelson2, A. Manari1 and N. Chiang3, 1UCSF, San Francisco, CA 2CPMC, San Francisco, CA and 3NIDA, Bethesda, MD

SYMPOSIUM XIII - INITIATING OPIOID AGONIST THERAPY IN U.S. JAILS AND PRISONS: FEASIBILITY AND EVIDENCE FROM THREE ONGOING STUDIES
Chairs: Josiah D. Rich and Robert Schwartz

Pre- and post-release opiate agonist therapy
    Josiah D. Rich, The Miriam Hospital/Brown Medical School, Providence, RI
A randomized clinical trial of methadone treatment in pre-release prison
    Timothy Kinlock, Friends Research Institute, Baltimore, MD
Buprenorphine treatment for pre-release prisoners in San Juan
    Carmen Albizu-Garcia, University of Puerto Rico, San Juan, PR

SYMPOSIUM XIV - CAFFEINE AS A GATEWAY TO ADDICTION?
Chair: Roland R. Griffiths

Links from coffea to Erythroxylum coca: A different gateway?
    James C. Anthony, Michigan State University, College of Human Medicine, East Lansing, MI
Adenosine receptor heteromers: New targets for caffeine in the brain
    Sergi Ferré, NIDA/NIH, Intramural Research Program, Baltimore, MD
Adopting DSM-IV dependence criteria for caffeine: DSM-V implications
    Catherine Striley and Linda B. Cottler, Washington University School of Medicine, St. Louis, MO

Late-Breaking Research News
Chair: Scott E. Lukas

Thursday, June 21, 2007

POSTER SESSION IV - OPIOIDS: ANIMAL STUDIES

Gender differences in MOP-r mRNA levels in Long-Evans rats 1

C.E. Smith1, S.D. Schlussman1, D. White2, C. Michaels2, K. Easterling2, A. Ho1, S.G. Holtzman2 and M.J. Kreek1, 1Laboratory of the Biology of Addictive Diseases, Rockefeller University, New York, NY and 2Emory University, Atlanta, GA

μ-*Opioid and chemokine receptor colocalization in the rat brain* 2

L. Kirby and S. Heinisch, Anatomy and Cell Biology and Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA

Naltrexone reverses JDTic blockade of human kappa opioid receptors expressed in CHO cells

H. Navarro, K. Warner and F.I. Carroll, Center for Organic and Medicinal Chemistry,
Research Triangle Institute International, Research Triangle Park, NC

Evidence for an important role of protein phosphatases in morphine tolerance

F.L. Smith1, B.H. Gabra1, A.V. Sanders1, C.P. Bailey2, G. Henderson2 and W.L. Dewey1, 1Pharmacology & Toxicology, Virginia Commonwealth University, Richmond, VA and 2Pharmacology, University of Bristol, Bristol, United Kingdom

Evaluation of acute opioid dependence in three rat strains

R.W. Morgan, R.L. Balster and K.L. Nicholson, Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA

The blocking mechanisms of Leu-Ile against methamphetamine and morphine dependence in mice

A. Nitta1, X. Cen1, M. Niwa1, Y. Yamada1, A. Nakajima1, T. Nabeshima1, K. Saito2, M. Seshima2, M. Suzuki2, L. Shen4, S. Furukawa3 T. Nabeshima1, 1Nagoya U. Grad. Sch. Med., Nagoya, 2Gifu U. Grad. Sch. Med. and 3Gifu Pharm. U., Gifu, Japan, and 4NCI, Bethesda, MD

Effects of buprenorphine on fentanyl withdrawal in rats

C. Marcinkiewcz, S. Isaac, M.S. Gold and A.W. Bruijnzeel, Psychiatry, University of Florida, Gainesville, FL

Tumor necrosis factor- α and its inducer inhibit drug-induced dependence

T. Nabeshima1, M. Niwa1, Y. Yamada1, K. Saito2, M. Seishita2, Y. Noda3 and A. Nitta1, 1Nagoya University, Nagoya, Japan. 2Gifu University Graduate School of Medicine, Gifu, Japan and 3Meijo University, Nagoya, Japan

Role of CREB in morphine-dependent conditioned behavior

J. Moron Concepcion1, S. Gullapali2, L. Devi2 and T. Shippenberg3, 1Center for Addiction Research, UTMB, Galveston, TX, 2Pharmacology, Mount Sinai, New York, NY and 3Integrative Neuroscience, NIDA, Baltimore, MD

Retention of drug stimulus control in pigeons trained to a three-key morphine discrimination

M. Evola1, J.D. McCorvy3 and A.M. Young1,2, 1Pharmacology and Neuroscience, Texas Tech University Health Sciences Center, and 2Psychology, Texas Tech University, Lubbock, TX and 3Medicinal Chemistry and Molecular Pharmacology, Purdue, West Lafayette, IN

Effects of naltrexone and opioid agonists on responding maintained by different reinforcers in untreated and morphine-treated squirrel monkeys

C.A. Paronis, J. Bergman and J. Connolly, McLean Hospital, Harvard Medical School, Belmont, MA

Effects of morphine dependence on the reinforcing properties of remifentanil, cocaine, and food in rats

Z.D. Cooper1, Y.G. Shi2 and J.H. Woods1,2, 1Psychology, University of Michigan, Ann Arbor, MI and 2Pharmacology, University of Michigan, Ann Arbor, MI

Strain differences in (-)-U50-488H-induced conditioned taste aversions

C.M. Davis1, K.C. Rice2 and A.L. Riley1, 1Psychology Department, American University, Washington, DC and 2Laboratory of Medicinal Chemistry, NIDDK, Bethesda, MD

Temporal determinants of in vivo affinity estimates for naltrexone in rhesus monkeys

L.R. Gerak and C.P. France, Pharmacology, University of Texas Health Science Center, San Antonio, TX

Effects of pre-exposure to morphine on later morphine-induced locomotor activity and conditioned place preference in adult C57BL/6J mice

Y. Zhang, E.R. Butelman, A. Ho and M.J. Kreek, The Laboratory of the Biology of the Addictive Diseases, The Rockefeller University, New York, NY

Does the heroin metabolite morphine-3-glucuronide play a role in the development of heroin addiction?
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NICOTINE: ANIMAL STUDIES

Involvement of the opioidergic system in nicotine-induced antinociception, but not corticosterone, increases in mice
S. Kishioka, T. Maeda, N. Kiguchi, A. Yamamoto and C. Yamamoto, Pharmacology, Wakayama Medical University, Wakayama, Japan

Nicotine-associated environmental stimuli increases brain reward function in rats
M. Itasaka1,2, H. Miyata3, N. Hironaka1 and K. akayama3, 1Japan Science and Technology Agency, Atsugi-shi, 2Graduate School of Senshu University, Kawasaki-shi, and 3Jikei University School of Medicine, Minato-ku, Japan

Effects of repeated nicotine administration on responding for electrical brain stimulation under a progressive-ratio schedule in rats
A.C. Harris1,2, P.R. Pentel1,2 and M.G. LeSage1,2, 1Minneapolis Medical Research Foundation,Minneapolis, MN and 2Department of Medicine, University of Minnesota, Minneapolis, MN

Nicotine and cocaine self-administration using a multiple schedule of intravenous drug and sucrose reinforcement in rats
D.J. Stairs, N.M. Neugebauer and M.T. Bardo, Psychology, University of Kentucky, Lexington, KY

Tissue plasminogen activator-plasmin-protease activated receptor 1 system regulates rewarding effect of nicotine
T. Nagai1,2, M. Ito2, N. Nakamichi2, H. Kamei2, A. Fukakusa2, T. Nabeshima1, K. Takuma2 and K. Yamada2, 1Neuropsychopharmacology and Hospital Pharmacy, Nagoya Graduate School of Medicine, Nagoya, and 2Kanazawa University, Kanazawa, Japan

Effects of novel tris-quaternary ammonium nicotinic antagonists on locomotor activity and nicotine-induced hyperlocomotion in rats
J.T. Ross1, Z. Zhang2, P.A. Crooks2, L.P. Dwoskin2 and M.T. Bardo1, 1Psychology, University of Kentucky, Lexington, KY and 2College of Pharmacy, University of Kentucky, Lexington, KY

Nicotine-conditioned hyperactivity in D2-primed adolescent rats
L. Amine, A.B. Sheppard and R.W. Brown, Psychology, East Tennessee State University, Johnson City, TN

Discriminative stimulus effects of monoamine oxidase inhibitors in nicotine-trained rats
T. Wooters and M. Bardo, Psychology, University of Kentucky, Lexington, KY

STIMULANTS: ANIMAL STUDIES

Withdrawal from repeated cocaine up-regulates PI3K activity in the PFC: Link to Homer proteins
A.W. Ary1,2 and K.K. Szumlinski1,2, 1Psychology, and 2Neuroscience Research Institute, University of California, Santa Barbara, Santa Barbara, CA

Changes in Arc mRNA expression in rats engaged in cue-elicited cocaine-seeking behavior
A.R. Zavala1, T. Osredkar2, J.N. Joyce2 and J.L. Neisewander1, 1Psychology, Arizona State University, Tempe, AZ and 2T.H. Christopher Center for Parkinson's Disease, Sun Health Research Institute, Sun City, AZ

Effects of withdrawal from escalating-dose 'binge' cocaine on mRNA levels of dynorphin and orexin genes in rat amygdala and lateral hypothalamus
Y. Zhou, M. Randesi, M. Johncilla, A. Ho and M. Kreek, Laboratory on the Biology of Addictive Diseases, The Rockefeller University, New York, NY

Protein expression and subcellular localization of the serotonin (5-HT) 2C receptor (5-HT2CR) and its binding partners after repeated intermittent cocaine administration
M.F. Lanfranco, P.K. Seitz and K.A. Cunningham, Center for Addiction Research, University of Texas Medical Branch, Galveston, TX

Environmental enrichment produces a consistent behavioral phenotype indicative of decreased cAMP response element transcriptional activity in the nucleus accumbens
T.A. Green1, M.T. Bardo2 and E.J. Nestler1, 1Psychiatry, UT Southwestern, Dallas, TX and 2Psychology, University of Kentucky, Lexington, KY

Mu opioid receptors in the nucleus accumbens but not the ventral tegmental area are necessary for cocaine-induced conditioned reinforcement
A.R. Soderman1,2 and E.M. Unterwald1,2, 1Pharmacology, and 2Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA

Hippocampal tyrosine kinase B receptors and amphetamine-induced associative learning
> F. Shen1,3, G.E. Meredith2 and T.C. Napier3, 1Loyola University Medical Center, Maywood, IL, 2Chicago Medical School, North Chicago, IL and 3Rush University Medical Center, Chicago, IL

Implication of ã-aminobutylic acid transporter subtype-3 (GAT-3) in the development of sensitization to morphine-, methamphetamine- and cocaine-induced hyperlocomotion
> T. Suzuki, K. Kurokawa, S. Hirayama, M. Suzuki and M. Narita, Department of Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences, Tokyo, Japan

Methylphenidate administration alters vesicular monoamine transporter-2 function in cytoplasmic and membrane-associated vesicles
> T.J. Volz, G.R. Hanson and A. Fleckenstein, Pharmacology and Toxicology, University of Utah, Salt Lake City, UT

Blockade of dopamine D3 receptors by SB-277011A inhibits incubation of craving for cocaine in rat
> Z. Xi1, X. Li1, J. Gilbert1, X. Peng1, C. Ashby, Jr.2, C. Heidbreder3 and E. Gardner1, 1NIDA, Baltimore, MD, 2Saint John's University, New York, NY and 3GlaxoSmithKline Pharmaceuticals, Verona, Italy

Serotonergic modulation of cocaine priming-induced reinstatement: Focus on 5-HT2C receptor mechanisms
> D. Ruedi-Bettschen, K. Bano, R.D. Spealman and D.M. Platt, Behavioral Biology, Harvard Medical School/NEPRC, Southborough, MA

Differential effects of ó1 receptor blockade on self-administration and conditioned reinstatement motivated by cocaine vs. natural reward
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Neuroadaptations caused by active self-administration of methamphetamine: Upregulation of sigma-1 receptors in locus ceruleus
> T. Hayashi1, Z. Justinova2, G. Cormaci1, S.R. Goldberg2 and T.P. Su1, 1Cellular Pathobiology Unit/DPS/CNRB, and 2Preclinical Pharmacology Section, Intramural Research Program, NIDA-NIH, Baltimore, MD

Dendritic arborization and anchorings of NMDA and AMPA receptors in primary hippocampal neurons are controlled by sigma-1 receptors at ER
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Dopamine via reactive oxygen species upregulates sigma-1 receptors in a biological system: Implication for cellular survival and neuroplasticity
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Acute methamphetamine exposure reduces NMDA-induced neurotoxicity
> K.J. Smith, R.L. Self, M.T. Bardo and M.A. Prendergast, Psychology, University of Kentucky, Lexington, KY

Methamphetamine induces dopaminergic neurotoxicity via cross-talk between neurodegenerative process and inflammatory stress pathway
> D. Ikegami, M. Narita, K. Kurokawa, M. Asato, K. Niikura, K. Miyoshi, K. Miyagawa, K. Nanjo, Y. Nagumo, M. Takatsu, S. Enomoto, M. Suzuki and T. Suzuki, Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences, Tokyo, Japan

Methamphetamine vaccine in rodents
> F. Orson1,2, C.N. Haile1,2, B. Kinsey1,2, T.A. Kosten1,2, R. Rossen1,2, R. Baughn1,2 and T.R. Kosten1,2, 1Baylor College of Medicine, Houston, TX and 2Michael E. DeBakey VA Medical Center, Houston, TX

Effects of cocaine esterase following its repeated administration with cocaine in mice
> M.C. Ko1, J.E. Pascoe1, D. Narasimhan1, N.W. Lukacs2, R.K. Sunahara1 and J.H. Woods1, 1Pharmacology, and 2Pathology, University of Michigan, Ann Arbor, MI

Human cocaine hydrolase as treatment for cocaine overdose and abuse
> S. Brimijoin1, Y. Gao1 and M.E. Carroll2, 1Molecular Pharmacology, Mayo Clinic, Rochester, MN and 2Psychiatry, University of Minnesota, Minneapolis, MN

MARIJUANA: HUMAN STUDIES

Elevated ratings of craving at baseline predict a robust response to smoked placebo marijuana
> L.D. Nickerson1,2, K.P. Lindsey1,2, E.T. Ryan1 and S.E. Lukas1,2, 1BIC/BPRL, McLean Hospital, Belmont, MA and 2Psychiatry, Harvard Medical School, Boston, MA

Marijuana drug and expectancy effects on subjective and behavioral measures
> J. Metrik1, P.M. Monti1,2, D.J. Rohsenow1,2, C.W. Kahler1 and J. McGeary1,2, 1Center for Alcohol and Addiction Studies, Brown University, and 2Veterans Affairs Medical Center, Providence, RI

Atomoxetine for treatment of marijuana dependence: Limited efficacy and high incidence of GI adverse events in a pilot study

C.F. Tirado1, M. Goldman2, K. Kampman2 and C. O'Brien2, 1Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX and 2University of Pennsylvania, Philadelphia, PA

Utility of a contingency management strategy to improve retention in a pharmacologic treatment trial targeting cannabis dependence

F.R. Levin1,2, J. Mariani1,2, M. Chicurel1, S.M. Evans1 and D.J. Brooks1, 1Substance Abuse, NYSPI, and 2Psychiatry, Columbia University, New York, NY

Methylphenidate-SODAS improves Attention-Deficit Hyperactivity Disorder symptoms in adolescents with illicit substance use disorder: A randomized crossover clinical trial

C.M. Szobot1,2, B. Katz1, T. Schaefer1,2, P. Ruaro1,2, M. Walcher1,2, F. Pechansky1 and L. Rohde1, 1Federal University of Rio Grande do Sul, and 2Universidade Luterana do Brasil, Porto Alegre, Brazil

Methylphenidate-SODAS reduces DAT binding in adolescents with ADHD plus substance use disorder: A Single Photon Emission Computed Tomography with [Tc99m]TRODAT-1 study

L. Rohde1, M. Shih2, T. Schaefer1,3, M. Hoexter2, E. Estrela3, Y. Fu5, F. Pechansky1, R. Bressan2 and C. Szobot1,3, 1Fed. U. Rio Grande do Sul, Porto Alegre, 2U. Fed. de São Paulo, 3Sta Casa de Misericórdia, Porto Alegre, 4ULBRA, Canoas, Brazil and 5INER, Taiwan, China

Prefrontal cortex morphometry in abstinent adolescent marijuana users: Subtle gender effects

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Laboratory measures of impulsivity in adolescent marijuana users

E.E. Shannon1, C.R. Duncan1, C.W. Mathias1, D.M. Marsh1, A. Liguori2 and D.M. Dougherty1, 1Psychiatry and Behavioral Medicine, and 2Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC

Relation between neurobehavior disinhibition and substance use during adolescence in males and females

L. Kirisci, R. Tarter, S.B. Aytaclar and M. Vanyukov, Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA

Trajectories of drug use and contextual factors among minority youth

Y.F. Thomas1, M.F. Lopez1, Z. Tang2 and R. Orwin2, 1NIDA/NIH, Bethesda, MD and 2WESTAT, Rockville, MD

Impact of adolescents' perceived need for therapeutic assistance within the family on outcomes for adolescents in substance use treatment

G.D. Jones, 1Heritage Foundation Inc., Thomasville, GA and 2Harold Abel School of Psychology, Capella University, Minneapolis, MN

Heterogenity of treatment effects for adolescent SUDSs: A randomized clinical trial

H. Hops, H.B. Waldron, J.L. Brody, C.W. Turner and T.J. Ozechowski, Oregon Research Institute, Eugene, OR

Profile of adolescent cannabis consumers in the Autonomous Region of Valencia, Spain

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Marriage and illicit drug use

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Who's starting to smoke cannabis in the early 21st century? An international perspective F.A. Fiestas1,2, C.F. Rios-Bedoya1 and J.C. Anthony1, 1Epidemiology, Michigan State University, East Lansing, MI and 2Laboratorios de Investigacion y Desarrollo, Universidad Peruana Cayetano Heredia, Lima, Peru

Geographic clusters of recent cannabis use in New Zealand

K.M. Bohnert1, J.E. Wells2, L. Degenhardt3 and J.C. Anthony1, 1Epidemiology, Michigan State University, East Lansing, MI. 2University of Otago, Christchurch, New Zealand and 3University of New South Wales, Sydney, NSW, Australia

Modeling population heterogeneity via GLMM and GEE. Analyses of cannabis involvement among Hispanics in the U.S

S. Zhu1,2, P.L. Chapman2, D.C. Browne1 and F.A. Wagner1, 1DARP/CHDS/ DPHA, Morgan State University, Baltimore, MD and 2Department of Statistics, Colorado State University, Fort Collins, CO

Has onset of cannabis use shifted to younger ages? Results from the Epidemiological Survey on Substance Abuse in Germany

R. Augustin, L. Kraus and G. Bühringer, IFT Institut für Therapieforschung, Munich, Germany

The effects of counter advertising on the uses of alcohol and drugs among Hispanic adolescents

 D. Lee, Health Care Administration and Public Health, Cleveland State University, Cleveland, OH

Chronic marijuana abuse is associated with low blood pressure and low cholesterol levels

 W. Better, R.I. Herning and J.L. Cadet, Molecular Neuropsychiatry, NIDA/IRP, Baltimore, MD

Cognitive performance in HIV+ and HIV- marijuana smokers

 S.L. Collins1,2, R.W. Foltin1,2 and M. Haney1,2, 1Psychiatry, Columbia University College of Physicians & Surgeons, and 2New York State Psychiatric Institute, New York, NY

Dronabinol and marijuana in HIV+ marijuana smokers: Caloric intake, mood and sleep

 M. Haney1, E.W. Gunderson1, J. Rabkin1, C.L. Hart1,2, S.K. Vosburg1, S.D. Comer1 and R.W. Foltin1, 1Psychiatry, and 2Psychology, Columbia University, New York, NY

Development of a model-based self-report measure of marijuana's subjects effects: A preliminary Web-based study

 J. Hopper1, A.J. Tracy2 and S.E. Lukas1, 1Behavioral Psychopharmacology Research Lab, McLean Hospital/Harvard Medical School, Belmont, MA and 2Wellesley Centers for Women, Wellesley, MA

Cannabis dependence and early cannabis use are associated with reduced educational attainment in young adults from two offspring-of-twins studies

 J.D. Grant1, A.C. Heath1, J.F. Scherrer1,2, A.E. Duncan1, M.T. Lynskey1, J.R. Haber3, T. Jacob3 and K.K. Bucholz1, 1Psychiatry, Washington University School of Medicine, and 2St. Louis VAMC, St. Louis, MO and 3Palo Alto VAHCS, Menlo Park, CA

A twin study of the associations between cannabis and alcohol use/symptomatology

 M. Lynskey1, J.D. Grant1, K.K. Bucholz1, P.A. Madden1, A.C. Heath1 and N.G. Martin2, 1Psychiatry, Washington University School of Medicine, St. Louis, MO and 2Queensland Institute of Medical Research, Brisbane, QLD, Australia

From first use to regular use of cannabis and cocaine across subgroups of Hispanics

 F.A. Wagner, S. Zhu and D.C. Browne, DARP/CHDS/PSRC, Morgan State University, Baltimore, MD

Substance abuse and dependence prevalence rates among impoverished Americans: Examining racial differences

 L.C. Windsor, 1Special Populations Research, National Development and Research Institutes, New York, NY and 2Social Work, University of Texas, Austin, TX

Frequent cannabis consumers in the community: Use of other substances, schizotypy, aggressiveness, depressiveness, and sensation-seeking

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POLYDRUG TREATMENT II

Predictors of treatment outcomes among African-American veterans participating in substance abuse treatment with a contingency management component

 K.D. Griffith1, S. Ferrell1, K. Sorocco2,1 and A. Vincent3, 1University of Oklahoma Health Sciences Center, and 2VA Medical Center, Oklahoma City, OK, and 3C-SHOP, University of Oklahoma, Norman, O

Evaluating predictors of abstinence during abstinence-based reinforcement and a minimal contingency aftercare

 Lynch2,1 and K.C. Kirby1,2, 1Treatment Research Institute, Philadelphia, PA and 2University of Pennsylvania, Philadelphia, PA

Predicting continuous abstinence over three years among former polysubstance users: Toward a comprehensive model

 A.B. Laudet1 and W.L. White2, 1Center for the Study of Addictions and Recovery, NDRI, New York City, NY and 2Chestnut Health Systems, Bloomington, IL

Correlates of long-term recovery after treatment

 M.L. Dennis1, C.K. Scott2 and M.L. Foss2, 1Chestnut Health Systems, Bloomington, IL and 2Lighthouse Institute - Chicago, Chestnut Health Systems, Chicago, IL

A procedure to retrieve dropout subjects from a cohort study of patients with multiple addictions (substance and non-substance) in Aquitaine, France

 M.P. Rousselet, E. Lavie, C. Denis, M. Fatseas and M. Auriacombe, Addiction Psychiatry JE2358/INSERM-IFR99, Universite Victor Segalen Bordeaux 2, Bordeaux, France

Time to remission from alcohol, nicotine, and illegal drug dependence in the U.S.

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Changes in the social networks of heroin and cocaine users after quitting

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The association of participation in spiritually based after-care programs (12-step) with drugfree status and secondary treatment outcomes at one year
> R.A. Denisco1, Y. Gayane2 and N. Fink2, 1National Institute on Drug Abuse, Bethesda, MD and 2Johns Hopkins School of Public Health, Baltimore, MD

Is polysubstance use a predictor of AA disaffiliation?
> M.P. Bogenschutz2,1 and J.S. Tonigan1,2, 1Center on Alcoholism, Substance Abuse, and Addiction, University of New Mexico, and 2Psychiatry, University of New Mexico School of Medicine, Albuquerque, NM

Legal status of dependent subjects seeking treatment in outpatient addiction centers in Aquitaine, France
> Z. Massida1, M. Augis1, C. Denis1, V. Beltran1,2, E. Lavie1, M. Fatseas1, J.P. Daulouede2,1 and M. Auriacombe1,2, 1Addiction Psychiatry JE2358/INSERM-IFR99, Universite Victor Segalen Bordeaux 2, Bordeaux, and 2Bizia Addiction Center, Bayonne, France

Illicit substance use amongst gang youth in Los Angeles
> B. Sanders1,2, S.E. Lankenau1,2 and J. Jackson-Bloom2, 1University of Southern California, Hollywood, and 2Childrens Hospital Los Angeles, Los Angeles, CA

Relationship between abstinence-based drug treatment centers and crime
> S.J. Boyd1, K.M. Armstrong2, L.J. Fang1, D.R. Medoff1, D.A. Gorelick3 and L.B. Dixon1, 1Psychiatry, University of Maryland, Baltimore, 2Geography, UMBC, Catonsville, and 3NIDA/NIH, Intramural Research Program, DHHS, Baltimore, MD

The association between parental drug use and sex trade among drug-using women
> A.L. Lawson, L.J. Floyd and W.W. Latimer, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Latinas in primary relationships: Acculturation, relationship power, substance use and sexual risk behaviors
> K. Ragsdale1 and C. Gore-Felton2, 1National Development & Research Institutes, New York, NY and 2Stanford University School of Medicine, Stanford, CA

Substance use among transgender women in New York City
> L.A. Nuttbrock, S. Hwahng and A. Rosenblum, Institute for Treatment and Services Research National Development and Research Institutes, New York, NY

Substance use and behavioral health in medical students
> D. Haller1, M.C. Acosta1, I. Wood2 and M.E. Olbrisch2, 1Psychiatry, St. Luke's-Roosevelt Hospital and Columbia University, New York, NY and 2Psychiatry, Virginia Commonwealth University, Richmond, VA

The self-perceived motivation for using addictive substances. A cross-sectional study of substance-dependent patients
> M. Fatseas, E. Lavie, C. Denis and M. Auriacombe, Addiction Psychiatry JE2358/INSERMIFR99, Universite Victor Segalen Bordeaux 2, Bordeaux, France

Trends in substance abuse treatment admissions among older adults from 1992-2004
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Acculturation and polysubstance abuse
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Ethnic differences in the psychosocial correlates of dropout from a residential therapeutic community
> W.M. Aklin, L.M. Maccarelli and S.A. Ball, Psychiatry, Yale School of Medicine, New Haven, CT

Why some injection drug users lick their needles
> M. Deutscher and D.C. Perlman, Division of Infectious Diseases, Beth Israel Medical Center, New York, NY

Injection risk behaviors reported by audio computer-assisted and interviewer-administered surveys
> B. Leigh1, R.X. Lee2, D.D. Brewer3 and H.C. Hagan4, 1University of Washington, 2Public Health - Seattle King County, and 3Interdisciplinary Scientific Research, Seattle, WA, and 4National Development and Research Institutes, New York, NY

Changes in response mode for the Balloon Analogue Risk Task
> D.E. Baruch1, T.J. Pleskac2, T.S. Wallsten1, W. Aklin1 and C. Lejuez1, 1University of Maryland, College Park, MD and 2University of Basel, Basel, Switzerland

Can we assess lifetime substance use by telephone in less than 10 minutes? Findings from the CARDIA study
> S. Kertesz1, M. Pletcher2, S. Samples1, C. Balentine1, J. Tucker1 and J. Schumacher1, 1University of Alabama, Birmingham, AL and 2University of California San Francisco, CA

MORTALITY

Increases in methadone-related adverse events: Pills or liquid?
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Prescription drug mortality among older women in rural Virginia

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Breaking the news or fueling the story? Impact of media reporting on opioid-related mortality

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Life-time overdose in Swedish prisoners with opioid use. Risk factors identified with the Addiction Severity Index

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Recent drug use, homelessness and increased short-term mortality in people with HIV and alcohol problems

J.H. Samet1, A.Y. Walley1, D.M. Cheng1, H. Libman2, D. Nunes1, C.R. Horsburgh1 and R. Saitz1, 1General Internal Medicine, Boston University School of Medicine, and 2Harvard Medical School, Boston, MA

Femoral blood concentrations of opiates in forensic autopsy cases

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Toward an understanding of differential pathways to non-suicidal self-injury and suicide

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PREVENTION

Hepatitis B vaccination at syringe-exchange programs

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Reducing risky relationships for HIV: Developing an intervention for hi-risk women

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Reducing HIV infection among injecting drug users in the China-Vietnam Cross-Border Project

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Patterns of HIV testing among drug users in St. Petersburg, Russia

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Externalizing behaviors among children of HIV+ drug users: Drug users in parent's network as social ecological risks

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Couples- vs. individual-based therapy for maternal drug users: Effects on children's adjustment

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Preliminary findings on dyadic interactions from the Mothers and Toddlers Program, an attachment-based parenting intervention for substance-abusing mothers

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Psychopathology as mediator in the prediction of substance use by parental child abuse potential in girls

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Enhancing identification of child maltreatment risk with indirect substance abuse items

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The impact of parent gender on predictors of preschool problems in substance-abusing families

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The effect of intimate partner violence on receptive syringe sharing among young female injection drug users: An analysis of mediation effects

K.D. Wagner1, S.M. Hudson2, M. Latka3, S.A. Strathdee4, H. Thiede5, M.E. Mackesy-Amiti and R.S. Garfein4, 1USC Sch. Med. Alhambra, 2Health Res. Assoc., Los Angeles, CA, 3NY Academy of Medicine, NY, NY, 4UCSD Sch. of Medicine, San Diego, CA, 5Public Health - Seattle & King County, Seattle, WA and 6U. of Illinois, Chicago, IL

Female IDUs' sex work and diminishing social support: Tanzanian women's independence and isolation

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Treatment site differences in retention of mentally ill patients under state-wide performance-based contracting of outpatient drug and alcohol services

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CRIMINAL JUSTICE

Results on the use of illicit drugs in arrestees in Santiago Chile, 2005

L.H. Caris1, P. Hurtado2 and M. Martin3, 1School of Public Health, Universidad de Chile, 2Paz Ciudadana, and 3Ministry of Health, Santiago, Chile

Characteristics of male drug users in a prison population in Sri Lanka

A. Stadlin1, L.O. Dissabandara1,2 and S. Dias2, 1School of Medical Science, Griffith *University, Southport, QLD, Australia and 2Faculty of Medicine, University of Peradeniya, Kandy, Sri Lanka*

Characteristics of amphetamine users in a sample of Swedish prisoners

M. Berglund1, A. Hakansson1 and F. Schlyter2, 1Lund University, Malmo, Sweden and 2Swedish Prison and Probation Service, Norrkoping, Sweden

Incarceration and drug of choice in South Africa

A.G. Moleko2, C. Maroga2, K. Cole1, S. Molonyane2, F. Mantlwa2, S.G. Severtson1 and W.W. Latimer1, 1Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD and 2University of Pretoria, Pretoria, South Africa

Effectiveness of buprenorphine maintenance in jail: A pilot study

S. Magura1, J. Hershberger2, A. Rosenblum1, H. Joseph1, N. Santana1, L. Marsch1, J.D. Lee3, C. Shropshire4, A. Glick4 and J. Liautaud4, 1NDRI, Inc., 2New York City Dept. of Health & Mental Hygiene, 3New York University, and 4Prison Health Services, New York, NY

A randomized clinical trial of methadone maintenance for prisoners: 6-month outcomes

M.S. Gordon, T.W. Kinlock and R.P. Schwartz, Social Research Center, Friends Research Institute, Baltimore, MD

Predictors of successful graduation and retention in an outpatient Jamaican drug court

K.E. Goulbourne1 and K.L. Cropsey2, 1Epidemiology and Community Health, Virginia Commonwealth University, Richmond, VA and 2Virginia Commonwealth University, Richmond, VA

The treatment needs of females with a substance use disorder in the Puerto Rican prison system: Implications for treatment planning

A. Hernandez and C. Albizu-Garcia, Center for Evaluation and Sociomedical Research, UPRMedical Sciences Campus, San Juan, Puerto Rico

Group IPT for women prisoners with comorbid substance use and depression

J.E. Johnson and C. Zlotnick, Psychiatry and Human Behavior, Brown University, Providence, RI

Predictors of drug treatment completion among parole violators

D.A. Zanis1,2, D.M. Coviello2 and J.J. Lloyd1, 1Temple University, and 2University of Pennsylvania, Philadelphia, PA

Effects of a history of violent crime on treatment retention at the Substance Treatment and Research Service of Columbia University

B.R. Nordstrom, J. Mariani, A. Bisaga, E. Nunes, D. Brooks and F.R. Levin, Division on Substance Abuse, Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, NY

Treatment response of incarcerated female substance abusers

J.Y. Sacks, CIRP, NDRI, Inc., New York, NY

Do research intermediaries reduce perceived coercion in drug court research?

D.S. Festinger, D.B. Marlowe, J.R. Croft, K.L. Dugosh, K.M. Benasutti, N.S. Patapis and P.A. Lee, Treatment Research Institute, Philadelphia, PA

Attitudes toward research among female offenders and generalizable methods for improving research ethics among high-risk populations

    J.M. DuBois1, L.B. Cottler2 and C. Callahan2, 1Saint Louis University, and 2Washington University School of Medicine, St. Louis, MO

HIV risk behaviors and intention to change among heterosexual methamphetamine-using offenders in drug treatment

    M. Brecht and E. Evans, Integrated Substance Abuse Programs, UCLA, Los Angeles, CA

Methamphetamine use and high-risk sexual risk behaviors among incarcerated female adolescents with a sexually transmitted disease in Los Angeles County Juvenile Halls

    J. Steinberg1, M. Boudov1, P. Kerndt1, C. Grella2, and C. Kadrnka3, 1Los Angeles County Dept. of Public Health, 2UCLA Integrated Substance Abuse Programs, Los Angeles, CA, and 3Juvenile Court Health Ser., Dept. of Health Services, USC, Los Angeles,CA

Gender effects on longitudinal models of marijuana use and sexual risk behavior among criminally involved adolescents

    S. Schmiege, K. Seals, M. Broaddus and A. Bryan, University of Colorado at Boulder, Boulder, CO

Prevalence of substance use disorders among adjudicated youth 134

    C. Hopfer1, S. Salomonsen-Sautel1, R. Corley2, S.H. Rhee2, T.J. Crowley1, C. Helmkamp1, R. Nichols1, C. Bryan1, J. Lubansky1, S. Hooks1, J. Pelle1, D. Malberg1 and C. Hartman1, 1UCDHSC, Denver, and 2University of Colorado at Boulder, Boulder, CO

Childhood adverse events and current traumatic distress: A comparison of men and women prisoners

    N.P. Messina and C. Grella, Integrated Substance Abuse Programs, UCLA, Los Angeles, CA

The daily struggle: A qualitative study of the process of long-term abstinence from heroin use among female ex-offenders

    N.J. Tiburcio, 1Educational Opportunity and Diversity, Graduate Center of New York, 2Criminal Justice, John Jay College of Criminal Justice, and 3Research, National Development and Research Institutes, New York, NY

The CO Women's Prison Project - Prelim. outcomes at 12 months post-prison exit: Comparing SA beh., HIV and other risk beh., and serv.needs/utiliz. of young and mature female offenders

    M.L. Schoeneberger1 and J.Y. Sacks2, 1NDRI-CIRP, Denver, CO and 2NDRI-CIRP, New York, NY

PROGRAM DESCRIPTION

A comprehensive Web-based screening system of multiple high risk behaviors for youth

    J.E. Sexton1, S. Libretto1, H. Wong1, S. Nemes2 and J. Hoffman1, 1Danya International, Inc., and 2Social Solutions International, Olney, MD

Focus Forward: A comprehensive wellness program for the workplace 139

    K.M. Rabon-Stith1, Y.H. Wong1, S. Libretto1, J. Namur-Karp2, S. Nemes2, C. Argueta1, J. Jones1 and A. Hernandez1, 1Public Health Research, Danya International, Silver Spring, and 2Social Solutions International, Olney, MD

StartSMART: Effect of tobacco prevention on middle school youth 140

    S.L. Zack1, Y.H. Wong1, J. Jones1, J. Weil2, S. Nemes2 and J. Hoffman1, 1Public Health Research, Danya International, Inc., Silver Spring, and 2Social Solutions International, Olney, MD

Developing a knowledge management system for tobacco use prevention and control professionals and advocates

    D. Petska1, Y.H. Wong1, S. Libretto1, J. Jones1, J. Hoffman1, V. Motaparthy1 and L. Hess2, 1Danya International, Inc., Silver Spring, and 2Social Solutions International, Inc., Olney, MD

How much science exists in our academic addiction counseling programs: A national survey to gauge the penetration level of the neuroscience and biology of drug abuse and addiction

    N.A. Roget1, M. Berry1, S. Clinkinbeard1, A. Broadus1, B. Larsen1 and A.H. Skinstad2, 1University of Nevada, Reno, Reno, NV and 2University of Iowa, Iowa City, IA

An international core addiction training curriculum: The Treatnet training package

    R. Rawson1, M. Zarza1, A. Bellows1, T. Freese1, A. Hasson1, M. Shawkey3, W. Ling1, D. Carise2, R. Ali4 and J. Tomas-Rosello5, 1UCLA, Los Angeles, CA, 2Treatment Research Institute, Philadelphia, PA, 3Assuit University, Assuit, Egypt, 4University of Adelaide, Australia and 5UN Office of Drugs and Crime, Vienna, Austria

Treatnet-international network of drug dependence treatment and rehabilitation resource centres

    J. Tomas-Rossello, T. Treatnet Network and A. Busse, Division of Operations/Prevention Treatment and Rehabilitation Unit, United Nations Office on Drugs and Crime, Vienna, Austria

Chase Brexton Health Services, Inc. Targeted capacity expansion program for substance abuse treatment and HIV/AIDS services

    A. de Jong, D. Haltiwanger and P. Clemmey, Behavioral Health, Chase Brexton Health Services, Baltimore, MD

The state of clinical supervision in Nevada's substance abuse treatment provider system: An examination of infrastructure and readiness to adopt evidence-based practices

S. Clinkinbeard[1], N.A. Roget[1], M. Berry[1], M. Canfield[2], F. Parenti[3] and A.H. Skinstad[4], 1University of Nevada, Reno, 2Nevada Substance Abuse Prevention & Treament Agency,
Carson City, and 3Nevada AADAPTS, Las Vegas, NV and 4University of Iowa, Iowa City, IA

A randomized, controlled, multi-site study of the effect of patient feedback on rates of attendance and abstinence in outpatient substance abuse treatment programs

B. McClure[1], A. Kulaga[1], J. Rotrosen[1], P. Crits-Christoph[2], S. Ring-Kurtz[2], M. Worley[2] and R. Forman[3], 1Psychiatry, NYU School of Medicine, New York, NY, 2Psychiatry, University of Pennsylvania, Philadelphia, PA and 3Alkermes, Inc, Boston, MA

Creating an electronic resource guide: Linking services to client needs

D.K. Loos, K.M. Casaletto and D. Carise, Treatment Systems Research, Treatment Research Institute, Philadelphia, PA

Adapting Washington Circle performance measures for publicly funded substance abuse treatment systems

D. Garnick, C. Horgan, M. Lee and A. Acevedo, Heller School of Social Policy and Management, Brandeis University, Waltham, MA

Tools for international drug abuse research partnerships and online education

C. Argueta[1], S. Libretto[1], Y.H. Wong[1], J. Hunt-Glassman[1], J. Hoffman[1], J. Harris[2] and B. Amend[2], 1Danya International, Silver Spring, MD and 2Medical Directions, Inc., Tucson, AZ

Need for technical assistance and training on problem gambling among substance use treatment and other social/health service providers

E. Evans and M. Brecht, Integrated Substance Abuse Programs, UCLA, Los Angeles, CA Evaluation of general organizational index for evidence-based practices in a community treatment agency

P.K. Horvatich, J.S. Knisely and D.R. Hall, Psychiatry, VCU, Richmond, VA

The evaluation of the dissemination of an integrated mental health intervention for alcohol and other drug treatment clients: PsyCheck Phase III

N. Lee, J. Cameron, T. Brooke and S. Roeg, Clinical Research, Turning Point Alcohol and Drug Centre, Fitzroy, VIC, Australia

SYMPOSIUM XV - INDIVIDUAL DIFFERENCES IN STRESS RESPONSE: SEX, SMOKING AND SNP'S (SINGLE NUCLEOTIDE POLYMORPHISMS)
Chairs: Harriet de Wit and Gary Wand

Determinants of acute stress response: Sex, personality, smoking and genetics

Emma Childs, University of Chicago, Chicago, IL

Stress cortisol response variation and risk for addiction

William R. Lovallo, VA Medical Center and University of Oklahoma Health Sciences Center, Oklahoma City, OK

Blunted opiate modulation of hypothalamic-pituitary-adrenocortical activity in smoking men and women

Mustafa al'Absi, University of Minnesota Medical School, Duluth, MN

Stress reactivity in cocaine-dependent individuals: The impact of gender and task

Kathleen Brady, Medical University South Carolina, Institute of Psychiatry, Charleston, SC

Relationship between cortisol responses to psychological stress and mesolimbic dopamine

Gary Wand, Johns Hopkins University School of Medicine, Baltimore, MD

ORAL COMMUNICATIONS 21 - EPIDEMIOLOGY: BY THE NUMBERS
Chairs: Meredith Smith and Carlos Rios-Bedoya

Early-onset cannabis use in opioid-dependent cases and neighborhood controls

E.C. Nelson[1], M.T. Lynskey[1], W. Howells[1], L. Degenhardt[2], R.P. Mattick[2] and N.G. Martin[3], 1Washington University, St. Louis, MO, 2University of New South Wales, Sydney, NSW, and 3Genetic Epidemiology, Queensland Institute of Medical Research, Brisbane, QLD, Australia

Who's starting to use cocaine in the early 21st century? An international perspective

C.F. Ríos-Bedoya, F. Fiestas and J.C. Anthony, Epidemiology, Michigan State University, East Lansing, MI

Gender and the prevalence and correlates of substance use disorders among 12-21 year-olds in the US

W. Becker[1], J.M. Tetrault[2,1], L. Sullivan[1] and D. Fiellin[1], 1Yale University, New Haven, CT and 2West Haven VA Hospital, West Haven, CT

Risk for cocaine use among non-medical users of prescription stimulants: Results of a longitudinal study of college students
   A. Arria1, K. Caldeira1, K. O'Grady2, K. Vincent1 and E. Wish1, 1Center for Substance Abuse Research, and 2Psychology, University of Maryland, College Park, MD
The effect of migration to the US on substance use disorders among return migrants and Mexican families of migrants
   G. Borges1, M. Medina-Mora1, J. Breslau2 and S. Aguilar-Gaxiola2, 1Epidemiology, Instituto Nacional de Psiquiatria & Universidad Autónoma Metropolitana-Xochimilco, Mexico, and 2Center for Reducing Health Disparities, UC, Davis, Sacramento, CA
Early onset cannabis problems and young adult major depression: Male-female variation
   V.S. Harder1, E.A. Stuart1 and J.C. Anthony2, 1Mental Health, Johns Hopkins University, Baltimore, MD and 2Epidemiology, Michigan State University, East Lansing, MI
From first cannabis use to cannabis use disorder: Age of onset and the risk and speed of transition in adolescence
   S. Behrendt1, H.U. Wittchen1, K. Beesdo1 and R. Lieb2, 1Institute of Clinical Psychology and Psychotherapy, Technical University Dresden, Dresden, Germany and 2Institute of Psychology, University of Basel, Basel, Switzerland
Predicting rates of admission to methadone maintenance treatment for heroin and opioid analgesic abuse as a function of community-level characteristics
   M.Y. Smith1, A. Rosenblum2 and C. Fong2, 1Purdue Pharma LP, Stamford, CT and 2NDRI, New York, NY

ORAL COMMUNICATIONS 22 - MARIJUANA AND CANNABINOIDS: WEEDING OUT MECHANISMS
Chairs: Scott Rawls and Diana Dow-Edwards

Effects of methanandamide in combination with Ä9 tetrahydrocannabinol (Ä9-THC) in C57BL/6J mice discriminating Ä9-THC
   L. McMahon, Pharmacology, University of Texas Health Science Center, San Antonio, TX
Discriminative stimulus effects of Ä9-tetrahydrocannabinol (Ä9-THC) in rhesus monkeys receiving morphine, heroin, or naltrexone
   J. Carlisle and L. McMahon, Pharmacology, University of Texas Health Science Center, San Antonio, TX
Cannabinoid-evoked hypothermia in rats is dependent on nociceptin/orphanin FQ receptor activation
   S.M. Rawls1, T. Rodriguez1, J.A. Schroeder2 and N. Zaveri3, 1Pharmaceutical Sciences, Temple University, Philadelphia, PA, 2Psychology, Connecticut College, New London, CT and 3Drug Discovery Program, SRI International, Menlo Park, CA
Sex-specific changes in opioid and dopamine receptors gene expression in striatum of CB1 transgenic mice
   T.M. Gerald1, A. Howlett2 and S.O. Franklin1, 1North Carolina Central University, Durham, NC and 2Wake Forest University, Winston-Salem, NC
Sex differences in the locomotion-depressing effects of tetrahydrocannabinol during adolescence
   L.C. Harte and D. Dow-Edwards, Physiology/Pharmacology, SUNY Downstate, Brooklyn, NY
Oral THC attenuates cue-induced marijuana craving in cannabis-dependent humans
   L.H. Lundahl1, L. Cederlind1 and C.E. Johanson2, 1Wayne State University School of Medicine, Detroit, MI and 2Loyola University, Chicago, IL
A pharmacological analysis of Δ^9-THC in humans
   J.A. Lile, T.H. Kelly, D.A. Medicine, Lexington, KY
Effects of adolescent marijuana use on fMRI brain activation to spatial working memory
   J. Winward1, A.D. Schweinsburg1, K.L. Medina2,1, T. McQueeny1 and S.F. Tapert2,1, 1VA San Diego Healthcare System, and 2University of California, San Diego, San Diego, CA

ORAL COMMUNICATIONS 23 - NOVEL PHARMACOTHERAPIES: SAY "NO" TO THE STATUS QUO
Chairs: Ryan Lanier and Adam Bisaga

Evaluation of a flexible-dosing strategy of varenicline for smoking cessation
   R. Niaura1, D.E. Jorenby2, J.T. Hays3, J.E. Pappas4 and F.T. Leone5, 1Brown University, Providence, RI, 2University of Wisconsin, Madison, WI, 3Mayo Clinic College of Medicine, Rochester, MN, 4Kentucky Medical Research Center, Lexington, KY and 5Thomas Jefferson University, Philadelphia, PA
Treating opioid dependence: Clinical evaluation of a transdermal buprenorphine formulation
   R.K. Lanier1, J.A. Harrison1, E.S. Nuwayser2, A. Umbricht1 and G.E. Bigelow1, 1Johns Hopkins School of Medicine, Baltimore, MD and 2Biotek, Inc., Wellesley, MA
Venlafaxine in the treatment of heroin withdrawal—a double blind, placebo-controlled trial
   S. Lin, Taipei City Psychiatric Center, Taipei, Taiwan

Randomized, double-blind, dose-effect evaluation of opioid blockade by extended-release naltrexone
G.E. Bigelow1, K.L. Preston2,1, J. Schmittner2, Q. Dong3 and D.R. Gastfriend3, 1Johns Hopkins University, Baltimore, MD. 2National Institute on Drug Abuse, Baltimore, MD and 3Alkermes, Inc., Cambridge, MA

Efficacy of a cocaine vaccine for the treatment of cocaine dependence in methadone-maintained patients
B.A. Martell1, E. Mitchell2,3, J. Poling2,3, T. Gardner4,5 and T.R. Kosten4,5, 1Medicine, and 2Psychiatry, Yale Univ. School of Medicine, New Haven, and 3West Haven, 4VAMC, West Haven, CT, Baylor College of Medicine, and 5Michael E. DeBakey VAMC, Houston, TX

Using contingency management with levodopa-carbidopa for cocaine treatment: A comparison of three different target outcomes
J.M. Schmitz1, M. Mooney2, F.G. Moeller1 and J. Grabowski1, 1University of Texas, Houston, TX and 2University of Minnesota, Minneapolis, MN

Memantine treatment of cocaine dependence
A. Bisaga, E. Aharonovich, F. Garawi, F. Levin, W. Raby, J. Mariani and E. Nunes, NYS Psychiatric Institute/Columbia University, New York, NY

Acute pretreatment with d-amphetamine enhances the subject-rated and cardiovascular, but not the reinforcing, effects of d-amphetamine
W.W. Stoops1, A.R. Vansickel1,2, J.A. Lile1, P.E. Glaser3 and C.R. Rush1,2,3, 1Behavioral Science, 2Psychology, and 3Psychiatry, University of Kentucky, Lexington, KY

Brunch with Champions

SYMPOSIUM XVI - STIMULANT-ASSOCIATED COGNITIVE ABNORMALITIES: MECHANISMS AND IMPACT ON REWARD-RELATED BEHAVIOR AND ADDICTION
Chairs: Ari D. Kalechstein and J. David Jentsch

Effects of self-administered cocaine on multiple memory system functioning in adult vs. adolescents
Kathleen Kantak, Boston University, Boston, MA

Dopaminergic adaptations are linked to poor cognitive control in a monkey model for methamphetamine dependence
J. David Jentsch, University of California, Los Angeles, Los Angeles, CA

Does pretreatment with modafinil reverse methamphetamine-associated neurocognitive impairment?
Ari D. Kalechstein, University of California, Los Angeles, Los Angeles, CA

ORAL COMMUNICATIONS 24 - CANNABINOID ABUSE: DIAGNOSIS AND TREATMENT
Chairs: Deborah Hasin and Aimee McRae

DSM-IV cannabis dependence: Categorical or dimensional phenotype?
D. Hasin1,2 and D. Alderson2, 1Columbia University, New York, NY and 2NYS Psychiatric Institute, New York, NY

Cannabis withdrawal is common among treatment-seeking adolescents with cannabis dependence and depression
J.R. Cornelius, T. Chung, C. Martin, D.B. Clark, D. Thatcher and D.S. Wood, Psychiatry, University of Pittsburgh, Pittsburgh, PA

Disturbance of sleep onset and sleep maintenance after discontinuation of marijuana use
K.I. Bolla1,2, S. Lesage1, C. Gamaldo1, D. Neubauer1, F. Funderburk1, P. David1 and J. Lud Cadet2, 1Neurology, Johns Hopkins Univ. School of Medicine, MD and 2DHHS, NIDA/NIH, Baltimore, MD

Effects of mitrazapine on withdrawal from dependent cannabis use
A. Frewen1,2, M.E. Montebello1, A. Baillie2 and F. Real, 1The Langton Centre, and 2Macquarie University, Sydney, NSW, Australia

Tolerability and effects of oral tetrahydrocannabinol in older adolescents with cannabis use disorders
K.M. Gray1, D. Christie1, C.L. Hart2 and H.P. Upadhyaya1, 1Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC and 2New York State Psychiatric Institute, New York, NY

Back to basics: The relationship of quantity, frequency and the duration of heaviest cannabis use to addiction
L.B. Cottler and A. Ben Abdallah, Psychiatry, Washington University School of Medicine, St. Louis, MO

Cannabis chronic users: Does abstinence change neuropsychological performance?
M.F. Novaes1,2, P.P. Almeida1,2, P.J. Cunha3, F. Jungerman1, R.R. Laranjeira1, A.L. Lacerda1,2 and R.A. Bressan1,2, 1Linc, Universidade Federal São Paulo, 2UNIAD, Universidade Federal São Paulo, and 3PAD, HIAE, São Paulo, Brazil

Baseline predictors for continuation to medication treatment for marijuana-dependent individuals
A. McRae1, R.E. Carter2, S.A. Simpson1, S.J. Anderson1, A.E. Herrin2 and K.T. Brady1, 1Psychiatry, and 2Biostatistics, Bioinformatics, and Epidemiology, Medical University of South Carolina, Charleston, SC

ORAL COMMUNICATIONS 25 - NICOTINE TREATMENT
Chairs: Ryan Vandrey and Carl Lejuez

Gender differences in tobacco dependence measures and withdrawal
M.E. Piper, S.S. Smith, M.C. Fiore and T.B. Baker, School of Medicine and Public Health, University of Wisconsin, Madison, WI

Menstrual phase effects on smoking cessation: A pilot feasibility study
M. Carpenter2, M. Saladin1, S. LaRowe1, A. Leinbach1 and H. Upadhyaya1, 1Psychiatry & Behavioral Sciences, and 2Hollings Cancer Center, Medical University of South Carolina, Charleston, SC

Distress tolerance as a predictor of early smoking relapse
B. Stipleman1, M. Bornovalova1, R. Brown2, C. Kahler2, D. Strong2, M. Zvolensky3 and C. Lejuez1, 1University of Maryland, College Park, MD, 2Brown University, Providence, RI and 3University of Vermont, Burlington, VT

Impulsivity as a predictor of smoking status and smoking cessation success in adolescents
S. Krishnan-Sarin1, B. Reynolds2, T. Liss1, A. McFetridge1, D. Cavallo1, T. Schepis1, A. Smith1, M. Potenza1 and K. Carroll1, 1Psychiatry, Yale University School of Medicine, New Haven, CT and 2Pediatrics, Ohio State University, Columbus, OH

Effects of nicotine exposure following brief abstinence: Examining human drug priming effects
R. Vandrey1, M.L. Stitzer1 and E.C. Donny2, 1Johns Hopkins University, Baltimore, MD and 2University of Pittsburgh, Pittsburgh, PA

Adolescent smokers' motivation to quit and point prevalence abstinence index
C.S. Parzynski, M. Jaszna-Gasior, L.A. Garver, K.M. Lee, C.E. Wieczorek and E.T. Moolchan, NIDA IRP, NIH, Baltimore, MD

Sustained-release bupropion combined with transdermal nicotine patch for smoking cessation in schizophrenia: Results of a double-blind, randomized, placebo-controlled clinical trial
A.H. Weinberger1, J.C. Vessicchio1, K.A. Sacco1, C.L. Creeden1, E.L. Reutenauer1 and T.P. George1,2, Psychiatry, Yale University School of Medicine, New Haven, CT and 2Psychiatry, Centre for Addiction and Mental Health, Toronto, ON, Canada

Characteristics of HIV+ cigarette smokers enrolling in a smoking treatment clinical trial
G. Humfleet, S. Hall, K. Delucchi, J. Dilley and G. Harrison, University of California San Francisco, San Francisco, CA

SYMPOSIUM XVII - PRIMARY FINDINGS FROM HIV/AIDS RESEARCH IN THE NIDA CLINICAL TRIALS NETWORK
Chair: Donald A. Calsyn

Primary results from CTN safer sex skills groups for men
Donald Calsyn, University of Washington, Seattle, WA

Primary results from CTN HIV/STD safer sex skills groups for women
Susan Tross, New York State Psychiatric Institute, New York, NY

Primary results from CTN HIV & HCV intervention in drug treatment settings
Robert Booth, University of Colorado Health Sciences Center, Denver, CO

NIDA DIRECTOR'S REPORT TO CPDD MEETING: PROGRESS, CHALLENGES & OPPORTUNITIES AT NIDA

Nora D. Volkow, Director

National Institute on Drug Abuse, Bethesda, MD

The following report summarizes the current drug abuse prevalence in the US, gives an update on relevant areas of research on HIV/AIDS and drugs, discusses emerging scientific opportunities for the field, and new NIH-wide initiatives that are poised to impact drug abuse research.

Specific drug problems in the US today

The most recent results of the Monitoring the Future (MTF) survey (that queries a nationally representative sample of high school students) reports a 23% decline over a 5 year period in the percent of students reporting past month use of illicit drugs (from 19.4% in 2001 to 14.9% in 2006). This trend is particularly significant because it pertains to a stage in life of high risk with drug experimentation and addiction.

The survey also reports that cigarette smoking among young people is at the lowest level ever recorded since the initiation of the survey in 1979. This is important not just because of its significance in terms of medical consequences associated with smoking, but also because of its potential impact on future drugs use. Indeed, epidemiological data document that early nicotine initiation is highly predictive of use and abuse of other drugs, preceding in most cases the use of marijuana [1]. Though the mechanisms that underlie this association are not properly understood and may reflect among others the easier access to cigarettes than other drugs; the possibility that early nicotine exposure can increase vulnerability for drug abuse in adulthood can not be ruled out. The decline in smoking among adolescents is also important because early onset of initiation is associated with a greater risk for nicotine addiction [2].

However, and despite overall reductions in use, the percentages of high school students abusing drugs are still unacceptably high. Fifteen percent of the combined 8th, 10th, and 12th graders report having taken an illicit substance in the past month. In addition, the survey did not register any decreases in the abuse of prescription medications (opiate analgesics, stimulants, sedatives, hypnotics). In fact, for opioid analgesics there are some indicators that suggest the rates may have actually increased. Oxicontin and Vicodin are the most frequently abused opioid analgesics, with 1 in 10 12th graders having used vicodin and 1 in 20 having used oxicontin for non medical purposes in the past month. Moreover vicodin is now the number 2 drug of abuse among 12th graders. Large increases in the use of opioid analgesics are not limited to young populations but have been detected across the lifespan. In this context, this is the first time we have seen a significant increase of initiation of illicit drug use among middle-age and elderly Americans.

HIV/AIDS

Substances of abuse play a very important role in the transmission and dissemination of HIV/AIDS. As a field, we have a unique opportunity to help prevent and treat HIV through the process of preventing and treating drug addiction.

At the beginning of the HIV epidemic, injection drug use (IDU) accounted for about 30% of all cases of HIV in this country. Since 1993, the number of cases and deaths associated with IDU has been reduced dramatically, just as the number of HIV-associated deaths, as a result of effective therapies and prevention interventions [3]. At the same time, we have witnessed a shift in the affected and at-risk populations. While men having sex with men (MSM) were the main drivers of the epidemic in the past, transmission among heterosexual individuals is increasing. In heterosexual contacts, the utilization of drugs facilitating risky behaviors appears to play a prominent role in the spread of the infection; this is true both, in the US and in other countries. Surprisingly, however, we don't quite know the number of new HIV cases that are a direct or indirect result of drug abuse. This would be an extremely important piece of information to acquire, particularly as a function of age groups, because it would enable us to target prevention interventions more effectively.

In some populations, non injection drug users display HIV prevalence rates that are similar to that of IDU. Indeed, a recent study of 2500 subjects recruited from two different populations showed that 13% of IDU patients in drug treatment programs were HIV[+] whereas 12% of the non injectors were HIV[+]. And, in a respondent-driven sample, injectors and non injectors had HIV seropositive prevalences of 15% and 17%, respectively [4]. Multiple factors are likely to contribute to these high rates in non injection drug users such as drug-induced intoxication states that facilitate risky behaviors, drug-induced physiological changes that facilitate infectivity as well as the dynamic of social groups that surround these individuals [5].

The following have been identified as relevant areas for research at NIDA:

- The need for a better understanding of the interactions between drugs and the HIV virus as they relate to brain function, impact on the immune system, and how they may induce deleterious epigenetic changes.
- The need to better understand the pharmacological dimension of how all these factors interact with antiretroviral therapy.
- In the clinical area, we need to further develop targets on prevention and treatment, recognizing the shifting nature of that epidemic in the United States that is increasingly impacting non IDU populations.
- HIV rapid testing and counseling in drug abuse treatment environments also offer unique opportunities in services research. Access to a $15 and 20-min result test makes it simple to implement during the counseling process. This would provide an opportunity for drug abuse treatment programs to implement on-site testing and provide counseling as an integral part of the process. Considering that 25% of HIV[+] cases in this country are not recognized, this offers an opportunity to identify and properly treat those patients with, for example, behavioral modification interventions designed to reduced their infectivity.
- NIDA will launch a new "Avant Garde Award", which is similar to the NIH-wide Pioneer Award but focused on supporting innovative researchers in the area of substance abuse and HIV.

Scientific opportunities and challenges

In the study of the vulnerability to drug abuse and addiction it is relevant to recognize not just the contribution of genes but also of an individual's developmental stage and the interactions between genes and the environment. We now realize that environmental factors –including drug exposures- will have different impacts upon substance abuse trajectories depending upon the developmental stage at which they occurred during an individual's life. This is likely to reflect the fact that the contributions of genes on brain function differs as a function of developmental stage, particularly for genes involved in the neuroplastic changes associated with brain growth. Thus, studies are needed that investigate the interactions between genes, environment, and development.

It is estimated that about 50% of the vulnerability for addiction is genetic. However, the ability of the implicated genes to mold behaviors and diseases in many instances require environmental factors to trigger these trajectories. The importance of incorporating development and environment into our approaches to assess vulnerability can be nicely exemplified by an epidemiological study of a large sample of 8600 subjects, in which the number of adverse childhood experiences (ACE) were plotted against the Odds Ratio (OR) of ever becoming addicted [6]. The data shows that individuals who had 5 or more adverse life events during childhood had an OR of having later addiction problems that was 10 times higher than individuals that experienced no such adverse events. As of now, we do not understand how these environmental factors affect the neurobiology of the brain to increase the greater risk in drug use, nor how do specific gene products facilitate or prevent those transitions. Moreover, the impact of adverse social factors is also likely to differ as a function of the developmental stage of an individual.

Although a prospective study that investigates these interactions would be ideal, such a study would be too expensive for the current budget of NIDA. Thus, we have launched a new initiative called "GEDI" (gene by environment by development interactions), to capitalize on those studies that NIDA, as well as other Institutes, such as NICHD, have been funding to evaluate prospective outcomes on children that were born to mothers that are cigarette smokers, or methamphetamine, or cocaine abusers, and follow them through adolescence. For a study to be eligible for a GEDI award, which will allow to genotype its subjects, it must have a proper characterization of the environment and of the individual. We expect this initiative to start genotyping at the beginning of 2008.

New NIH Initiatives of Relevance to Drug Abuse Research

Roadmap. The Roadmap (RM), launched by Dr. Zerhouni four years ago is preparing to start a new wave of projects under the rubric RM 1.5. The 2 projects to be funded during the next 5 to 8 years are the "Microbiome" and the "Epigenomic" initiatives. The epigenomic initiative, which will be jointly led by NIEHS and NIDA is directly relevant for drug abuse research.

Epigenetics refers to the mechanisms that modify gene expression profiles without changing the DNA sequence. Some of these modifications can be transmitted from cell to cell.

Epigenetic marks are extraordinarily important in stem cells, because they help determine specific pathways of cell differentiation by allowing cells –which otherwise carry essentially the same genetic information- to preferentially silence some genes while activating others. Consider that all the cells in all our tissues, from the neurons in our brains to the epithelial cells in our skin have the same number of genes and yet perform such diverse functions. This is due to epigenetic processes, which regulate which genes are expressed, when, where, and for how long.

Not surprisingly, epigenetic marks play a preponderant role in disease states, of which cancer has been the most intensely investigated. Indeed, studies of cancer sells have turned up multiple epigenetic changes. These findings are driving the identification of biomarkers that allow us to predict which patients will respond to treatment and also driving the development of new medications designed to target the mechanisms behind those epigenetic changes in malignant cells.

The excitement in epigenetic research has exploded in the recent past: from 2000 to 2005, the number of published papers on epigenetic research has increased from less than 500 to more than 4500. One can predict that this explosive trend will accelerate even further, because the information coming out of these studies is not only important to understand pathophysiology but also to manipulate the course of a disease, including that of drug addiction.

Table 1 provides a list of recognized epigenetic mechanisms. The two most widely investigated are DNA methylation and histone modification. DNA methylation silences genes by methylating the cytosine at CpG motifs. There are specific enzymes, called DNA Methyltransferases, in the nucleus of eukaryotic cells that carry out this modification. It was believed for many years that this process was irreversible, but recent work has shown this not to be the case, and that a process of demethylation can also take place that allows a silenced gene to become expressed once again. This is very important because it offers an opportunity to reversing some of the damage caused by hypermethylation. The second type of epigenetic mechanisms relates to various post-translational modifications of histones. Histones are the proteins around which the DNA becomes tightly packaged. Histones can be very close together or they can be sparsely positioned, making the chromatin less (heterochromatin) or more (euchromatin) open to transcription. Methylation, acetylation and even phosphorylation of histone proteins have all been shown to regulate the transition between hetero and euchromatin, determining how accessible the specific genes at that location will be toward the transcription machinery. In addition, there is evidence that non-coding RNAs, such as interference RNAs also play an important role in epigenetic control. It is likely that there are other, unidentified mechanisms; however, the ones that we do know about are already giving scientists a wide variety of targets for investigating disease processes.

An example of the importance of epigenetic changes is eloquently given by a study done in Agouti mice, which carry a mutation in the Agouti gene. These mice are yellow and obese, have hypercholesterolemia, diabetes and a higher propensity of cancer. Investigators took pregnant Agouti mice and "hypermethylated" their diet by lacing it with compounds that can methylate DNA (folate and B12), the idea being that by providing excess methyl donors they would be able to preemptively silence the gene that is responsible for the Agouti phenotype. A whole range of phenotypes was obtained, and in some of the offspring the Agouti phenotype was completely obliterated [7]. This case illustrates how an environmental factor during fetal development (i.e., diet) can rescue progeny from a devastating disease.

At NIDA we are focused, on a quintessential example of a disease in which an environmental factor modifies gene expression. Drugs are an environmental factor that produces significant changes in genetic output. Work from Eric Nestler's lab, for example, has clearly shown that drugs of abuse induce epigenetic changes [8]. His work has shown

that chronic cocaine is associated with a distinct patterns of histone acetylation, which removes transcriptional repressors, thereby allowing the transcription factor Delta FosB to assist in the transcriptional activation of regulated genes, including CDK 5, which is associated with the phenotypic expression observed with chronic drug administration [8].

These observations highlight the possibility that if there are defects in histone acetylation or methylation with chronic drug use then these epigenetic marks could become potential medication targets.

Blueprint

The NIH Blueprint consists of several across-institutes initiatives that offer opportunities for neuroscience-related researchers. Next year, the NIH Blueprint will be targeting "Neuroplasticity," which is an area that is extraordinarily important for our understanding of the dynamic brain changes associated with the process of addiction. These include the changes that accompany the normal progression through developmental stages, but also those that are brought about by the chronic abuse of drugs. We have seen, consistently, and across a wide variety of studies, that synapses are much more complex in animals that have been chronically exposed to cocaine or amphetamine [9], highlighting the importance of synaptic plasticity, a process that could be linked to the establishment of sensitization, i.e., enhanced sensitivity to these drugs.

The importance of neuroplasticity in addiction is also highlighted by the results obtained with whole genome association scans of addicted individuals. These studies uncovered, not only usual suspects or "reasonable" candidate genes[1], but also, surprisingly, genes involved in neuroplasticity. For example, the most significant hit coming out of a recent study that scanned over 2 million single nucleotide polymorphisms in search of loci associated with nicotine dependence [10], was neurexin, a critical element in the formation and strengthening of synapses, thus in the modulation of synaptic plasticity [11]. The emerging link between genetics and neuroplasticity brings forward an important question: if these genetic variants are somehow involved in drug addiction, and they are so prevalent -because addiction is so prevalent-, why are they not selected against? Do they confer other benefits to the organism that we have not yet identified? Is there an advantage to carrying some of these variants that compensates for their addiction liability? These questions, of course, come back to the critical role of neuroplasticity in the processes of memory and conditioning.

In summary, this is a period of extraordinary scientific opportunity and, as a consequence, our understanding of the genetics and the neurobiology of addiction is expanding rapidly. Out of this knowledge new medication targets are emerging that in the future are likely to help us treat drug addiction in ways that are similar to those we use to treat other medical conditions.

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[1] Like the $\alpha3$ and $\beta3$ nicotine receptors; very interesting in and of themselves, because they are not directly associated with the rewarding effects of nicotine, but are highly concentrated in the habenula which regulates aversive responses and firing rate of ventral tegmental area (VTA).

Table 1. Key epigenetic mechanisms recognized today, which have been shown to modulate the expression of genetic traits independently of DNA sequence changes and, sometimes in heritable fashion.

> ► **DNA Methylation** – silences gene by methylating the cytosine of a CpG motif
>
> ► **Histone Modification** – methylation, acetylation, or phosphorylation of histone can regulate transcription of genes (> 100 conserved, covalent modifications)
>
> ► **Noncoding RNAs** – interfere with transcription and post-transcriptional regulation of gene expression

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LIST OF EDDY AWARD RECIPIENTS

2007	Jack Mendelson and Nancy Mello
2006	Ivy Carroll
2005	Conan Kornetsky
2004	James H. Woods
2003	Charles P. O'Brien
2002	Horace H. Loh
2001	Kenner C. Rice
2000	William L. Dewey
1999	Mary Jeanne Kreek
1998	John W. Lewis
1997	Martin W. Adler
1996	Griffith Edwards
1995	Herbert D. Kleber
1994	Jerome H. Jaffe
1993	Lee N. Robins
1992	Joseph V. Brady
1991	Phillip S. Portoghese and Akira E. Takemori
1990	Charles Schuster
1989	Leo E. Hollister
1988	Albert Herz
1987	Clifton K. Himmelsbach
1986	Harold Kalant
1985	Louis S. Harris
1984	Raymond Houde
1983	Eric Simon
1982	Vincent Dole and Marie Nyswander
1981	Everette L. May
1980	Avram Goldstein
1979	E. Leong Way
1978	Hans Kosterlitz
1977	William Martin
1976	Abraham Wikler
1975	Harris Isbell
1974	Maurice Seevers

INTRODUCTION OF THE NATHAN B. EDDY MEMORIAL AWARD RECIPIENTS

Kenner C. Rice[1] and Louis S. Harris[2]

[1]National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism and [2]Virginia Commonwealth University, Richmond, VA

It is a distinct honor and privilege to introduce Drs. Jack Mendelson and Nancy Mello as the 2007 recipients of the Nathan B. Eddy Award. Jack is Professor of Psychiatry (Neuroscience) and Nancy is Professor of Physiology (Neuroscience) at Harvard Medical School. They are Co-Directors of the McLean Hospital/Harvard University Alcohol and Drug Abuse Center that they established in 1973. Their pioneering research in alcohol, opiate, cannabis, cocaine and nicotine abuse is well documented with Jack having published nearly 500 and Nancy about 400 original papers, review articles and books. Jack and Nancy have served in many prestigious positions including as consultants to the White House Special Action Office for Drug Abuse Prevention. Nancy is presently editor of Experimental and Clinical Psychopharmacology and Jack and Nancy co-edited of the Journal of Studies on Alcohol from 1983-1990. Their work has been recognized with numerous individual and shared research awards. Nancy is the recipient of the Betty Ford Award (Association for Medical Education and Research in Substance Abuse), Marian W. Fishman Memorial Award (CPDD) and the Brady Schuster Award (American Psychological Association). Jack is the recipient of the Hofheimer Prize (American Psychiatric Association), The Founders Award (American Association of Psychiatrists In Alcoholism and Addictions) and the Award of Merit (Journal of Nuclear Medicine). Their shared awards include the Jellinek Memorial Fund Award, (Research Society on Alcoholism), the Distinguished Research Award, (Research Society on Alcoholism) and they are Honorary Professors of Neuroscience, Guangzhou Medical College, China. Today, they have rightly become the joint recipients of the Nathan B. Eddy Award in recognition of their many research contributions and their role as leaders and mentors in drug abuse research. For this, I say thank you very much Jack and Nancy for all that you have done for our field.

And now I would like to ask Lou Harris to conclude the introduction.

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We are here to celebrate the long lasting love, dedication of Jack and Nancy to each other, their scientific research, training and service.

While thinking about the impressive contributions of Jack and Nancy, I began to muse about the contributions of couples to science. It struck me that contributions by couples in the field of substance abuse and addiction were rather remarkable and those of Nancy and Jack are exemplary.

Historically, there was little to be found prior to the 20th Century. In the first half of the century, we find Marie and Pierre Curie in Physics, Louis and Mary Fieser in Chemistry, Joseph Fruton and Sofia Simmonds in Biology and Gertrude Elion and George Hitchings for drug development and cancer immunotherapy. In the later half of the century, the record of contributions by couples to the field of drug dependence and substance abuse has been remarkable. For instance, they include Vincent Dole and Marie Nyswander, Avram and Dora Goldstein, Eva and Keith Killam, Bob Schuster and Chris-Ellyn Johanson, Shep Kellum and Peg Ensminger, Huda Akil and Stan Watson, Jim Woods and Gail Winger, Tom McClellan and Deni Carise, Roy Pickens and Dace Svikis, Jim Incardi and Hillary Surrat, and especially our awardees, Jack Mendelson and Nancy Mello.

Our field, the College and its predecessors should be proud of the distinguished records of these colleagues.

Jack H. Mendelson, M.D., Professor of Psychiatry (Neuroscience), Harvard Medical School. Co-Director, Alcohol and Drug Abuse Research Center, McLean Hospital

and

Nancy K. Mello, Ph.D., Professor of Psychology (Neuroscience), Harvard Medical School. Co-Director, Alcohol and Drug Abuse Research Center, McLean Hospital

Preface

In June of 2007, Jack H. Mendelson, M.D. and I received the Nathan B. Eddy Award from the College on Problems of Drug Dependence. In August of 2007, my beloved husband of 33 years died of biliary cancer. In addition to a wonderful marriage, we enjoyed a long and productive collegial relationship that spanned more than 40 years. I have prepared this paper at the request of CPDD to review some of our research that was most important to us. Many colleagues have contributed to our research efforts, as shown in the citations at the end of this commentary. This summary is followed by an obituary describing some of Jack's special accomplishments in this field. Our careers have been intertwined and the differences in our training have been complimentary. Jack was trained in psychiatry and neurology. During his internship at the Boston City Hospital, he became interested in alcoholism and the myriad associated medical and psychiatric problems. He is perhaps best known for his pioneering clinical research on the effects of alcohol on the neuroendocrine system and behavior in alcohol-dependent men. As described below, this research challenged many prevalent beliefs about alcoholism. Importantly, Jack was among the first to advance the concept that alcoholism is a disease, a medical disorder like diabetes or cardiac disease. The disease concept of alcoholism was a dramatic departure from the prevalent opinion of that time that alcoholism reflected moral weakness and a character defect. In the absence of objective research, the "moral weakness" hypothesis was pervasive and persistent. In the late 1960's, Jack was selected to lead the first federal agency dedicated to research on alcoholism, The National Center for the Prevention and Control of Alcoholism that later evolved into the National Institute on Alcohol Abuse and Alcoholism. In this role, Jack was able to promote the notion that alcoholism is a medical disorder and to stimulate a broad multidisciplinary program of extramural and intramural research.

During my initial training in clinical psychology, I became interested in behavioral science and physiology. I was fortunate to acquire postdoctoral training in the experimental analysis of behavior with B. F. Skinner at Harvard University and in physiology with J.L. Downer at Harvard Medical School. My goal at that time was to use operant behavioral techniques to study visual function in preclinical studies. I found that cats could be trained to discriminate a broad spectrum of colors when brightness was controlled (Mello and Peterson, 1964; Mello, 1968). These behavioral data were consistent with evidence from electrophysiology that cells in the cat visual cortex responded differently to different colors. I also was interested in developing a split-brain preparation in pigeons analogous to the preparation in monkeys developed independently by Roger Sperry, and my mentor J.L. Downer. I reported in *Science* that pigeons trained to discriminate symmetrical mirror-image shapes with only one eye open responded to the positive shape (associated with food reinforcement) as if it were the negative shape when the opposite untrained eye was open alone (Mello, 1965). I termed this phenomena interhemispheric reversal of visual information and found that it occurred with a variety of stationary mirror-image patterns as well as moving patterns (Mello, 1966; Mello, 1967). At this time, I began to collaborate with Jack in clinical studies of operant work-contingent drinking patterns in alcohol-dependent men (Mello and Mendelson, 1965). My interest in the experimental analysis of alcoholism and other forms of substance abuse has continued throughout my career.

(1) Behavioral analysis of alcohol and drug abuse patterns in humans: We were the first to apply procedures based on the experimental analysis of behavior to clinical studies of alcoholism and drug abuse. We published the first report of operant analysis of drinking patterns in chronic alcoholics in *Nature* in 1965 (Mello and Mendelson, 1965), and conducted the first long-term (1-2 month) inpatient studies of drinking and cigarette smoking in alcohol-dependent men (Mello and Mendelson, 1970b; Mello and Mendelson, 1971; Mello and Mendelson, 1972). Subsequently, we extended this approach to studies of chronic marihuana self-administration and concurrent availability of alcohol and marihuana (Mello et al., 1978; Mello and Mendelson, 1985). These studies provided the

first quantitative assessment of the quantity and frequency of alcohol, marihuana and alcohol + marihuana use over prolonged periods in human volunteers.

Our findings challenged many anecdotal accounts of the effects of alcohol and drug use. One important finding was that chronic alcohol intoxication is associated with increases in depression, anxiety, and feelings of unworth rather than the anticipated enhanced conviviality and pleasurable relaxation (Mello and Mendelson, 1970a; Mello and Mendelson, 1972). Chronic heroin self-administration had similar negative effects on mood in heroin-dependent men (Mello et al., 1981; Mello et al., 1982; Mendelson et al., 1982). Similarly, during chronic marihuana use, heavy smokers tended to become more socially isolated, less convivial, and intermittently despondent (Mendelson et al., 1976; Mello and Mendelson, 1985).

Patterns of alcohol use also differed from commonly accepted anecdotal and retrospective reports. Alcohol-dependent men alternated 2 or 3-day periods of heavy drinking with several days of voluntary abstinence over 30-60 consecutive days of operant response-contingent alcohol availability. An example appears in **Figure 1**. Even though men developed alcohol withdrawal signs and symptoms during the days of self-imposed abstinence, they readily tolerated the attendant discomfort and worked at an operant task to accumulate points for a subsequent episode of drinking, unencumbered by operant work (Mello and Mendelson, 1972). The withdrawal signs usually were mild to moderate tremor of the extremities and were associated with a rapid fall in blood alcohol levels. Interestingly, withdrawal signs were observed at blood alcohol levels as high as 100 mg/100ml. These data illustrate the now generally accepted belief that avoidance of withdrawal signs and symptoms (i.e. physical dependence) is not a necessary or sufficient condition to account for continued alcohol or other drug abuse. Periods of working for cigarettes tended to covary with periods of working for alcohol. All subjects accumulated points for cigarettes that they spent during the first drinking episode. The dissociation between periods of working for alcohol and cigarettes and periods of peak consumption persisted throughout the 60-day period of alcohol availability.
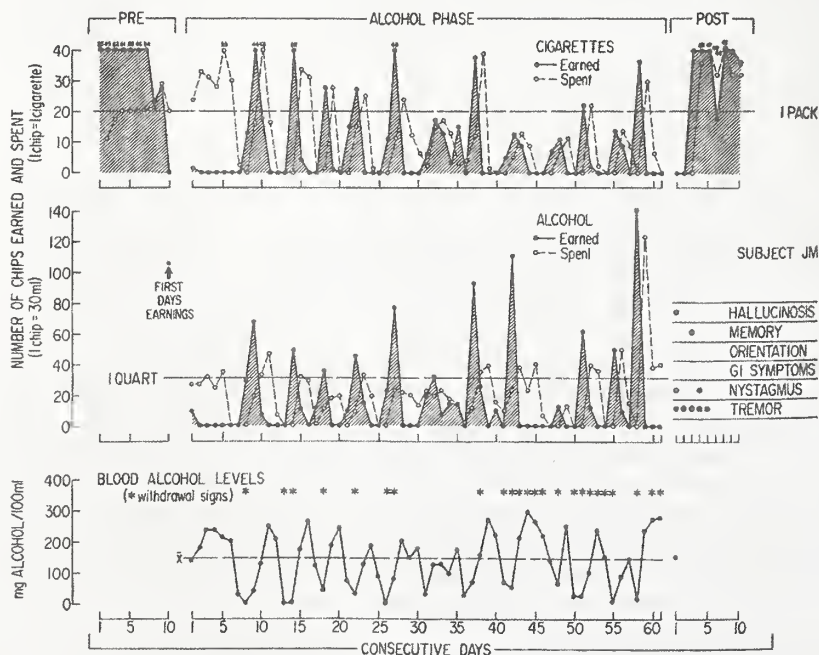
Figure 1. *The earning and spending pattern of a single subject working for cigarettes during a 10-day baseline period; for both cigarettes and alcohol during a 60-day alcohol available period and for cigarettes during a 10-day withdrawal period. Subjects worked to earn tokens to buy alcohol and cigarettes by pressing a button on a portable operant manipulandum (fixed ratio=1000). Each subject was paid for his previous days earning each morning at 8 a.m. Cigarettes and alcohol could be purchased from an automatic dispenser located on one wall of the dayroom. (One token bought one ounce of bourbon or one cigarette). Tokens earned for alcohol were not interchangeable with tokens earned for cigarettes. Tokens earned for alcohol could be spent at any time during the 60-day alcohol-*

available period. The pattern of earning (closed circles; shaded area) and spending (grey circles) for cigarettes is shown in the top row. The pattern of earning (closed circles; shaded area) and spending (open circles) for alcohol is shown in the middle row. Subjects were allowed to work for alcohol tokens during the last 24 hours of the baseline period, and these tokens could be spent after 8 a.m. on the first day of the drinking period. Tokens earned during this period are shown at the arrow as First Day's Earnings. The type and duration of withdrawal signs and symptoms observed upon cessation of drinking are shown at the right of the middle row. The daily mean blood alcohol levels based on three daily measurements and the average blood alcohol level maintained throughout the drinking period, are shown in the bottom row. The occurrence of partial withdrawal signs (mild tremulousness) is indicated as asterisks. Adapted from Mello and Mendelson, 1972.

(2) Behavioral Studies to Evaluate New Pharmacotherapies for Drug Abuse Treatment: During the late 1970's, we applied the operant behavioral research model that we developed for clinical studies of alcoholism and marihuana abuse to studies of heroin abuse with the goal of evaluating the effectiveness of new treatment medications. Operant techniques were used to provide an objective index of heroin acquisition patterns. Opioid-dependent men who had failed in methadone treatment were recruited for an inpatient study. In 1980, we published the first report that the opioid mixed agonist-antagonist buprenorphine significantly reduced heroin self-administration by heroin addicts, whereas placebo buprenorphine had no effect on heroin self-administration in double-blind studies (Mello and Mendelson, 1980). These data are shown in **Figure 2**. Buprenorphine's agonist properties are similar to those of methadone, yet its antagonist component blocks the subjective and physiologic effects of opiates and virtually precludes opiate overdose (Jasinski *et al.*, 1978)) see ((Mello and Mendelson, 1995)) for review). Buprenorphine was well tolerated and had mild opioid side effects that resolved in several days (Mello *et al.*, 1982). In 1981, we reported that the opiate antagonist naltrexone also significantly reduced heroin self-administration by heroin-dependent men in comparison to placebo naltrexone studied on a clinical ward under double-blind conditions (Mello *et al.*, 1981).
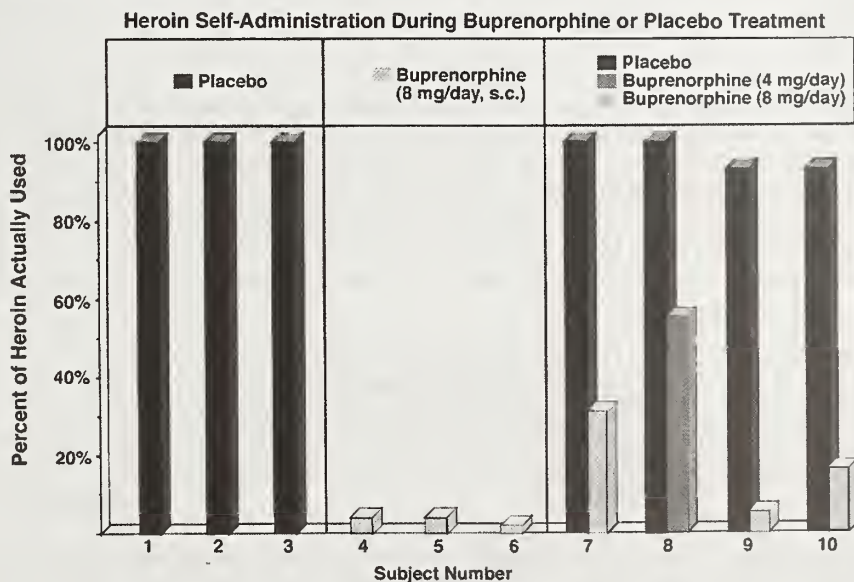
Figure 2. Percentage of available heroin used by individual opioid-dependent men during 10 days of treatment with buprenorphine or placebo buprenorphine. Three subjects were maintained on placebo-buprenorphine (left columns); three subjects were maintained on buprenorphine (8 mg/day, s.c.) (middle columns), and four subjects were studied under both buprenorphine and placebo-buprenorphine conditions (right columns). Adapted from Mello and Mendelson, Science (1980).

Although both naltrexone and buprenorphine effectively reduced heroin self-administration, buprenorphine was far more readily accepted by the patients as a potential pharmacotherapy because of its opioid agonist component. Outpatient studies have consistently reported that it was difficult to retain patients in naltrexone-maintenance programs (Meyer and Mirin, 1979) whereas outpatient studies of buprenorphine indicate good retention. Thus, these inpatient clinical trials not only provided objective measures of medication efficacy in reducing drug self-

administration, but also predicted relative clinical utility for outpatient maintenance. Twenty-two years after our first report in *Science*, buprenorphine was finally approved by the FDA for the outpatient treatment of opioid abuse and dependence in 2002.

We have conducted parallel studies of the effectiveness of new pharmacotherapies in the nonhuman primate model of drug self-administration. We found that buprenorphine also significantly suppressed opiate self-administration in the primate model (Mello *et al.*, 1983a). This report illustrated the potential value of using the primate drug self-administration model to evaluate and predict the effectiveness of new pharmacotherapies for the treatment of drug abuse. In 1989, we reported in *Science* that buprenorphine also selectively reduced cocaine self-administration by rhesus monkeys by 72-93%, with minimal effects on food self-administration (Mello *et al.*, 1989). Cocaine and food self-administration were maintained on a second-order schedule in four sessions each day. Fifteen days of baseline saline treatment were compared with two successive 15-day periods of treatment with 0.40 and 0.70 mg/kg/day buprenorphine. These data are shown in **Figure 3**. In an effort to determine if the mu opioid agonist component of buprenorphine was primarily responsible for buprenorphine's effects on cocaine self-administration, we administered the mu opioid antagonist naltrexone before buprenorphine treatment (Mello *et al.*, 1993b). Naltrexone alone had no significant effect on cocaine-maintained responding under conditions where buprenorphine significantly and selectively reduced cocaine self-administration (Mello *et al.*, 1990a). However, naltrexone treatment resulted in a significant dose-dependent decrease in buprenorphine's effects on cocaine. As the naltrexone dose increased, cocaine self-administration increased in comparison to a period of treatment with buprenorphine alone (Mello *et al.*, 1993b). These findings suggested that buprenorphine's mu opioid effects were critical in reducing cocaine self-administration by rhesus monkeys. Consistent with this conclusion, we later reported that low and high efficacy mu agonists also significantly reduced cocaine self-administration, but the mixed agonist-antagonists nalbuphine and butorphanol produced the most selective decreases in cocaine self-administration, with the fewest adverse side effects (Negus and Mello, 2002). These data were consistent with our earlier evaluation of the effects of nalbuphine and butorphanol on cocaine self-administration under the same experimental conditions (Mello *et al.*, 1993a).

Buprenorphine's dose-related decrease in cocaine self-administration suggested that it might be useful for the treatment of dual dependence on cocaine and opioid drugs. We subsequently evaluated the therapeutic usefulness of buprenorphine for treatment of dual cocaine and opiate dependence in outpatient clinical trials (Gastfriend *et al.*, 1993; Mello and Mendelson, 1995). Outpatient studies in daily cocaine and heroin abusers showed reductions in both cocaine and heroin abuse, measured by urine drug screens and retention in the treatment program. Most recently a report by investigators at the NIDA Intramural Program confirmed the effectiveness of buprenorphine for outpatient treatment of persons who are dually dependent on cocaine and opioids (Montoya *et al.*, 2004).
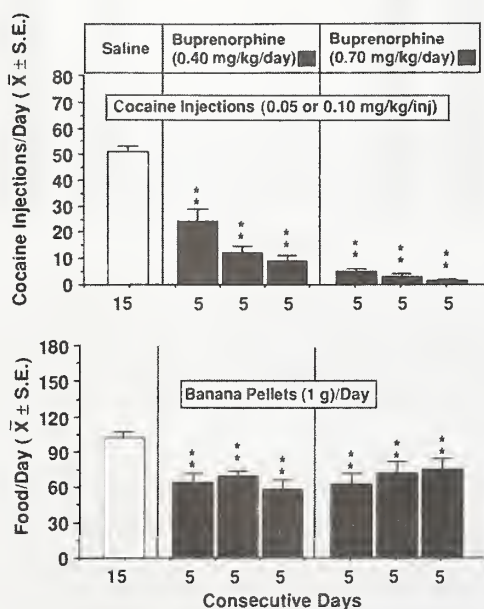
Figure 3. Buprenorphine reduces cocaine self-administration by rhesus monkeys. The effects of single daily infusions of buprenorphine or a saline control solution on cocaine and food self-administration are shown. Cocaine and food self-administration were maintained on a second-order FR4 (VR16:S) schedule of reinforcement in four daily sessions. Saline treatment is shown as an open bar in the left panel. Treatment with buprenorphine (0.40 mg/kg/day) is shown as closed bars in the middle panel, and buprenorphine (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 (**$p < 0.01$). Revised from Mello *et al.*, Science (1989).

3) Behavioral analysis of polydrug abuse: Although the simultaneous or sequential use of drugs with divergent or contradictory effects is a common form of drug abuse, the interactions between two or more drugs abused concurrently has been difficult to study experimentally. We have examined polydrug abuse in both clinical and preclinical studies. In 1978, we reported the first in-patient study of concurrent alcohol and marihuana availability in young men (Mello *et al.*, 1978). Patterns of concurrent alcohol and marihuana use during 10 days of operant response-contingent access were compared with consecutive 5-day periods when only alcohol or only marihuana were available. Contrary to expectation, concurrent availability of alcohol and marihuana did not increase the use of either drug. Rather, 14 of the 16 men studied drank significantly less alcohol when marihuana was concurrently available. Marihuana use increased gradually through time, independent of alcohol availability (Mello *et al.*, 1978). A gradual increase in marihuana use also occurred in clinical studies of marihuana smoking in young women (Mello and Mendelson, 1985).

We also examined the temporal co-variance between cigarette smoking and other drug self-administration. Cigarette smoking consistently increased during chronic drinking in alcohol-dependent men (Mello and Mendelson, 1970b; Mello and Mendelson, 1971; Mello and Mendelson, 1972). Consistent with these effects of alcohol, we discovered that smoking also increases significantly during heroin self-administration and during maintenance treatment with buprenorphine (Mello *et al.*, 1980b; Mello *et al.*, 1985; Mutschler *et al.*, 2002). In contrast, marihuana intoxication did not affect tobacco smoking in men or women, even though both drugs were usually smoked in close temporal contiguity (Mendelson *et al.*, 1976; Mello *et al.*, 1977; Mello *et al.*, 1978; Mello *et al.*, 1980a). The mechanisms underlying the co-variance between tobacco smoking and alcohol and opioid intoxication are not understood.

We also developed the first preclinical model of polydrug abuse involving the simultaneous IV administration of cocaine and heroin ("speedballs") in rhesus monkeys (Mello *et al.*, 1995). We evaluated nine combinations of cocaine and heroin for 10 days and compared our findings to self-administration of cocaine and heroin alone. Drug and food self-administration was maintained on an FR4 [VR16:S] schedule of reinforcement during four daily sessions. We found that the dose-effect curves for the cocaine + heroin combinations were similar to those for cocaine and heroin alone. No toxic effects were observed and intermediate doses of cocaine + heroin maintained the highest levels of responding.

This speedball model was designed to evaluate the effects of potential treatment medications on polydrug abuse under controlled conditions. We hypothesized that optimal treatment of speedball self-administration would require the combination of two medications, one targeted at the cocaine component and the second targeted at the opioid component of the speedball. This notion has been supported by our preclinical studies showing that a combination of the dopamine antagonist flupenthixol and the opioid antagonist quadazocine reduced speedball self-administration more effectively than either antagonist alone (Mello and Negus, 1999). A subsequent study of the monoamine reuptake inhibitor indatraline combined with the opioid mixed agonist antagonist buprenorphine also showed that this medication combination was more effective in reducing speedball self-administration than either medication alone (Mello and Negus, 2001). Most recently, we found that a combination of *d*-amphetamine and buprenorphine decreased some speedball combinations more effectively than either drug alone (Mello and Negus, 2007). **Figure 4** shows illustrative data for the effects of saline and a combination of *d*-amphetamine and buprenorphine on speedball dose-effect curves and concurrent food-maintained responding (Mello and Negus, 2007). Treatment with *d*-amphetamine and buprenorphine shifted the speedball dose-effect curve downwards and to

the right with minimal effects on food-maintained responding. This combination of *d*'amphetamine and buprenorphine was more effective than buprenorphine alone in reducing self-administration of speedballs consisting of high doses of cocaine + heroin (Mello and Negus, 1998). These findings also suggested that buprenorphine may have antagonized the rate-decreasing effects of high doses of speedballs on food-maintained responding. This innovative speedball model should be increasingly valuable for evaluating the effectiveness of possible treatment medications (Mello, 2005).
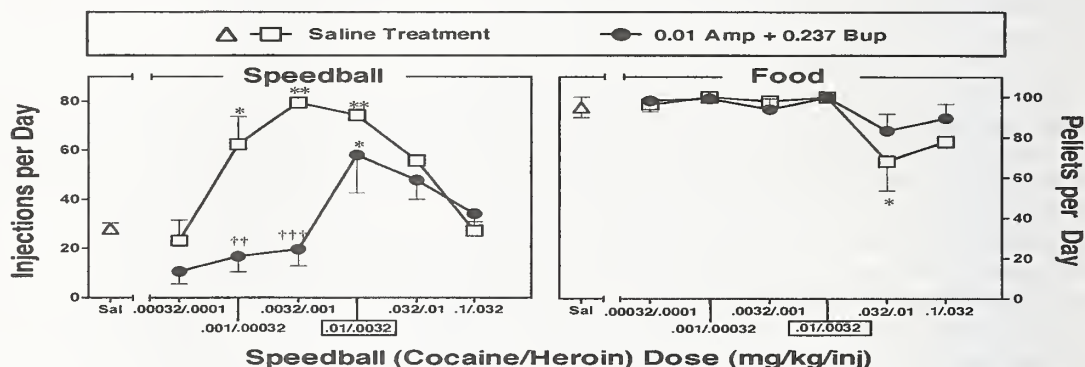
Figure 4: Effects of Chronic Treatment with Saline or a d-Amphetamine + Buprenorphine Combination on Speedball Dose-Effect Curves: Dose-effect curves for speedball combinations of cocaine (0.00032-0.10 mg/kg/inj) and heroin (0.0001-0.032 mg/kg/inj) are shown for a group of three monkeys (left panel). The unit doses of each cocaine and heroin combination are shown on the abscissae. The training dose is indicated by a box around one speedball dose combination (0.01 mg/kg/inj cocaine + 0.0032 mg/kg/inj heroin). Injections per day are shown on the left ordinate. Points above "Sal" show data when saline was the solution available for self-administration. Self-administration of each cocaine-heroin combination during saline treatment is shown as open squares. Speedball self-administration during treatment with the d-amphetamine (0.01 mg/kg/hr) + buprenorphine (0.237 mg/kg/day) combination is shown as closed circles. Food-maintained responding during saline self-administration and self-administration of speedball cocaine and heroin combinations during saline treatment (open squares) is shown in the right panel. The number of food pellets self-administered per day is shown on the right ordinate. Food-maintained responding during treatment with d-amphetamine (0.01 mg/kg/hr) + buprenorphine (0.237 mg/kg/day) is shown as closed circles. Each data point is the average of the last 3 days (12 sessions) of 10 consecutive days of speedball or food self-administration in a group of three monkeys ($\overline{x}$ ± S.E.M.). The asterisks indicate a significant difference from saline self-administration during saline treatment (*= P<0.05; **= P<0.01). The daggers indicate that the number of speedball injections self-administered at the same speedball dose combinations were significantly different during saline treatment and during d-amphetamine + buprenorphine treatment (†† = P<0.01; ††† = P<0.001). From Mello and Negus, 2007.

(4) Biologic Consequences of Drug Abuse: Many of the clinical behavioral studies described above were multidisciplinary with the goal of evaluating the biological consequences of drug abuse and studying the ways in which hormonal factors may modulate the complex process of alcohol and drug reinforcement (Mendelson *et al.,* 1992). We were among the first to study the neuroendocrine correlates and consequences of drug abuse and alcoholism. There is now increasing evidence that anterior pituitary, gonadal and adrenal hormones may influence the abuse-related effects of cocaine and other drugs (Mello and Mendelson, 2002). We have examined the interactions between the acute subjective effects of cocaine and changes in anterior pituitary, gonadal and adrenal hormones. One major finding was that when subjective effects and hormonal changes were measured every two minutes after IV cocaine administration to cocaine abusers, increases in LH, ACTH, cortisol, DHEA, cocaine plasma levels and reports of positive subjective effects were significantly correlated (Mendelson *et al.,* 2002). We subsequently found that intravenous cocaine and cigarette smoking each stimulate rapid increases in LH, ACTH, cortisol and DHEA that were temporally correlated with reports of subjective "high." These data illustrate the

similarities between the behavioral and hormonal effects of cocaine and nicotine (Mendelson *et al.,* 2003; Mendelson *et al.,* 2005).

The hormonal and behavioral effects of nicotine are shown in **Figures 5** and 6. We compared the effects of a high- and a low-nicotine cigarette on hypothalamic-pituitary-adrenal (HPA) hormones, subjective responses and cardiovascular measures in 20 nicotine-dependent men under double-blind conditions. Subjects were abstinent from nicotine after midnight on the study day, and all had baseline CO levels below 4 ppm. Subjects smoked for 12 min using a controlled smoking procedure (24 puffs of 5 sec duration, 25 sec inter-puff interval). Within four puffs (2 min), plasma nicotine levels increased significantly from baseline, and reached peak levels of 23.9 ng/ml within 14 min after smoking a high nicotine cigarette and peak levels of 3.63 ng/ml within 12 min after smoking a low nicotine cigarette. **Figure 5** shows that smoking a high-nicotine cigarette rapidly stimulated significant increases in HPA axis hormones whereas smoking a low-nicotine cigarette either decreased or had no significant effect. Ratings of subjective effects on a Visual Analog Scale (VAS) were also nicotine dose-dependent **(Figure 6)**. Interestingly, VAS ratings of "High," "Rush" and "Liking" were highest at the initiation of smoking when plasma nicotine was increasing rapidly. However, these subjective effects ratings decreased during the 12 min smoking period while plasma nicotine levels continued to increase. VAS ratings of craving for nicotine were high before smoking began and rapidly decreased during smoking while plasma nicotine levels were rising. Decreases in craving were greatest after smoking a high-nicotine cigarette. Although VAS ratings of craving remained significantly below baseline for 30 min or 100 min after smoking a low- or high-nicotine cigarette respectively, craving ratings began to increase within 16 or 18 min. The time course of increases in reports of craving paralleled the decreases in HPA axis hormones. Of particular interest are the smoking-induced changes in DHEA and cortisol in relation to increases in craving. A single cigarette stimulates increases in DHEA two or three times higher than DHEA levels used to treat major and minor depression (Schmidt *et al.,* 2005; Morales *et al.,* 1994). The possible relation between nicotine-induced increases in DHEA and the reinforcing effects of smoking is provocative. It is possible that medications that mimic or attenuate the hormonal effects of cigarette smoking may be useful adjuncts to treatment (Mendelson *et al.,* 2005; Marx *et al.,* 2006; Mendelson *et al.,* 2007). There are recent reports that low cortisol levels may be associated with relapse to smoking (al'Absi *et al.,* 2003; al'Absi *et al.,* 2004). We hypothesized that the rapid changes in anterior pituitary, gonadal and adrenal hormones that accompany acute administration of cocaine and nicotine may contribute to the abuse-related effects of these drugs.

In 1990, we were first to report that the acute administration of cocaine abruptly increased luteinizing hormone levels (LH) in nonhuman primates (Mello *et al.,* 1990b). In parallel clinical studies, we found that acute IV cocaine administration also rapidly increases LH in women and men (Mendelson *et al.,* 2001). The extent to which a rapid increase in LH may be significantly related to cocaine's alleged increases in sexual arousal remains to be determined. We recently discovered that both cocaine and cigarette smoking increase LH and reports of subjective "high" (Mendelson *et al.,* 2003). These rapid endocrine responses further illustrate a biologic similarity between cocaine and cigarette smoking that may have implications for future approaches to treatment.

In preclinical studies in nonhuman primates, we are exploring the interactions between the neuroactive steroid hormones, the reinforcing effects of cocaine and the contribution of sex differences. When reinforcing doses of cocaine were used to maintain behavior, administration of estradiol did not enhance cocaine self-administration by female rhesus monkeys (Mello *et al.,* 2007b). However, in ongoing studies, both progesterone and testosterone reduced cocaine self-administration and shifted the cocaine dose-effect curve to the right (Mello *et al.,* 2007). When we studied the effect of sex on cocaine self-administration maintained on a progressive ratio schedule of reinforcement, females reached significantly higher progressive ratio breakpoints than males across a range of cocaine unit doses (Mello *et al.,* 2007a). These data converge to suggest that analysis of the behavioral effects of neuroactive steroids may be important for our understanding of the neurobiology of stimulant drugs.
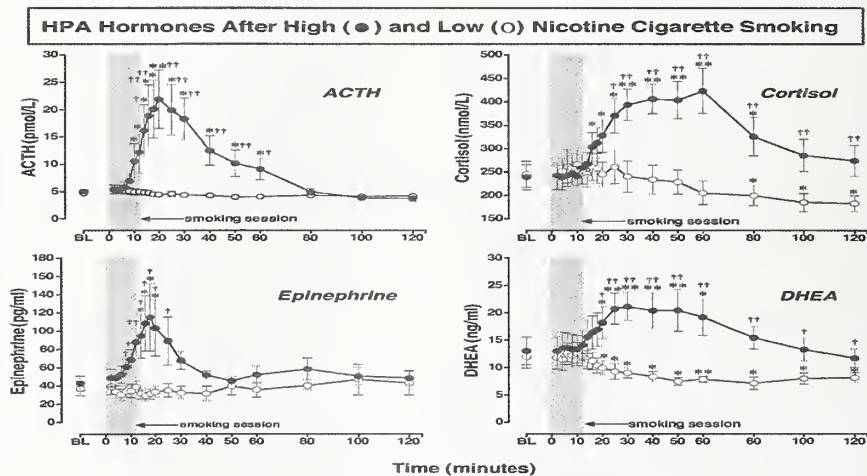
Figure 5: ACTH, Cortisol, DHEA and Epinephrine Levels after Smoking a Low- or High-Nicotine Cigarette. Hormone levels after smoking a high-nicotine cigarette (filled circles) and a low-nicotine cigarette (open circles) are shown on the left ordinates. Time (min) is shown on the abscissae. Points above BL were collected 10 min before cigarette smoking began at time 0. The 12-min cigarette-smoking period is indicated by a grey rectangle. Each data point is the average (± S.E.M.) of 10 subjects. Statistical analyses indicated significant changes from baseline in ACTH levels [df=18, F= 8.8, P=.005], epinephrine levels [df=18, F=3.9, P=.05], DHEA levels [df=18, F=8.7, P=.0006], and cortisol levels [df=18, F=9.0, P=.002] after high dose nicotine. ACTH (pmol/L) and epinephrine (pg/ml) are shown in the left column; cortisol (nmol/L) and DHEA (ng/ml) are shown in the right column. Asterisks indicate points that were significantly different from baseline (* = P< 0.05; ** = P< 0.01). Daggers indicate points at which hormone levels were significantly different after high nicotine cigarette smoking than after low nicotine cigarette smoking († = P< 0.05; †† = P< 0.01); ACTH [df=1, F=7.0, P=.016], Epinephrine [df=1, F=5.8, P=.026], DHEA [df=1, F=4.8, P=.048], and cortisol [df=1, F=5.5, P=.03]. From Mendelson *et al.*, 2005.
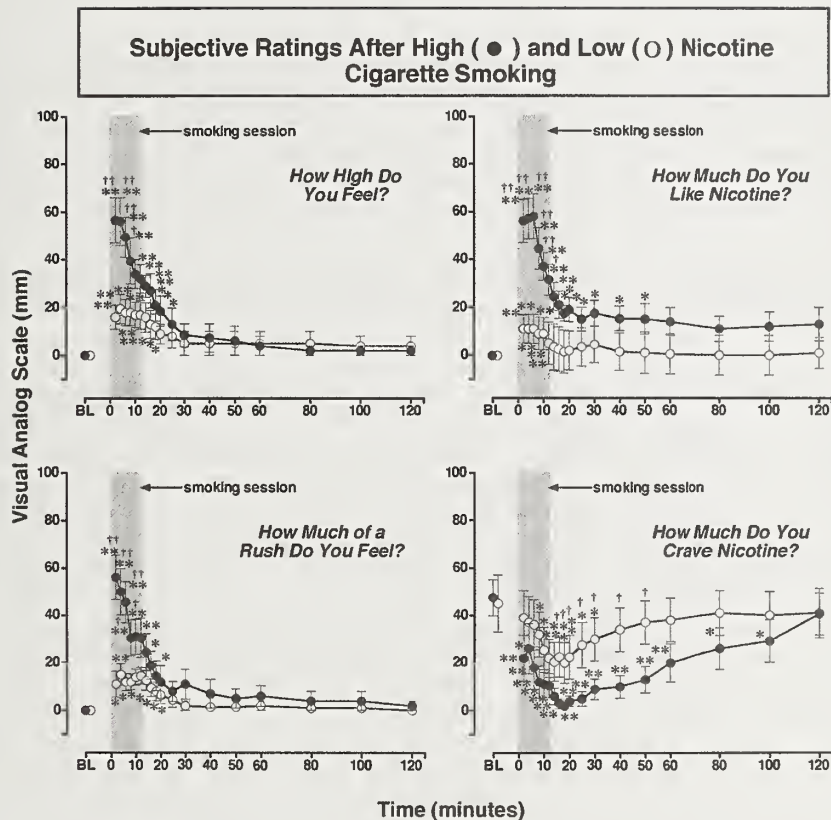
Figure 6: Reports of Subjective Effects After Smoking a Low- or High-Nicotine Cigarette. Subjective ratings on a Visual Analogue Scale (VAS) (0-100) are shown on the left ordinates and time (min) is shown on the abscissae. Points above BL were collected 10 min before smoking began at time 0. Each data point is the average (± S.E.M.) of 10 subjects. The 12 min cigarette smoking period is indicated by a grey rectangle. Asterisks indicate points that were significantly different from baseline (* = P< 0.05; ** = P< 0.01). Statistical analyses indicated significant changes from baseline in reports of "high" after high-nicotine cigarettes [df=18, F=16.9, P<.0001] and low-nicotine cigarettes [df=18, F=5.2, P=.01; reports of "liking" after high-nicotine cigarettes [df=18, F=14.1, P<.0001] and low-nicotine cigarettes [df=18, F=3.9, P=.05]; reports of "rush" after high-nicotine cigarettes [df=18, F=13.2, P<.0001] and low-nicotine cigarettes [df=18,[Mendelson, 2007 #8859] F=5.1, P=.009; and reports of "craving" after high-nicotine cigarettes [df=18, F=8.1, P=.0007] and after low-nicotine cigarettes [df=18, F=5.6, P=.007]. Daggers indicate points that were significantly different after high-nicotine cigarette smoking than after low-nicotine cigarette smoking († = P< 0.05; †† = P<0.01) "high " [df=1, F=4.5 P=.049], "like"[df=1, F=6.2, P=.023], "rush" [df=1, F=6.3, P=.02], and "craving" [df=1, F=5.6, P=.04]. From Mendelson *et al.*, 2005.

Alcohol, cocaine, opioids and nicotine each have many complex effects on the endocrine system. In our early studies of the hormonal effects of chronic drinking in alcohol-dependent men, we found that testosterone levels were depressed to female levels (Mendelson and Mello, 1974a). Cortisol levels and urinary catecholamines were elevated during drinking and usually paralleled increases in blood alcohol levels (Mendelson *et al.*, 1971; Ogata *et al.*, 1971). Increases in cortisol and catecholamines also occurred following chronic alcohol intoxication in men who experienced severe withdrawal signs and symptoms (Mendelson *et al.*, 1971; Ogata *et al.*, 1971). Chronic alcohol intoxication also induced hyperlipidemia and increased levels of beta lipoproteins in alcohol-dependent men (Mendelson and Mello, 1973; Mendelson and Mello, 1974b). This observation highlighted the importance of

familial and genetic factors in the causation of alcohol-induced disorders of lipid metabolism. This study, reported in *Science* (Mendelson and Mello, 1973), also heralded the now widely recognized salient effect of moderate alcohol consumption for stimulating increased production of high-density lipoproteins which may reduce risk for premature coronary artery disease.

It is well established that chronic exposure to abused drugs can disrupt the menstrual cycle in women and compromise fertility, but it is often difficult to determine the relative contribution of malnutrition/other illnesses often associated with chronic substance abuse. In preclinical studies, we were the first to report that a nonhuman primate model of alcoholism developed the same pattern of reproduction dysfunctions often seen in alcohol-dependent women (Mello *et al.*, 1983b). This model made it possible to rule out malnutrition, illness, or alcohol-induced hyperprolactinemia as the determinants of amenorrhea during chronic intoxication. Subsequently, we extended this approach to determine if cocaine or other factors accounted for disruptions of the menstrual cycle often seen in chronic cocaine abusers. We found that chronic cocaine self-administration over 2-3 years produced profound disruptions of the menstrual cycle, including luteal phase dysfunction and prolonged amenorrhea in rhesus females (Mello *et al.*, 1997).

During our inpatient evaluations of naltrexone for opioid abuse treatment, we collected blood samples for analysis of anterior pituitary, adrenal and gonadal hormones (Mello *et al.*, 1981). One unexpected finding from these early studies was that naltrexone increased the amplitude and frequency of the pulsatile release of luteinizing hormone (LH) in men (Mendelson *et al.*, 1980). It was known that a mid-cycle surge in LH was necessary to trigger ovulation, but the critical role of the *frequency* of pulsatile LH release patterns for normal ovulatory menstrual cycles was not appreciated until the seminal studies of Ernst Knobil in the early 1970s (Knobil, 1974; Knobil, 1980). Knobil found that pulsatile administration of synthetic luteinizing-hormone-releasing-hormone (LHRH) restored LH and FSH secretory patterns, whereas continuous administration of synthetic LHRH did not (Knobil, 1974; Knobil, 1980). This fundamental discovery was rapidly translated into clinical practice where it was found that disorders of the menstrual cycle are often characterized by abnormal LH secretory patterns (Crowley *et al.*, 1985; Santoro *et al.*, 1986a; Santoro *et al.*, 1986b). Administration of LHRH at a normal physiologic frequency restored normal menstrual cycle function and fertility in some women (Hammond *et al.*, 1979; Crowley *et al.*, 1985; Santoro *et al.*, 1986a; Santoro *et al.*, 1986b). We later found that administration of the opioid antagonist, naltrexone, also stimulated gonadotropin release in women during the follicular as well as during the luteal phase of the menstrual cycle (Mendelson *et al.*, 1986) see (Mendelson and Mello, 2008 in press). Subsequent clinical studies conducted in Germany have shown that naltrexone is useful for the treatment of infertility, secondary to hypothalamic amenorrhea (Wildt *et al.*, 1981; Lyendecker and Wildt, 1983). These findings were consistent with the well known inhibitory effects of endogenous opioid peptides on the HPG and HPA axis. Exogenous opioid antagonists block endogenous opioid inhibition of HPG and HPA axis hormones, usually resulting in stimulation of hormone release. Thus opioid antagonists have proved useful for treatment of a number of endocrine disorders including infertility, hypothalamic amenorrhea and male impotence (see (Mendelson and Mello, 2008 in press) for review).

(5) Organizational Accomplishments: We founded the Alcohol and Drug Abuse Research Center at McLean Hospital and Harvard Medical School in 1974. The Alcohol and Drug Abuse Research Center conducts multidisciplinary research on the behavioral and biological aspects of substance abuse. This approach is based on the premise that substance abuse reflects a complex interaction between the individual, the abused drugs and society. One goal of this research program is to improve understanding of the multiple determinants of drug abuse and alcoholism, and to develop more effective treatment and prevention programs. A second goal is to evaluate the behavioral and biological consequences of substance abuse and dependence in clinical studies, and in preclinical models of drug abuse. A third goal is to train young scientists in research on the determinants, consequences and treatment of substance abuse in parallel clinical and preclinical studies. Ongoing research involves the disciplines of behavioral science, brain imaging, endocrinology, medicinal chemistry, neurobiology and pharmacology.

The Alcohol and Drug Abuse Research Center consists of four major laboratories, each containing several research programs: (1) The Behavioral Science Laboratory studies preclinical models of substance abuse and dependence, and evaluates the safety and effectiveness of new medications for the treatment of drug abuse and the alleviation of pain as well as the interactions between abused drugs and the neuroendocrine system. The Behavioral Science Laboratory includes four programs; a Behavioral Pharmacology Program, a Behavioral Endocrinology Program, a Neurobiology Program and a Neuroscience Program. (2) The Biological Psychiatry Laboratory studies the

interactions between biological factors and psychiatric and substance abuse disorders. The Biological Psychiatry Laboratory includes a Psychopharmacology Research Program, a Substance Abuse Research Program, a Child and Adolescent Research Program and a Psychiatric Epidemiology Program. (3) The Clinical Research Laboratory examines biological and behavioral aspects of substance abuse in men and women who abuse or are dependent upon drugs, including nicotine, cocaine, opioids and alcohol. The Clinical Research Laboratory includes a Brain Imaging Program, a Neuroendocrinology Program and a Policy Research Program. (4) The Medicinal Chemistry Laboratory focuses on developing new compounds that will be used as molecular tools to modulate the activity of a variety of proteins (receptors) found in the brain and other complex biological systems. The Center's research programs have been continuously funded by competitive research grants and contracts from the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the National Institutes of Health (NIH), as well as by private donors.

(6) Scholarly Contributions and Honors: In addition to our original research contributions, we have also written and edited a number of reviews and texts. We edited three editions of a textbook, *Medical Diagnosis and Treatment of Alcoholism (McGraw Hill)* (Mendelson and Mello, 1979; Mendelson and Mello, 1985b; Mendelson and Mello, 1992) and edited *The Journal of Studies on Alcohol*. We wrote a book entitled *Alcohol, Use and Abuse in America (Little-Brown)* ((Mendelson and Mello, 1985a). I edited a series entitled *Advances in Substance Abuse, Biological and Behavioral Research* (Mello, 1980; Mello, 1982; Mello, 1983) and have recently been selected by the American Psychological Association to edit the journal *Experimental and Clinical Psychopharmacology*. We have been selected to write the chapter on Cocaine and Other Commonly Abused Drugs for *Harrison's Principles of Internal Medicine* since 1982. We also wrote the chapter on "Cocaine, Hormones, and Behavior: Clinical and Preclinical Studies" for the textbook on *Hormones, Brain and Behavior* (Mello and Mendelson, 2002). Jack Mendelson has published 480 scientific papers and reviews, and I have published 391 scientific papers and reviews.

We have shared several awards for our research, including the Jellinek Memorial Award for Research on Alcoholism and the Distinguished Research Award from the Research Society on Alcoholism. I received the Mary Cullen Research Trust Award, the Betty Ford Award from AMERSA, the Marian W. Fischman Memorial Award from CPDD, and the Brady-Schuster Award from Division 28 of the American Psychological Association. Jack received the Hoffheimer Prize from the American Psychiatric Association, the APA Award for Research in Alcoholism, and the Founders Award from AAPAA. We both have received Senior Scientist Awards (K05) from the National Institute on Drug Abuse and, since 1983, we both have been asked to nominate candidates for the Nobel Prize. We were deeply honored to receive the Nathan B. Eddy Award from the College on Problems of Drug Dependence in 2007.

Jack Harold Mendelson, M.D.
August 30, 1929 – August 15, 2007

Jack H. Mendelson, M.D., (77) Professor of Psychiatry (Neuroscience) at the Harvard Medical School, Co-Director of the Alcohol and Drug Abuse Research Center at the McLean Hospital, and beloved husband of Nancy K. Mello, died on August 15, 2007 after a brief illness. He leaves his wife of 33 years, two sons, one daughter, and four grandchildren. After graduation from the University of Maryland Medical School, he interned in Medicine at the Boston City Hospital and completed a residency in Psychiatry at the Massachusetts General Hospital, in Boston.

Dr. Mendelson devoted his research career to studying the behavioral and biological aspects of alcoholism and drug abuse. As Chief of The National Center for Prevention and Control of Alcoholism, National Institute of Mental Health (1966-1970), the first federal program to focus on alcoholism, he effectively promoted the concept that alcoholism is a medical disorder and persuaded leading scientists of the importance of research on this complex biobehavioral disorder. Today, that program has evolved into the National Institute on Alcohol Abuse and Alcoholism, NIH.

In 1970, Dr. Mendelson became Professor of Psychiatry at the Harvard Medical School and Chief of the Department of Psychiatry at the Boston City Hospital. In 1973, Dr. Mendelson and Dr. Mello established the Alcohol and Drug Abuse Research Center at the McLean Hospital in Belmont, MA. Today, this Center includes research programs in behavioral science, pharmacology, medicinal chemistry, neurobiology, neuroscience and neuroimaging.

Dr. Mendelson published over 480 scientific papers and books, and contributed chapters to leading textbooks such as Harrison's Principles of Internal Medicine and Hormones, Brain and Behavior. He edited the Journal on Studies of Alcohol (1984-1991), and was on the Editorial Board of many leading scientific journals in substance abuse and psychiatry. He was awarded the Hofheimer Prize from the American Psychiatric Association (1965), the Jellinek Memorial Award for Research on Alcoholism (1978), a Research Scientist Award from the National Institute on Drug Abuse (1979-2007), the Distinguished Research Award from the Research Society on Alcoholism (1989), the Founders Award from the American Academy of Psychiatrists in Alcoholism and Addictions (1990) and in June of this year, the Nathan B. Eddy Award for distinguished research contributions from the College on Problems of Drug Dependence (2007). Dr. Mendelson served on the nominating committee for the Nobel Prize for Physiology and Medicine since 1982.

Dr. Mendelson is best known for his multidisciplinary clinical research on addiction to alcohol, heroin, cocaine, marijuana, and tobacco. His pioneering studies involved direct observation of the effects of chronic drug and alcohol intoxication and his findings challenged many prevalent beliefs. In inpatient clinical studies of drinking patterns in alcohol-dependent men, he found that contrary to anecdotal reports, chronic alcohol intoxication induced profound depression, dysphoria, and anxiety. Moreover, the prospect of alcohol withdrawal did not appear to control drinking behavior.

In treatment-related research, Dr. Mendelson conducted the first inpatient clinical trials of the effects of the novel opioid mixed agonist-antagonist, buprenorphine, on heroin self-administration by opioid-dependent men. He found that buprenorphine, as well as an opioid antagonist, naltrexone, significantly reduced heroin self-administration in comparison to placebo treatment administered under double-blind conditions. Buprenorphine was more readily accepted by the patients because of its opioid agonist component, and today buprenorphine is a widely used for the outpatient treatment of heroin abuse and dependence.

Dr. Mendelson was fascinated by the interactions between drugs, hormones and behavior. His innovative studies of the neuroendocrine correlates of addiction revealed that the hormonal milieu may influence the abuse-related effects of drugs. Dr. Mendelson's research has directed attention to the importance of studying not only the effects of drugs on the endocrine system, but also the ways in which hormones may enhance or diminish the saliency of drug effects.

In addition to his preeminence as a scientist, scholar and educator, friends will remember him for his warmth and generosity, his ebullient sense of humor, an inexhaustible reservoir of stories and jokes, and perfect delivery. He was also an accomplished photographer, a collector of antique maps and fine wines, an enthusiastic traveler, gardener and cook. He will be greatly missed by all who knew him.

In honor of his scientific legacy, the Jack H. Mendelson Memorial Research Award for advances in understanding the biological and behavioral aspects of substance abuse has been established at McLean Hospital.

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MARIAN W. FISCHMAN LECTURESHIP RECIPIENTS

2007   Dorothy K. Hatsukami

2006   Dr. Linda Dyskstra

2005   Dr. Mary Jeanne Kreek

2004   Dr. Nancy Mello

2003   Dr. Maxine Stitzer

2002   Dr. Chris-Ellyn Johanson

Introduction of Dr. Dorothy K. Hatsukami for the 2007 Marian W. Fischman Lectureship Award

Jack E. Henningfield and Pinney Associates

Bethesda, MD

This is a joyous occasion because it commemorates the truly enduring impact of a pioneer in our field, and a powerful force in the College, Dr. Marian W. Fischman. Marian Fishman was a pioneering scientist, deeply appreciated mentor, inspiring teacher, a leader among leaders, a mother, and a friend to so many. Our memories are mixed with love, respect, and sadness.

But this occasion is joyous because we are here to celebrate and be inspired by another of our colleagues who embodies the spirit of Marian Fischman. Like earlier Lectureship Awardees, Dr. Hatsukami is a pioneer and leader greatly respected and admired in our organization and beyond. Let me remind you of the earlier Awardees:

- Dr. Chris-Ellyn Johanson
- Dr. Maxine Stitzer
- Dr. Nancy Mello
- Dr. Mary Jeanne Kreek
- Dr. Linda Dyskstra

What a powerhouse! What an enormous collective impact on the field, on the organization, and on public health! What a tribute to Marian Fischman! By the way, all of these leaders, like Dr. Fischman, have actively worked to support the recruitment and development of underrepresented populations to CPDD. And there are still more amongst us, yet to be honored in years to come, and more who have not yet joined, have not yet been born who will be honored in years to come.

Let me take just a few minutes to introduce Dr. Hatsukami. You have her biographical details. The problem is that space allowed only the equivalent of a few snowflakes on the tip of the Hatsukami iceberg of achievement. Her achievements include collaborations with Marian Fischman such as their provocative and influential 1996 JAMA review comparing powder and crack forms of cocaine which argued that the criminal sentencing disparities were not supported by the science.

Her impact is global. For example, her opinions aided the implementation of the first international treaty negotiated by the World Health Organization: The Tobacco Treaty or Framework Convention on Tobacco Control. But what is amazing is that her global impact involves so many efforts in such a diverse array of scientific domains: cocaine, tobacco, treatment, abuse liability testing, drug abuse prevention, psychometric scale development, and so much more.

But then such biographical facts are easily available to you so I thought I would do a bit of investigative reporting.

I remember being introduced to Dorothy at the University of Minnesota, I believe with both Roy Pickens and John Hughes claiming mentorship rights. Of course she was only about 9 years old then, but already identified as an emerging leader.

As I discovered, many others, like me, make the time to serve on efforts organized or led by Dorothy because we know she will lead us to the highest level of excellence, that it will be led and run well, and that we will experience the warmth and dignity that she exudes.

Some of Roy Pickens's favorite memories reflected his own sense of humor, which tested Dorothy's cool demeanor. While she was still a graduate student she was about to give her first formal presentation: It was on alcoholism treatment and the audience included representatives from Iceland. Just before the presentation, Roy told Dorothy that Iceland's Science Minister would be present. She managed to get over her shock and gave a brilliant lecture. Roy Pickens wrote: "Dorothy is one of my beloved people and was a graduate student anyone would be proud to

claim." His only concern was that she might yet try to get even with him for his numerous humorous tests of her character.

John Hughes dispelled any notion that Dorothy's deferential style reflected insecurity. As he put it, and I quote: "Actually it was more me under Dorothy's wing than the other way around". He said she reminds him of the Rodin "Thinker" sculpture because of the way she would ponder and consider what she heard, and then challenge the idea in a thoughtful way that he felt was a characteristic she shared with Marian Fischman."

One of her supporters for this award, and a Marian Fischman awardee herself, wrote with passion that she felt honored to know Dorothy and to write on her behalf. She commented on the enormous range of Dr. Hatsukami's accomplishments and had great accolades for Dorothy's leadership. Let me read from this letter of support: "Despite her quiet demeanor, Dr. Hatsukami is a very strong and determined leader but she leads by building consensus and always behaves with humility, civility and integrity.

Equally insightful were the accolades from Dorothy's mentees and staff. Dr. Dace Svikis is one of the many who are proud to call Dorothy her mentor and who was deeply appreciative of Dorothy's patience and generosity with her time and nurturing. Dace also commented on Dorothy's being highly tuned to how other people feel and her ability to put them at ease and catalyze their development and contributions.

Such accolades were similar from her staff. People such as Kathy Longley, are proud and appreciative of the opportunities. Amazingly, even under times of severe stress such as working round the clock to make a major grant application deadline. In such times, she leads with strength and clarity, setting high standards of excellence but never demanding more from staff than from herself – even, by the way, during times that are so stressful than she might come to the office wearing shoes that were not from the same pair. Her staff also recounted one of Dorothy's many secrets to excellence and creativity: She said that in staff meetings Dr. Hatsukami makes sure that every voice and opinion is welcomed, treated with respect, and given consideration, no matter how outlandish or naïve, and regardless of the person's official status. This is the mark of a true and effective and respected leader.

Finally, I would be remiss if I did not comment on Dorothy's ability to do all of this while raising two boys – now off to college. As her staff recounted, she always emphasized the importance of family first in policy and deed.

Well there is so much more to tell about this most remarkable person, leader in science and policy, wife and mother of two sons, and friend and colleague to so many of us. But I think I have given you a sense of why so many of us feel her award will honor Marian Fischman. Dorothy Hatsukami embodies Marian Fischman's own spirit and legacy.

It is a privilege to know, collaborate, and be led by Dorothy and it is an honor for me to have this opportunity to thank her on behalf of all of us.

Newsflash from Roy Pickens: He says that the Prime Minister of Canada is in the audience to hear what Dr. Hatsukami has to say.

AN OVERVIEW OF THE STUDIES PERFORMED BY THE DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2007)

Andrew Coop

DEPARTMENT OF PHARMACEUTICAL SCIENCES, UNIVERSITY OF MARYLAND SCHOOL OF PHARMACY, BALTIMORE, MD

THE DRUG EVALUATION COMMITTEE

The Drug Evaluation Committee (DEC) evaluates compounds for preclinical physical dependence potential and abuse liability as a public health service. DEC works with researchers from academia, industry, and also governmental organizations (FDA, DEA, NIDA, WHO) to characterize the pharmacological profile of compounds in order to facilitate decisions on matters ranging from medication development to drug scheduling. The Biological Coordinator of DEC (Dr. A. Coop) receives samples for evaluation and distributes 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/DEC_ARCHIVES/dec.pdf) which contains archived DEC annual reports and the DEC indices (http://www.pharmacy.umaryland.edu/faculty/acoop/dec%20folder/DEC%20indices2003web.xls), a list of all compounds evaluated by DEC and reference to their year of publication and links to original data in the on-line DEC annual reports. The other members of DEC are in the two analgesic testing groups, at Virginia Commonwealth University (VCU, Drs. L. Harris, M. Aceto, P. Beardsley) and the University of Michigan (UM, Drs. J. Woods [DEC Chair], J. Traynor, H. Ko), and four 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), University of Michigan (UM, Drs. G. Winger, J. Woods), and Yerkes National Primate Research Center, Emory University (Dr. W. Fantegrossi). Drs. T. Cicero and A. Jacobson are emeritus members.

DEC reports to the CPDD Committee on Abuse Liability Testing (CALT; formerly the DEC Liaison Committee; Dr. S. Negus, Chair). Members of both the 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 Richmond in May 2007 to discuss the work which has been accomplished and future plans for DEC. Separate meetings have been held at VCU 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. McCann), to discuss the results obtained from the VCU testing and research program.

This report provides an overview of the results obtained by all groups within DEC; precise values and details of the procedures are given in the VCU and UM reports (Aceto *et al.*, 2008; Traynor and Woods, 2008). 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 84 compounds evaluated by the Analgesic Testing Program (Figure 1). This figure remains high by historical standards. Of these 83 compounds, 59 were evaluated at VCU (antinociceptive assays in mice: tail-flick, hot-plate, and phenylquinone anti-writhing, and the tail-flick antagonist assay; as well as substitution for morphine and precipitated withdrawal assays in rhesus monkeys and rats), and 74 at UM (warm water tail withdrawal in rhesus monkeys, binding affinity to the μ, δ, and κ opioid receptors, and GTPγS functional studies). Compounds were submitted primarily from academia, but a significant number of compounds (25%) came from industrial submitters this year. Two compounds were also released from the Stimulant/Depressant program this year and evaluated for amphetamine, benzodiazepine, and PCP discriminative stimulus effects and also self-administration effects in cocaine-maintained monkeys. The two programs give a total of 85 releases. Three publications based on the data gathered under DEC auspices were published since the last annual report (Li *et al.*, 2007, Cheng *et al.*, 2007, Aceto *et al.*, 2007)

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 13. As in previous years (Coop, 2007), the compounds are classified according to their molecular structure: 4,5-epoxymorphinans in Table 2; Prodrugs of oxycodone in Table 3; 6,7-benzomorphans in Tables 4-7; analogs of potent opioids in Table 8; analogs of oxymorphindole in Table 9; peptides in Table 10; small molecules in Table 11; compounds with miscellaneous structures in Table 12. Compounds evaluated by the stimulant/depressant group are shown in Table 13. Numerous interesting compounds were released this year, and they 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 (1998-2007)
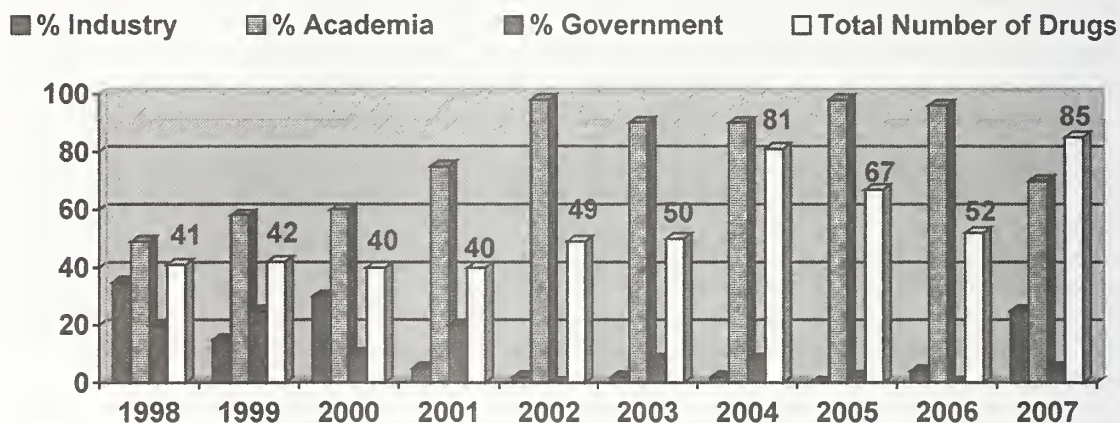
As reported previously (Coop, 2005, 2006), the 14-phenylpropyloxy morphinans represent a unique class of opioids with extraordinary potency as antinociceptive agents (10,000 x morphine), and high affinity for all three opioid receptors (Greiner *et al*., 2003, Spetea *et al*., 2004). One member of this class, **NIH 11121** (Table 2) was evaluated for its efficacy at mu and delta receptors, and shown to be an extremely potent full mu agonist, and a potent delta partial agonist. This is consistent with previous animal assays where antinociceptive effects of NIH 11121 were reversed by the mu antagonist β–FNA, but not the delta antagonist NTI.

NIH 11333, NIH 11334, and **NIH 11335** (Table 2) are analogs of morphine lacking hydroxyl groups. As anticipated, NIH 11334 containing a 3-hydroxyl group had the greatest affinity for opioid receptors, but it was interesting that losing the 6-hydroxyl between NIH 11333 and 11335 led to an increase in opioid receptor affinity.

NIH 11227 (Table 3), a peptidic prodrug of hydrocodone, displayed only modest antinociceptive activity in mice, and was inactive in the 50°C warm water tail withdrawal assay in monkeys, indicating that the putative active metabolite, hydrocodone, may not be forming. Table 3 contains numerous peptidic prodrugs of oxycodone. As a class, these compounds have low affinity at opioid receptors and very weak partial agonist activity in GTPγS functional assays. An interesting compound in this series is NIH 11243, which displays modest delta affinity and selectivity. Unfortunately, GTPγS assays indicate the compound to be a very weak partial delta agonist.

Table 4 contains (-)-N-alkyl benzomorphans which contain oxygen functions as a continuation of our previous studies to determine the effects of N-substituents in this series (May *et al*., 2003; May *et al*., 1998). Interestingly, a separation of activities in vitro and in vivo was observed with **NIH 11210**, where high affinity at mu receptors does not translate to activity in neither mice nor monkeys. The *N*-ethoxyethyl analog **(NIH 11288)** shows high affinity at mu and kappa opioid receptors, a corresponding antinociceptive activity in mice, and fully substitutes for morphine in monkeys. Thus, NIH 11288 has properties typical of a mu agonist. Adding a hydroxyl group to the terminal carbon on the N-substituent of NIH 11288 gives **NIH 11347**, and a great decrease in affinity at opioid

receptors. Reducing the size of the N-substituent of NIH 11288 by one carbon gives methoxyethyl analog **NIH 11352** which has very high affinity for all three opioid receptors. This indicates that alkoxyethyl N-substituents are well tolerated in the benzomorphan series, and should receive study in other opioid classes for the preparation of high affinity ligands. Benzomorphans in Table 4 with ketone groups as part of the N-substituent were generally less well tolerated, yielding low affinity ligands at opioid receptors. The corresponding (+)-benzomorphans are shown in Table 5 and are, as anticipated, generally less active as opioids. The exception being the *N*-ethoxyethyl analog **NIH 11287** which has a high affinity and selectivity for mu opioid receptors (mu K_i = 2 nM, kappa/mu=100). Interestingly, NIH 11287 has no antinociceptive nor morphine antagonist activity in mice, indicating additional separation of activities in this series.

NIH 11116 (Table 8) was previously reported to be an antinociceptive agent and also delta opioid selective. Studies were performed to determine the origin of the antinociceptive activity to determine if the compound was displaying delta-opioid mediated antinociception. This was shown not to be the case with GTPγS assays, as NIH 11116 is a full agonist at mu receptors and has low efficacy (37% stimulation) at delta receptors. This is consistent with in vivo data showing that NTI did not reverse the antinociception of NIH 11116. 4-phenolic morphinans are generally of low opioid activity, yet **NIH 11221-11223** (Table 8) with an additional long alkyl group at position 7 shows good opioid binding affinity, although this does not translate to antinociceptive activity in mice. Thienorphine (**NIH 11310**, Table 8) was reported to display a profile of mu agonism, but this did not appear consistent with previous SAR patterns (Li *et al*., 2007). GTPgS functional assays showed that NIH 11310 is actually a kappa agonist/mu antagonist, and any antinociceptive activity of NIH 11310 is almost certainly mediated through kappa opioid receptors.

Oxymorphindole (**NIH 11319**, Table 9) is a selective delta opioid. Studies into the effect of halogen substitution on the indole ring led to the finding that **NIH 11318** (dichloro) possesses similar affinity for mu and delta receptors and acts as an antinociceptive agent. This is an excellent lead for the development of mu agonist/delta antagonist ligands which have the potential to yield analgesic agents to which tolerance does not develop (Ananthan, 2006). The peptides in Table 10 were evaluated for opioid activity and were shown to be generally lacking in such activity.

NIH 11296 (Table 11) is an analog of meperidine in which the nitrogen has been replaced by an oxygen. The lack of opioid activity suggests that the basic nitrogen is essential for opioid activity in this series. The other small amines shown in Table 11 all possess no significant opioid activity, and important finding for their development into medications acting selectively at neurotransmitters.

NIH 11211 (Table 12) is an analog of the delta selective agonist SNC80, and was shown to be inactive in animal antinociceptive assays. The phenylmorphans, **NIH 11289** and **NIH 11290** (Table 12) are potent antinociceptive agents in mice, and their substitution for morphine in monkeys strongly suggests the activity occurs through mu opioid receptors. These two compounds are representative examples from an extremely interesting series of high efficacy mu agonists (Cheng *et al*., 2007).

Salvinorin A (**NIH 11228**, Table 12) has been reported as a naturally occurring non-nitrogenous kappa opioid agonist with hallucinogenic activity (Harding *et al*., 2005). These studies confirm the selectivity for kappa opioid receptors and antinociceptive activity in mice. Salvinorin A was also evaluated by the Stimulant/Depressant group as **CPDD 0070** (Table 13). CPDD0070 was not recognized as PCP, amphetamine, nor benzodiazepines in discriminative stimulus assays. The amphetamine prodrug, **CPDD 0069** (Table 13) was recognized in amphetamine discriminative stimulus assays and was self-administered in cocaine-maintained monkeys. This compound would be predicted to possess stimulant-like properties in humans.

TABLE 1. EVALUATED COMPOUNDS

NIH#	COMPOUND NAME	TABLE #- Evaluator
	ANALGESIC TESTING PROGRAM	
11107	Oxycodone.HCl	3-UM
11116	4,5α-epoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]indolo[2',3':6,7]morphinan-3-ol	8-UM
11121	4,5α-epoxy-3-hydroxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one.HBr	2-UM
11199	Acetyl-Arg-Phe(4-COOH)-Tyr-Arg-Trp-Arg-NH$_2$	10-VCU/UM
11200	Acetyl-Arg-Phe(4-F)-Tyr-Arg-Trp-Arg-NH$_2$	10-VCU/UM
11201	Acetyl-Arg-Phe(4-OCH$_3$)-Tyr-Arg-Trp-Arg-NH$_2$	10-VCU/UM
11202	Acetyl-Arg-Phe(4-CN)-Tyr-Arg-Trp-Arg-NH$_2$	10-VCU/UM
11203	Acetyl-Arg-Tyr-Tyr-Arg-Trp(5-CN)-Arg-NH$_2$	10-VCU/UM
11204	Acetyl-Arg-Tyr-Phe(4-F)-Arg-Trp-Arg-NH$_2$	10-VCU/UM
11205	Acetyl-Arg-Tyr-Phe(4-NHAc)-Arg-Trp-Arg-NH$_2$	10-VCU/UM
11206	Acetyl-Arg-Tyr(3-Cl)-Tyr-Arg-Trp-Arg-NH$_2$	10-VCU/UM
11207	Acetyl-Arg-Tyr-Phe(4-benzyl)-Arg-Trp-Arg-NH$_2$	10-VCU/UM
11208	Heptanoyl-Arg-Tyr-Phe-Arg-Trp-Arg-NH$_2$	10-VCU/UM
11209	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl	5-VCU/UM
11210	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl	4-VCU/UM
11211	9(8-Azabicyclo[3.2.1]oct-3-ylidene)-15,5R-9H-xanthene-3-carboxylic acid diethylamide.HCl	12-VCU/UM
11213	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-2-butenyl)-6,7-benzomorphan.oxalate	6-UM
11221	5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(4-phenylbutyl)morphinan-6-carbonitrile	8-VCU/UM
11222	5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(5-phenylpentyl)morphinan-6-carbonitrile	8-VCU/UM
11223	5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(6-phenylhexyl)morphinan-6-carbonitrile	8-VCU/UM
11224	7β-Benzyl-5,6-didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-morphinan-6-carbonitrile	8-VCU/UM
11225	6,7-Didehydro-4,5-epoxy-6-idimazolyl-3-methoxy-17-methyl-14-(3-phenylpropyloxy)morphinan	8-VCU/UM
11226	4-Cinnamyloxy-5,6,7,8-tetradehydro-14β-hydroxy-3-methoxy-17-methyl-morphinan-6-carbonitrile	8-VCU/UM
11227	Tyr-Tyr-Phe-Phe-Ile-(6-O)-hydrocodone.HCl	3-VCU/UM
11228	Salvinorin A	12-VCU

TABLE 1. EVALUATED COMPOUNDS (continued)

NIH#	COMPOUND NAME	TABLE #- Evaluator
	ANALGESIC TESTING PROGRAM	
11238	Oxycodone-enol ether prodrug. .2Trifluroacetate	3-UM
11239	Oxycodone-enol ether prodrug. .2Trifluroacetate	3-UM
11240	Oxycodone-enol ether prodrug. .2Trifluroacetate	3-UM
11241	Oxycodone-enol ether prodrug. .2Trifluroacetate	3-UM
11242	Oxycodone-enol ether prodrug. .2Trifluroacetate	3-UM
11243	Oxycodone-enol ether/valine prodrug. .Trifluroacetate	3-UM
11244	6-O-(2,2,2-trimethylacetyl)oxycodone-enol ether. HCl	3-UM
11245	Oxycodone-enol ether prodrug. .Trifluroacetate	3-UM
11285	(+)-(1S,5S,9S)- 2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	7-VCU
11286	(-)-(1R,5R,9R)- 2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	6-VCU
11287	(+)-(1S,5S,9S)- 2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.Oxalate	5-VCU
11288	(-)-(1R,5R,9R)- 2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.Oxalate	4-VCU
11289	(1R,5R,9R)-5-(3-Hydroxyphenyl)-2-phenethyl-2-aza-bicyclo[3.3.1]nonan-9-ol.HCl	12-VCU
11290	(1R,5R)-3-(9-Methylene-2-phenethyl-2-aza-bicyclo[3.3.1]nonan-5-yl.]-phenol.Oxalate	12-VCU
11292	4-Phenyltetrahydro-2H-pyran-4-ol	11-VCU/UM
11293	N,N-Dimethyl-2-(3-phenylpropoxy)ethylamine	11-VCU/UM
11294	1-(2-[3-phenylpropoxy]ethyl)pyrrolidine	11-UM
11296	4-Phenyltetrahydro-2H-pyran-4-yl propionate	11-VCU/UM
11304	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-oxopropyl)-6,7-benzomorphan.HCl	5-VCU/UM
11305	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-oxopropyl)-6,7-benzomorphan.HCl	4-VCU/UM
11306	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(5-oxohexyl)-6,7-benzomorphan.HCl	5-VCU/UM
11307	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(5-oxohexyl)-6,7-benzomorphan.HCl	4-VCU/UM
11308	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-oxobutyl)-6,7-benzomorphan.HCl	5-VCU/UM
11309	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-oxobutyl)-6,7-benzomorphan.HCl	4-VCU/UM
11310	Thienorphine.HCl	8-UM

TABLE 1. EVALUATED COMPOUNDS (continued)

	COMPOUND NAME	TABLE #-Evaluator
NIH#	**ANALGESIC TESTING PROGRAM**	
11312	5'-Fluorooxymorphindole.HCl	9-VCU/UM
11313	5'-Chlorooxymorphindole.HCl	9-VCU/UM
11314	5'-Brorooxymorphindole.HCl	9-VCU/UM
11315	5'-Iodooxymorphindole.HCl	9-VCU/UM
11316	7'-Fluorooxymorphindole.HCl	9-VCU/UM
11317	5',7'-Difluorooxymorphindole.HCl	9-VCU/UM
11318	5',7'-Dichlorooxymorphindole.HCl	9-VCU/UM
11319	Oxymorphindole.HCl	9-VCU/UM
11320	7α-(o-Methylcinnamoylaminomethyl)-6,14-endoethanotetrahydrooripavine.HCl	8-VCU
11321	7α-(p-Methylcinnamoylaminomethyl)-6,14-endoethanotetrahydrooripavine.HCl	8-VCU
11322	6β-o-Nitrocinnamoylnaltrexamine.Oxalate	8-VCU
11323	(+)-(1S,5S,9S)-5,9-Dimethyl-2-(5-hexynyl)-2'-hydroxy-6,7-benzomorphan	7-VCU/UM
11324	(-)-(1R,5R,9R)-5,9-Dimethyl-2-(5-hexynyl)-2'-hydroxy-6,7-benzomorphan.	6-VCU/UM
11325	(-)-(1R,5R,9R)-5,9-Dimethyl-2-(5-cyanopentyl)-2'-hydroxy-6,7-benzomorphan.	6-VCU/UM
11326	(+)-(1S,5S,9S)-5,9-Dimethyl-2-(5-cyanopentyl)-2'-hydroxy-6,7-benzomorphan.	7-VCU/UM
11327	N-(4-Phenylbutyl)-4-phenylpiperidine-4-nitrile. Oxalate	11-UM
11328	N-(Benzyl)-4-phenylpiperidine-4-nitrile. Oxalate	11-UM
11329	N-Allyl-4-phenylpiperidine-4-nitrile. HCl	11-UM
11330	N-Crotyl-4-phenylpiperidine-4-nitrile. HCl	11-UM
11331	N-(2-Methylallyl)-4-phenylpiperidine-4-nitrile. HCl	11-UM
11332	N-Methyl-4-phenylpiperidine-4-nitrile. HCl	11-UM
11333	3-Desoxy-7,8-dihydromorphine.Oxalate	2-UM
11334	6-Desoxymorphine.Oxalate	2-VCU/UM
11335	3,6-Didesoxydihydromorphine.HCl	2-UM

TABLE 1. EVALUATED COMPOUNDS (continued)

NIH#	COMPOUND NAME	TABLE #-Evaluator
	ANALGESIC TESTING PROGRAM	
11345	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-oxo-3,3-dimethylbutyl)-6,7-benzomorphan.Oxalate	4-VCU/UM
11346	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-oxo-3,3-dimethylbutyl)-6,7-benzomorphan.HBr	5-VCU/UM
11347	(-)-(1R,5R,9R)-5,9-Dimethyl-2-(2-(2-hydroxyethoxy)ethyl)-2'-hydroxy-6,7-benzomorphan.HCl	4-VCU/UM
11348	(+)-(1S,5S,9S)-5,9-Dimethyl-2-(2-(2-hydroxyethoxy)ethyl)-2'-hydroxy-6,7-benzomorphan.HCl	5-VCU/UM
11349	(-)-(1R,5R,9R)-2-(3-Cyanopropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6-VCU/UM
11350	(+)-(1S,5S,9S)-2-(3-Cyanopropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11351	(+)-(1R,5R,9R)-2-(2-Methoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-VCU/UM
11352	(-)-(1S,5S,9S)-2-(2-Methoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	4-UM
11353	3-Isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine	12-VCU/UM
CPDD#	**Stimulant/Depressant Program**	
0069	(2S,2'S)-2,6-Diamine-N-(1-phenylpropan-2-yl)hexanamide.dimesylate	13-SD
0070	Salvinorin A	13-SD

NOTES FOR TABLES 2 - 10

Salt forms are shown. Rounded numbers are used (2 significant figures); precise values and details of the procedures are given in the VCU and UM reports (Aceto *et al.*, 2008; Traynor and Woods, 2008). "Inactive" is stated when an ED_{50} or AD_{50} is not obtained at 30 mg/kg. NTI = naltrindole (delta antagonist); norBNI = norbinaltorphimine (kappa antagonist); β–FNA = β-funaltrexamine (mu antagonist administered i.c.v as μg/brain).

1) Antinociceptive reference data:

Morphine ED_{50} (mg/kg): Hot Plate = 0.8; Phenylquinone ant writhing = 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. 4.5-EPOXYMORPHINANS

NIH 11121   NIH 11333   NIH 11334   NIH 11335

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) and GTPγS (EC$_{50}$, nM and % stimulation)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11121	0.0001[a]	0.00016[a]	0.00008[a] Naltrexone vs. ED$_{80}$: AD$_{50}$=0.05 βFNA vs. ED80: AD50=3.59. NTI and norBNI: inactive[a]	Inactive[a]	μ=0.02, δ=0.55, κ=0.09[a] New data: GTPγS: μ EC$_{50}$=0.06 nM, 104% stimulation δ EC$_{50}$=2.6 nM, 52% stimulation	Substitution for morphine at 0.04[a]
11333	-	-	-	-	μ=120, δ=4900, κ=5300	-
11334	0.33	0.03	0.2	Inactive	μ=2.9, δ=46, κ=12	-
11335	-	-	-	-	μ=23, δ=590, κ=240	-

a) Previously reported (Coop, 2005)

TABLE 3. PRODRUGS OF OXYCODONE

NIH 11107

NIH 11227

NIH 11239

NIH 11238

NIH 11240

NIH 11241

NIH 11242

NIH 11243

NIH 11244

NIH 11245

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) and GTPγS (EC$_{50}$, nM and % stimulation)	Studies in Monkeys (s.c., mg/kg)
	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
11107	1.4[a]	0.38[a]	0.94[a]	Inactive[a]	[b]μ=210,δ, κ>10,000 (Phosphate buffer) GTPγS: μ EC$_{50}$=850 nM, 97% stimulation	Complete substitution for morphine at 0.75[a]

11227	Inactive	3.4	Inactive	Inactive	μ=52, δ=80, κ=350	Neither attenuated nor precipitated withdrawal in morphine dependant monkeys at 1,10 Inactive in 50°C warm water ta withdrawal assay at 10
11238	-	-	-	-	μ=460, δ=7400, κ=7100 GTPγS: μ 12% stimulation	-
11239	-	-	-	-	μ=440, δ=6500, κ=7800 GTPγS: μ <5% stimulation	-
11240	-	-	-	-	μ=510, δ=7500, κ=6400 GTPγS: μ <5% stimulation	-
11241	-	-	-	-	μ=380, δ=5500, κ>10,000 GTPγS: μ <5% stimulation	-
11242					μ=1300, δ=1100, κ=6800	
11243					μ=170, δ=26, κ=4300 GTPγS: μ <10% stimulation; δ EC$_{50}$=1600 nM, 38% stimulation	
11244					μ=52, δ=160, κ=7900 GTPγS: μ EC$_{50}$=1800 nM, 56% stimulation; δ EC$_{50}$=2900 nM, 30% stimulation	
11245					μ=240, δ=190, κ=1700 GTPγS: μ <10% stimulation; δ 17% stimulation	

a) Previously published (Coop, 2003)

b)   New data

TABLE 4. (-)-N-OXO- AND HYDROXY-ALKYL BENZOMORPHANS

N-Substituent (N-R)

NIH 11210   NIH 11288   NIH 11352   NIH 11347

NIH 11307   NIH 11305   NIH 11309   NIH 11345

	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)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11210	Inactive	6.3	Inactive	Inactive	μ=6.3, δ=43, κ=44	Neither substituted for morphine nor exacerbated withdrawal at 10
11288	0.3	0.18	0.86	Inactive	μ=1.2, δ=30, κ=2.0[a]	Substitution for morphine at 3. Slowing and Salivation noted
11305	Inactive	8.0	Inactive	1.3	μ=77, δ=890, κ=120	Precipitated withdrawal at 1.5 and 6
11307	Inactive	13	Inactive	Inactive	μ=21, δ=370, κ=140	-
11309	Inactive	Inactive	Inactive	5.3	μ=72, δ=850, κ=71	Neither substituted for morphine nor exacerbated withdrawal at 10
11345	Inactive	7.9	Inactive	Inactive	μ=300, δ=2100, κ=200	-
11347	Inactive	Inactive	Inactive	Inactive	μ=230, δ=1100, κ=64	-
11352	-	-	-	-	μ=0.32, δ=2.1, κ=0.24	-

a) Previously reported (Coop, 2007)

TABLE 5. (+)-N-ALKYL-BENZOMORPHANS

N-Substituent (N-R)

NIH 11209

NIH 11287

NIH 11351

NIH 11348

NIH 11306

NIH 11304

NIH 11308

NIH 11346

	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)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11209	Inactive	13	Inactive	Inactive	μ=70, δ=3200, κ=300	Neither attenuated nor exacerbated withdrawal at 2 and 8
11287	Inactive	Inactive	Inactive	Inactive	μ=2.1 δ=2600, κ=220[a]	-
11304	Inactive	3.4	Inactive	Inactive	μ=6300, δ,κ>10,000	-
11306	Inactive	Inactive	Inactive	Inactive	μ=3400, δ>10,000, κ=5100	-
11308	Inactive	Inactive	Inactive	Inactive	μ,δ>10,000, κ=9500	-
11346	Inactive	Inactive	Inactive	Inactive	μ,δ>10,000, κ=4900	-
11348	Inactive	Inactive	Inactive	Inactive	μ=1200, δ>10,000, κ=580	-
11351	Inactive	2.6	Inactive	Inactive	μ=250, δ=1800, κ=120	-

a) Previously reported (Coop, 2007)

TABLE 6. (-)-N-ALKYL-BENZOMORPHANS

N-Substituent (N-R)

NIH 11213   NIH 11324   NIH 11349   NIH 11325   NIH 11286

	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) and GTPγS (% stimulation and EC$_{50}$, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11213	Inactive[a]	1.2[a]	Inactive[a]	Inactive[a]	μ=6.8, δ=120, κ=8.1[a] New data: GTPγS: μ 4% stimulation; δ 9% stimulation	-
11286	Inactive	Inactive	Inactive	Inactive	μ=9.4, δ=39, κ=77[a]	-
11324	1.5	0.76	4.6	Inactive	μ=4.3, δ=55, κ=7.5	Attenuated withdrawal at 2.5
11325	Inactive	2.8	8.7	Inactive	μ=17, δ=210, κ=8.1	Attenuated withdrawal at 2.5
11349	5.1	0.14	0.3	Inactive	μ=3.1, δ=9.9, κ=0.32	-

a) Previously reported (Coop, 2007)

TABLE 7. (+)-N-ALKYL-BENZOMORPHANS

N-Substituent (N-R)

NIH 11323   NIH 11350   NIH 11326   NIH 11285

	MOUSE ANTINOCICEPTIVE ASSAYS			*IN VITRO*
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)
11285	Inactive	Inactive	Inactive	Inactive	μ=380, δ=3100, κ=530[a]
11323	Inactive	15	Inactive	Inactive	μ=630, δ>10,000, κ=240
11326	Inactive	Inactive	Inactive	Inactive	μ=2200, δ>10,000, κ=300
11350	Inactive	Inactive	Inactive	Inactive	μ=1900, δ=7100, κ=180

a) Previously reported (Coop, 2007)

TABLE 8. ANALOGS OF POTENT OPIOIDS

NIH 11116

NIH 11221 n=1
NIH 11222 n=2
NIH 11223 n=3

NIH 11224

NIH 11225

NIH 11226

NIH 11310

NIH 11320 R=Me
NIH 11322 R=NO$_2$

NIH 11321

| NIH # | MOUSE ANTINOCICEPTIVE ASSAYS | | | | *IN VITRO* |
	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) and GTPγS (% stimulation and EC$_{50}$, nM)
11116	8.8[a]	6.5[a]	10[a] NTI vs. ED$_{80}$: Inactive[a]	Inactive[a]	μ=80, δ=3.3, κ=76[a] New data: GTPγS: μ EC$_{50}$=230 nM, 86% stimulation; δ EC$_{50}$=3.5 nM, 37% stimulation
11221	Inactive	4.0	Inactive	Inactive	μ=7.0, δ=120, κ=1500
11222	Inactive	3.0	Inactive	Inactive	μ=0.63, δ=78, κ=510
11223	Inactive	Inactive	Inactive	Inactive	μ=0.32, δ=140, κ=570
11224	Inactive	Inactive	Inactive	Inactive	μ=1500, δ=87, κ=2000
11225	2.7	0.66	Inactive	Inactive	μ=0.96, δ=1.3, κ=0.42
11226	Inactive	2.8	12	Inactive	μ=0.83, δ=460, κ=1200
11310					μ=0.22, δ=0.69, κ=0.14 GTPγS: μ EC$_{50}$=1.9 nM, 19% stimulation; δ no stimulation κ EC$_{50}$=0.3 nM, 75% stimulation
11320	1.0	0.63	1.8	Inactive	–
11321	2.3	2.7	6.4	Inactive	–
11322	-	19	-	-	–

a) Previously reported (Coop, 2006)

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TABLE 9. ANALOGS OF OXYMORPHINDOLE
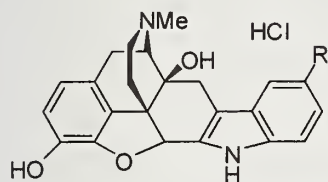
NIH 11312 R=F
NIH 11313 R=Cl
NIH 11314 R=Br
NIH 11315 R=I
NIH 11319 R=H
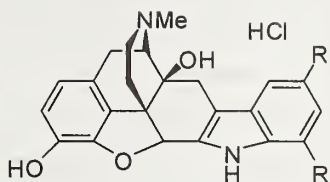
NIH 11316 R=H, R'=F
NIH 11317 R=F, R'=F
NIH 11318 R=Cl, R'=Cl

	MOUSE ANTINOCICEPTIVE ASSAYS				IN VITRO
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) and GTPγS (% stimulation and EC$_{50}$, nM)
11312	Inactive	Inactive	Inactive	Inactive	μ=21, δ=2.3, κ=310 GTPγS: μ EC50=1100 nM 24% stimulation δ EC50=16 nM 16% stimulation
11313	Inactive	Inactive	Inactive	Inactive	μ=47, δ=5.1, κ=360
11314	Inactive	Inactive	Inactive	Inactive	μ=71, δ=8.6, κ=250
11315	Inactive	Inactive	Inactive	Inactive	μ=66, δ=3.8, κ=160
11316	Inactive	Inactive	Inactive	Inactive	μ=65, δ=0.5, κ=270
11317	Inactive	Inactive	Inactive	Inactive	μ=59, δ=1.1, κ=210
11318	Inactive	2.4	Inactive	Inactive	μ=29, δ=6.7, κ=380
11319	Inactive	Inactive	Inactive	Inactive	μ=110, δ=0.9, κ=520

TABLE 10. PEPTIDES

NIH 11199:	Acetyl-Arg-Phe(4-COOH)-Tyr-Arg-Trp-Arg-NH$_2$
NIH 11200:	Acetyl-Arg-Phe(4-F)-Tyr-Arg-Trp-Arg-NH$_2$
NIH 11201:	Acetyl-Arg-Phe(4-OCH$_3$)-Tyr-Arg-Trp-Arg-NH$_2$
NIH 11202:	Acetyl-Arg-Phe(4-CN)-Tyr-Arg-Trp-Arg-NH$_2$
NIH 11203:	Acetyl-Arg-Tyr-Tyr-Arg-Trp(5-CN)-Arg-NH$_2$
NIH 11204:	Acetyl-Arg-Tyr-Phe(4-F)-Arg-Trp-Arg-NH$_2$
NIH 11205:	Acetyl-Arg-Tyr-Phe(4-NHAc)-Arg-Trp-Arg-NH$_2$
NIH 11206:	Acetyl-Arg-Tyr(3-Cl)-Tyr-Arg-Trp-Arg-NH$_2$
NIH 11207:	Acetyl-Arg-Tyr-Phe(4-benzyl)-Arg-Trp-Arg-NH$_2$
NIH 11208:	Heptanoyl-Arg-Tyr-Phe-Arg-Trp-Arg-NH$_2$

MOUSE ANTINOCICEPTIVE ASSAYS   *IN VITRO*

NIH #	Hot Plate (ED$_{50}$, i.c.v. µg/brain)	Phenylquinone (ED$_{50}$, i.c.v. µg/brain)	Tail Flick (ED$_{50}$, i.c.v. µg/brain)	Tail Flick Antagonist (AD$_{50}$, i.c.v. µg/brain)	Binding Affinity, (K$_i$, nM)
11199	Inactive	1.8	Inactive	Inactive	µ=2800, δ=2000, κ>10,000
11200	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	µ=740, δ>10,000, κ=720
11201	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	µ=670, δ>10,000, κ=1000
11202	Inactive	Inactive	Inactive	Inactive	µ=1500, δ>10,000, κ=990
11203	-	Inactive	Inactive	-	µ=270, δ>10,000, κ=1400
11204	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	µ=190, δ=5900, κ=780
11205	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	µ=470, δ>10,000, κ=1200
11206	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	µ=600, δ>10,000, κ=2700
11207	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	µ=220, δ=5900, κ=570
11208	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	µ=110, δ=3300, κ=130

a) Also inactive S.C.

TABLE 11. SMALL MOLECULES
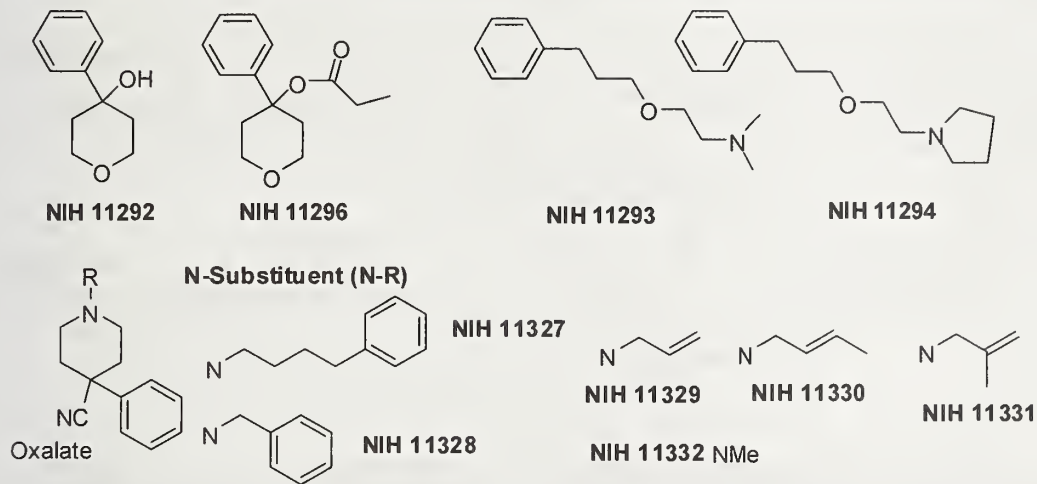
NIH 11292   NIH 11296   NIH 11293   NIH 11294

N-Substituent (N-R)

NIH 11327
NIH 11328
NIH 11329   NIH 11330   NIH 11331
NIH 11332 NMe

Oxalate

	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*
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)
11292	Inactive	Inactive	Inactive	Inactive	$\mu,\delta,\kappa>10,000$
11293	Inactive	Inactive	Inactive	Inactive	$\mu,\delta,\kappa>10,000$
11294	-	-	-	-	$\mu=3100, \delta,\kappa>10,000$
11296	Inactive	Inactive	Inactive	Inactive	$\mu,\delta,\kappa>10,000$
11327	-	-	-	-	$\mu=9800,\delta,\kappa>10,000$
11328	-	-	-	-	$\mu=5900,\delta,\kappa>10,000$
11329	-	-	-	-	$\mu,\delta,\kappa>10,000$
11330	-	-	-	-	$\mu,\delta,\kappa>10,000$
11331	-	-	-	-	$\mu,\delta>10,000, \kappa=5000$
11332	-	-	-	-	$\mu,\delta,\kappa>10,000$

TABLE 12. COMPOUNDS WITH MISCELLANEOUS STRUCTURES

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 Monkeys (s.c., mg/kg)
11211	Inactive	Inactive	Inactive	Inactive	–	Inactive in 50°C tail withdrawal at doses between 0.01 and 3
11228	Inactive	0.59	2.0	Inactive	κ=42; μ, δ, >10,000	-
11289	0.0018	0.0023	0.0043	-	-	Complete substitution for morphine at 0.005 and 0.03
11290	0.017	0.023	0.03	-	-	Complete substitution for morphine at 1
11353	23	3.1	Inactive	Inactive	μ, δ, κ>10,000	Neither substituted for morphine nor precipitated withdrawal at 2.5 and 10

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TABLE 13. COMPOUNDS EVALUATED BY STIMULANT DEPRESSANT PROGRAM

2 CH₃SO₃H

CPDD 0069

CPDD 0070
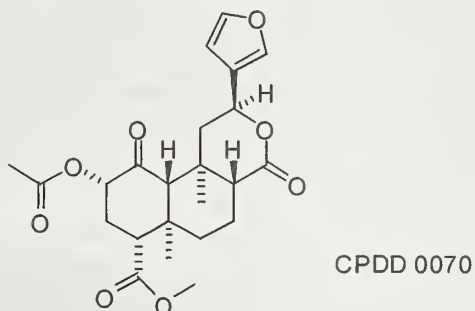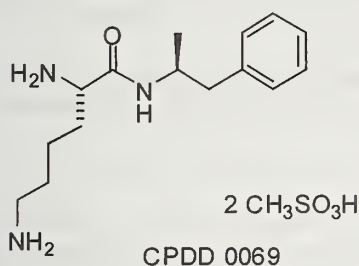
	Discriminative Stimulus Effects in Benzodiazepine-Trained Monkeys	Self-Administration in Cocaine-Maintained Monkeys	Drug Discrimination in Amphetamine-Trained Monkeys	Discriminative Stimulus Effects in PCP-Trained Rats
0069	Shares no discriminative stimulus effects with either flumazenil or midazolam at doses up to 5.6 mg/kg	Reinforcing effects at 0.03 and 0.1 mg/kg/inj	Full appropriate responding at 3 mg/kg s.c.	-
0070	Shares no discriminative stimulus effects with either flumazenil or midazolam at doses up to 0.56 mg/kg	-	No amphetamine discriminative stimulus effects in doses up to 1 mg/kg i.g.	No significant PCP-like responding

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ACKNOWLEDGEMENT

DRUG EVALUATION COMMITTEE REPORT ON:
EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (2007)

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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 for opioid activity. In addition, the compounds may be evaluated for discriminative and reinforcing effects. Analgesic and respiratory function assays are also possible. These 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 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 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 and available for release during the past year are shown in the following Table. Also shown are dates of Reports to the Biological Coordinator.

NIH #	Date Submitted to Biological Coordinator	NIH #	Date Submitted to Biological Coordinator
11107	21 November 2003	11296	2 March 2006
11116	4 August 2006	11303	29 November 2005
11121	4 August 2006	11309	2 March 2006
11199	2 April 2004	11306	2 March 2006
11200	2 April 2004	11306	2 March 2006
11201	2 April 2004	11307	15 August 2006
11202	2 April 2004	11306	15 August 2006
11203	2 April 2004	11309	15 August 2006
11204	2 April 2004	11312	15 August 2006
11205	2 April 2004	11313	15 August 2006
11206	2 April 2004	11319	15 August 2006
11207	2 April 2004	11315	15 August 2006
11208	2 April 2004	11319	15 August 2006
11209	24 December 2003	11317	15 August 2006
11210	24 December 2003	11319	15 August 2006
11211	19 September 2005	11319	15 August 2006
11213	4 August 2006	11325	15 August 2006
11221	10 November 2004	11326	15 August 2006
11222	10 November 2004	11327	15 August 2006
11223	10 November 2004	11328	15 August 2006
11224	10 November 2004	11326	15 August 2006
11225	10 November 2004	11330	15 August 2006
11226	10 November 2004	11331	15 August 2006
11227	10 November 2004	11332	15 August 2006
11238	10 November 2004	11333	15 August 2006
11239	8 March 2005	11334	15 August 2006
11240	8 March 2005	11345	18 October 2006
11201	8 March 2005	11345	18 October 2006
11242	8 March 2005	11346	18 October 2006
11243	8 March 2005	11347	15 December 2006
11244	8 March 2005	11348	15 December 2006

NIH #	Date Submitted to Biological Coordinator	NIH #	Date Submitted to Biological Coordinator
11245	8 March 2005	11349	15 December 2006
11292	2 March 2006	11350	15 December 2006
11293	2 March 2006	11352	15 December 2006
11294	2 March 2006	11353	15 December 2006
11295	2 March 2006		

METHODS

Opioid Receptor Binding and *In Vitro* Efficacy Assessment

Details of the binding assay 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 κ 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 concentration. EC_{50} values (nM) for standard compounds are as follows: μ receptor (morphine, 65 nM; DAMGO, 34 nM; fentanyl, 13 nM), δ receptor (SNC80, 9 nM; DPDPE 8.3 nM), and κ 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.

Behavioral Assessments in Rhesus Monkeys.

One compound assessed in rhesus monkeys was made available for release this year (NIH 11211). It appears at the end of this report. A detailed description of this and other assays available to submitters is included in the reference list.

NIH 11107   **Oxycodone.HCl**
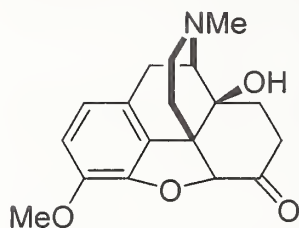
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 485 ± 134
δ-receptor: >3000
κ-receptor: > 3000

OPIOID RECEPTOR BINDING (nM): Phosphate buffer*

μ-receptor: 207 ± 12.8
δ-receptor: $45 \pm 3\%$ inhibition at 10 μM
κ-receptor: $19 \pm 5 \%$ inhibition at 10 μM

*These studies were performed in phosphate buffered solutions (pH 7.4) as requested by the submitter.
[NOTE: These studies were performed in parallel with studies on NIH 11198 as requested by the submitter.]

GTPγS ASSAY:
μ-receptor: $88.2 + 3.3 \%$ maximal stimulation; $EC_{50} = 605 \pm 82.6$

GTPγS ASSAY: Phosphate buffer*

μ-receptor: $97.0 \pm 1.9 \%$ maximal stimulation; $EC_{50} = 854 \pm 147$
δ-receptor: Not done
κ-receptor: Not done

*These studies were performed in phosphate buffer at pH 7.4 as requested by the submitter.

SUMMARY

NIH 11107 has low affinity for μ opioid receptors in the phosphate buffer. It has no appreciable affinity for the δ or κ receptor. NIH 11107 is an efficacious μ agonist of low potency.

NIH 11116   4,5α-epoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]indolo[2',3':6,7]-morphinan-3-ol

GTPγS ASSAY (nM)
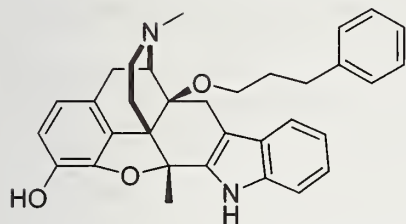
μ-receptor: 86 ± 2 % of maximal stimulation EC$_{50}$ = 229 ± 78
δ-receptor: 37 ± 3 % of maximal stimulation: EC$_{50}$ = 3.5 ± 1.3
κ-receptor: 42 ± 3 % of maximal stimulation; EC$_{50}$ = 39 ± 8

SUMMARY

NIH 11116 is a full agonist with low potency at the μ opioid receptor, a low efficacy partial agonist with high potency at the δ opioid receptor, and a partial agonist with potency at the κ opioid receptor. Binding and behavioral data on this compound are available in the 2005 Annual Report (NIDA Monograph 186).

* * *

NIH 11121   4,5α-epoxy-3-hydroxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one.HBr
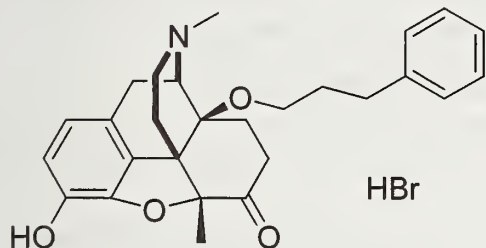
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.02 ± 0.004
δ-receptor: 0.55 ± 0.22
κ-receptor: 0.09 ± 0.05

GTPγS ASSAY (nM)

μ-receptor: 104 ± 2 % of max; EC$_{50}$ = 0.06 ± 0.02
δ-receptor: 52 ± 5 % of max; EC$_{50}$ = 2.6 ± 0.9
κ-receptor: not requested

SUMMARY

NIH 11121 has extremely high affinity for μ and κ receptors with very high affinity for δ receptors. It is a full agonist with extremely high potency at the μ opioid receptor and a partial agonist with high potency at the δ opioid receptor. Behavioral data on this compound are in the 2005 Annual Report (NIDA Monograph 186)

[Note: This compound is extremely "sticky" and difficult to work with.]

NIH 11199   **Acetyl-Arg-Phe(4-COOH)-Tyr-Arg-Trp-Arg-NH$_2$**

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 2770 ± 281
δ-receptor: 2024 ± 374
κ-receptor: 30 ± 7.5% inhibition at 10 μM

SUMMARY

NIH 11199 has very low affinity for opioid receptors.

> [Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

<p style="text-align:center">* * *</p>

NIH 11200   **Acetyl-Arg-Phe(4-F)-Tyr-Arg-Trp-Arg-NH$_2$**

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 744 ± 106
δ-receptor: 41 ± 1.0% inhibition at 10 μM
κ-receptor: 715 ± 324

SUMMARY

NIH 11200 has low affinity for μ and κ opioid receptors and no appreciable affinity for δ receptors.

> [Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

<p style="text-align:center">* * *</p>

NIH 11201   **Acetyl-Arg-Phe(4-OCH$_3$)-Tyr-Arg-Trp-Arg-NH$_2$**

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 674 ± 80
δ-receptor: 42 ± 6.0 inhibition at 10 μM
κ-receptor: 1037 ± 485

SUMMARY

NIH 11201 has low affinity for μ and κ opioid receptors and no appreciable affinity for δ receptors.

> [Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

NIH 11202   **Acetyl-Arg-Phe(4-CN)-Tyr-Arg-Trp-Arg-NH$_2$**

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1472 ± 484
δ-receptor: 32 ± 3.5% inhibition at 10 μM
κ-receptor: 986 ± 499

SUMMARY

NIH 11202 has low affinity for μ and κ opioid receptors and no appreciably affinity for δ receptors.

> [Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

* * *

NIH 11203   **Acetyl-Arg-Tyr-Tyr-Arg-Trp(5-CN)-Arg-NH$_2$**

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 266 ± 115
δ-receptor: 41 ± 4.5% inhibition at 10 μM
κ-receptor: 1446 ± 657

SUMMARY

NIH 11203 has low affinity for μ, very low affinity for κ and no appreciable affinity for δ receptors.

> [Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

* * *

NIH 11204   **Acetyl-Arg-Tyr-Phe(4-F)-Arg-Trp-Arg-NH$_2$**

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 189 ± 87
δ-receptor: 5898 ± 845
κ-receptor: 773 ± 38

SUMMARY

NIH 11204 has low affinity for μ and κ receptors and very low affinity for δ receptors.

> [Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM and captopril (10 μM).]

NIH 11205   Acetyl-Arg-Tyr-Phe(4-NHAc)-Arg-Trp-Arg-NH₂

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 467 ± 109
δ-receptor: 49 ± 1.0% inhibition at 10 μM
κ-receptor: 1215 ± 560

SUMMARY

NIH 11205 has low affinity for μ, very low affinity for κ and no appreciable affinity for δ receptors,

> [Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM and captopril (10 μM).]

<div align="center">*   *   *</div>

NIH 11206   Acetyl-Arg-Tyr(3-Cl)-Tyr-Arg-Trp-Arg-NH₂

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 597 ± 121
δ-receptor: 45 ± 6.0% inhibition at 10 μM
κ-receptor: 2745 ± 1633

SUMMARY

NIH 11206 has low affinity for μ, very low affinity for κ and no appreciable affinity for δ receptors.

> [Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM and captopril (10 μM).]

<div align="center">*   *   *</div>

NIH 11207   Acetyl-Arg-Tyr-Phe(4-benzyl)-Arg-Trp-Arg-NH₂

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 223 ± 19
δ-receptor: 5901 ± 540
κ-receptor: 570 ± 36

SUMMARY

NIH 11207 has low affinity for μ and κ receptors with very low affinity for δ receptors.

> [Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM and captopril (10 μM).]

NIH 11208   Heptanoyl-Arg-Tyr-Phe-Arg-Trp-Arg-NH$_2$

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 107 ± 36
δ-receptor: 3349 ± 214
κ-receptor: 127 ± 7

SUMMARY

NIH 11208 has equivalent affinity for μ and κ receptors with very low affinity for δ receptors.

> [Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

*   *   *

NIH 11209   (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl
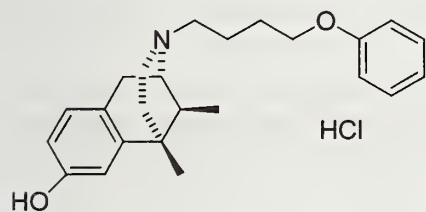
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 70.1 ± 6.4
δ-receptor: 3243 ± 184
κ-receptor: 303 ± 27.7

SUMMARY

NIH 11209 has affinity for the μ receptor > κ receptor with very low affinity for the δ receptor.

*   *   *

NIH 11210   (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl
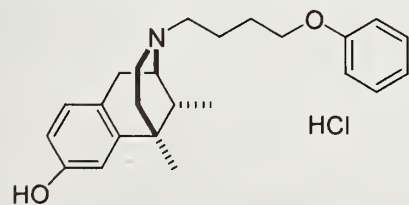
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 6.3 ± 0.6
δ-receptor: 42.8 ± 0.7
κ-receptor: 43.5 ± 3.8

SUMMARY

NIH 11210 has high affinity for the μ receptor and approximately 7-fold selectivity for μ over δ = κ receptors.

NIH 11213   (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-2-butenyl)-6,7-benzomorphan .oxalate
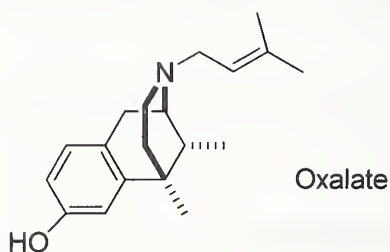
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 6.8± 1.0
δ-receptor: 117± 32.9
κ-receptor: 8.1 ± 2.0

Oxalate

GTPγS ASSAY (nM)

μ-receptor: 4.4 ± 0.9 % of max; EC_{50} = not available
δ-receptor: 8.7 ± 3.3 % of max; EC_{50} = not available
κ-receptor: 37 ± 6 % of max; EC_{50} = 34 ± 10

SUMMARY

NIH 11213 has high affinity for μ = κ receptors and has approximately 15-fold less affinity for δ receptors. It is a low efficacy partial agonist with potency at the κ opioid receptor and has no effect at the μ and δ opioid receptors, suggesting μ and δ antagonism. Behavioral data on this compound are available in the 2005 Annual Report (NIDA Monograph 186).

<p style="text-align:center">*   *   *</p>

NIH 11221   5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(4-phenylbutyl)-morphinan-6-carbonitrile
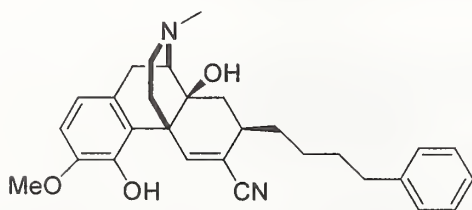
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 7.0 ± 3.1
δ-receptor: 120 ± 30
κ-receptor: 1461 ± 390

SUMMARY

NIH 11211 has high affinity for μ opioid receptors > δ opioid receptors with approximately 15-fold selectivity. It has very low affinity for κ opioid receptors.

NIH 11222   5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(5-phenylpentyl)-morphinan-6-carbonitrile
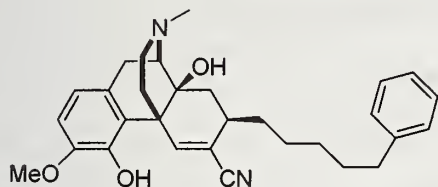
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.63 ± 0.12
δ-receptor: 77.8 ± 17.0
κ-receptor: 506 ± 109

SUMMARY

NIH 11222 has very high affinity for μ opioid receptors. It is 120-fold selective for μ over δ receptors and 800-fold selective for μ over κ receptors.

* * *

NIH 11223   5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(6-phenylhexyl)-morphinan-6-carbonitrile
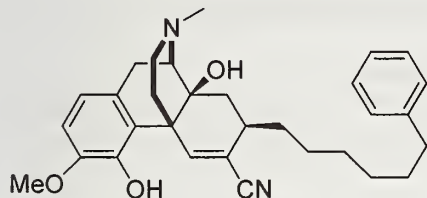
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.32 ± 0.11
δ-receptor: 135 ± 22
κ-receptor: 566 ± 192

SUMMARY

NIH 11223 has very high affinity for μ opioid receptors. It is 120-fold selective for μ over δ receptors and 800-fold selective for μ over κ receptors.

* * *

NIH 11224   7β-Benzyl-5,6-didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-morphinan-6-carbonitrile
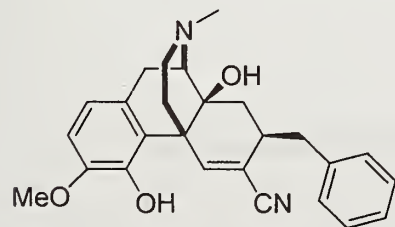
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1515 ± 240
δ-receptor: 86.8 ± 6.6
κ-receptor: 2015 ± 289

SUMMARY

NIH 11224 has affinity for δ opioid receptors with 17-fold selectivity over μ. It has very low affinity for μ and κ opioid receptors.

NIH 11225   6,7-Didehydro-4,5-epoxy-6-idimazolyl-3-methoxy-17-methyl-14-(3-phenylpropyloxy)-morphinan
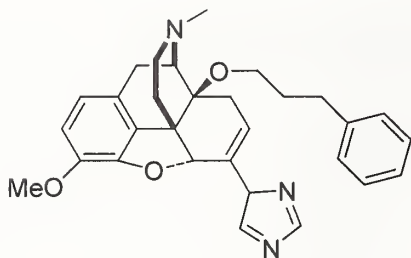
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.96 ± 0.41
δ-receptor: 1.34 ± 0.34
κ-receptor: 0.42 ± 0.09

SUMMARY

NIH 11225 has very high affinity for μ, δ, and κ opioid receptors.

*   *   *

NIH 11226   4-Cinnamyloxy-5,6,7,8-tetradehydro-14β-hydroxy-3-methoxy-17-methyl-morphinan-6-carbonitrile
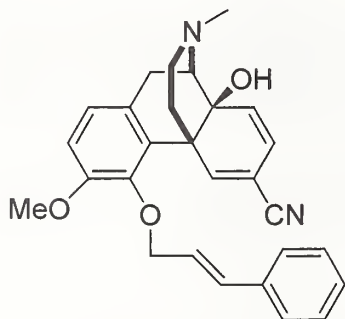
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.83 ± 0.24
δ-receptor: 462 ± 154
κ-receptor: 1150 ± 257

SUMMARY

NIH 11226 has very high affinity for μ and low affinity for δ and κ opioid receptors with over 500-fold selectivity for μ over δ or κ opioid receptors.

*   *   *

NIH 11227   Tyr-Tyr-Phe-Phe-Ile-(6-O)-hydrocodone.HCl
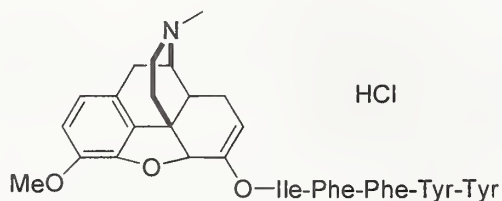
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 51.9 ± 3.6
δ-receptor: 80.2 ± 25.4
κ-receptor: 351 ± 114

SUMMARY

NIH 11227 has affinity for μ ≥ δ > κ opioid receptors.

122

NIH 11238   Oxycodone-enol ether prodrug. .2Trifluroacetate

$2CF_3CO_2H$
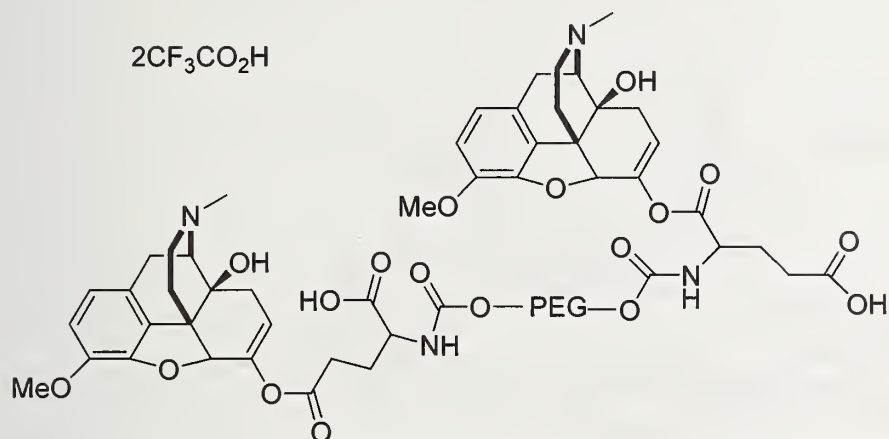
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 456 ± 187
δ-receptor: 7410 ± 590 (n=2)
κ-receptor: 7100 ± 890 (n=2)

GTPγS ASSAY

μ-receptor: 12 ± 6% of maximal stimulation; EC_{50}
                   not available
δ-receptor: not done
κ-receptor: not done

SUMMARY

NIH 11238 has low affinity for μ opioid receptors and very low affinity for δ and κ opioid receptors. It has very little measurable agonist effect at the μ opioid receptor.
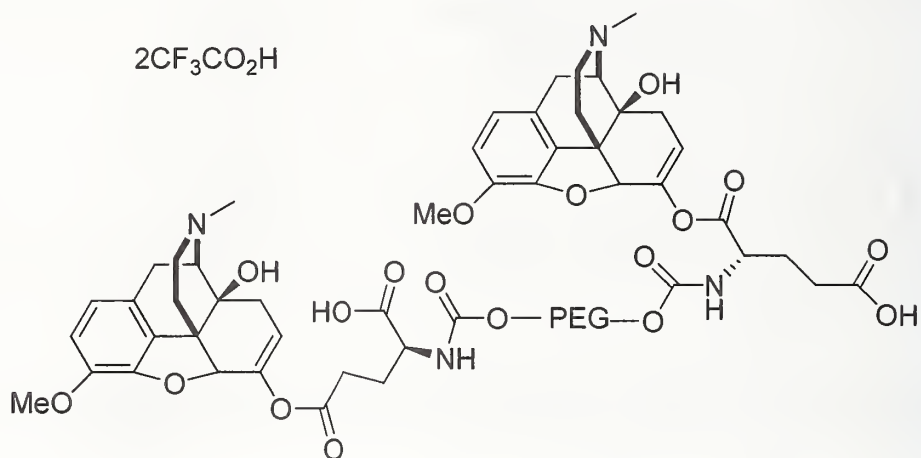
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 443 ± 56
δ-receptor: 6530 ± 710
κ-receptor: 7760 ± 770 (n=2)

GTPγS ASSAY (nM)

μ-receptor: <5% of maximal stimulation; EC_{50} not available
δ-receptor: not done
κ-receptor: not done

SUMMARY

NIH 11239 has no measurable agonist effect at the μ opioid receptor. It has low affinity for μ opioid receptors and very low affinity for δ and κ opioid receptors.
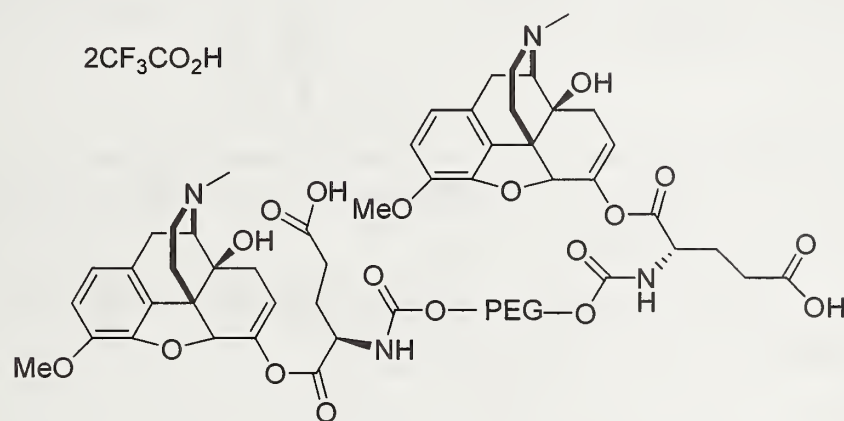
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 512 ± 92
δ-receptor: 7500 ± 20 (n=2)
κ-receptor: 6420 ± 750 (n=2)

GTPγS ASSAY (nM)

μ-receptor: <5% of maximal stimulation; EC_{50} not available
δ-receptor: not done
κ-receptor: not done

SUMMARY

NIH 11240 has no measurable agonist effect at the μ opioid receptor. It has low affinity for μ opioid receptors and very low affinity for δ and κ opioid receptors.

NIH 11241   Oxycodone-enol ether prodrug. .2Trifluroacetate
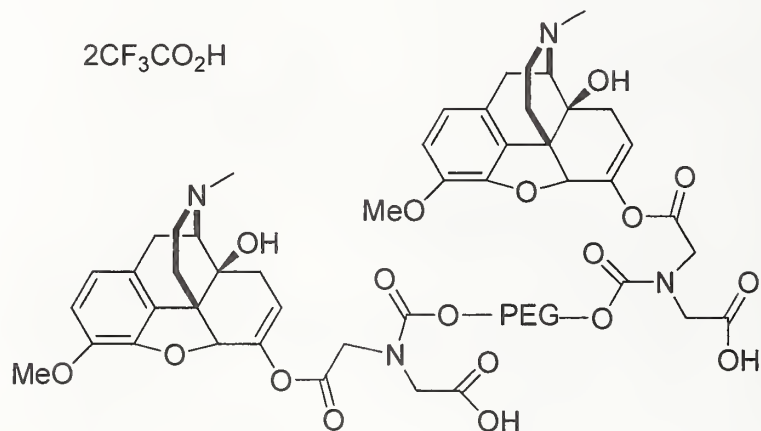
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 381 ± 32
δ-receptor: 5470 ± 300 (n=2)
κ-receptor: 25 ± 8% inhibition at 10 μM

GTPγS ASSAY (nM)

μ-receptor: <5% of maximal stimulation; EC_{50} not available
δ-receptor: not done due to very low binding
κ-receptor: not done due to very low binding

SUMMARY

NIH 11240 has no measurable agonist effect at the μ opioid receptor. It has low affinity for μ opioid receptors, very low affinity for δ opioid receptors and no affinity for κ opioid receptors.

* * *

NIH 11242   Oxycodone-enol ether prodrug. .2Trifluroacetate

126
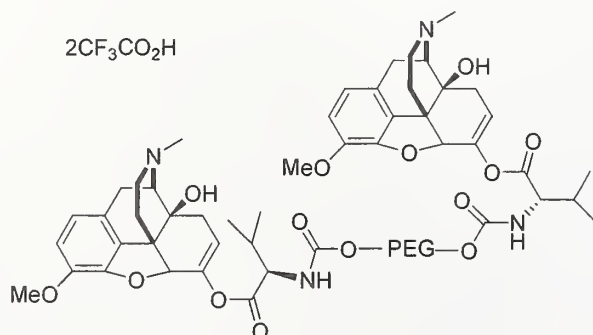
NIH 11242 (continued)

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1290 ± 200
δ-receptor: 1110 ± 160
κ-receptor: 6820 ± 2140 (n=2)

GTPγS ASSAY (nM)

μ-receptor: not done due to very low binding affinity
δ-receptor: not done due to very low binding affinity
κ-receptor: not done due to very low binding affinity

SUMMARY

NIH 11242 was not evaluated for agonist activity due to very low receptor binding affinity at each of the opioid receptors. It had very low affinity for μ, δ, and κ opioid receptors.

* * *

NIH 11243   **Oxycodone-enol ether/valine prodrug. .Trifluroacetate**

CF_3CO_2H
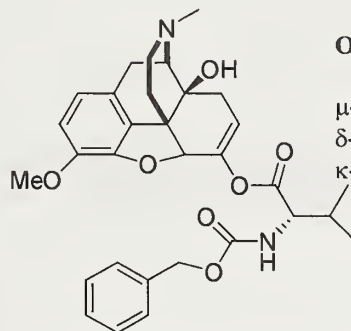
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 169 ± 11
δ-receptor: 25.8 ± 6.1
κ-receptor: 4260 ± 550

GTPγS ASSAY (nM)

μ-receptor: <10% of maximal stimulation; EC_{50} not available
δ-receptor: $37 \pm 8\%$ of maximal stimulation; $EC_{50} = 1620 \pm 540$
κ-receptor: not done

SUMMARY

NIH 11243 has an affinity for δ opioid receptors with 6.5-fold selectivity over μ opioid receptors, and 165-fold selectivity over κ opioid receptors. It has no measurable effect at the μ opioid receptor and is a weak partial agonist with very low potency at the δ opioid receptor. Activity at the κ opioid receptor was not evaluated.

NIH 11244   6-O-(2,2,2-trimethylacetyl)oxycodone-enol ether. HCl

OPIOID RECEPTOR BINDING (nM)

HCl
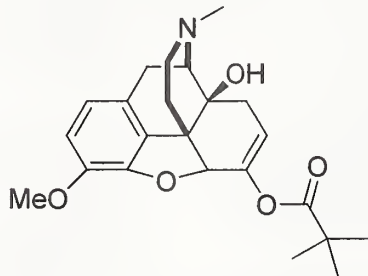
μ-receptor: 51.6 ± 6.7
δ-receptor: 163 ± 33
κ-receptor: 7930 ± 870

GTPS ASSAY (nM)

μ-receptor: 56 ± 10% of maximal stimulation: $EC_{50} = 1820 \ 140$
δ-receptor: 30 ± 5% of maximal stimulation: $EC_{50} = 2900 \ 1300$
κ-receptor: not done due to very low binding affinity

SUMMARY

NIH 11244 lt has affinity for μ > δ >> κ opioid receptors. lt is a partial agonist with very low potency at the μ opioid receptor and a weak partial agonist with very low potency at the δ opioid receptor. Activity at the κ opioid receptor was not evaluated.

*   *   *

NIH 11245   Oxycodone-enol ether prodrug. .Trifluroacetate

OPIOID RECEPTOR BINDING (nM)

CF_3CO_2H
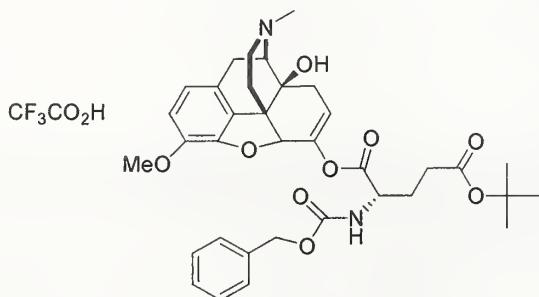
μ-receptor: 238 ± 28
δ-receptor: 190 ± 25
κ-receptor: 1720 ± 280

NIH 11245 (continued)

GTPγS ASSAY (nM)

μ-receptor: <10% of maximal stimulation: EC_{50} not available
δ-receptor: 17 ± 7% of maximal stimulation: EC_{50} not available
κ-receptor: not done

SUMMARY

NIH 11245 has low affinity for μ and δ receptors and very low affinity for κ opioid receptors. It is a very weak partial agonist at the δ opioid receptor and has no measurable agonist effect at the μ opioid receptor. Activity at the κ opioid receptor was not evaluated.

* * *

NIH 11292   **4-Phenyltetrahydro-2*H*-pyran-4-ol**
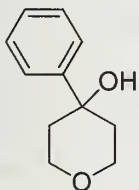
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 11% inhibition at 10 μM
δ-receptor: 26% inhibition at 10 μM
κ-receptor: 15% inhibition at 10 μM

SUMMARY

NIH 11292 has no affinity for μ, δ, or κ opioid receptors.

* * *

NIH 11293   ***N,N*-Dimethyl-2-(3-phenylpropoxy)ethylamine**
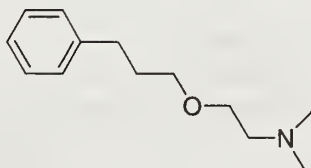
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 23% inhibition at 10 μM
δ-receptor: 25% inhibition at 10 μM
κ-receptor: 18% inhibition at 10 μM

SUMMARY

NIH 11293 has no affinity for μ, δ, or κ opioid receptors.

NIH 11294   **1-(2-[3-phenylpropoxy]ethyl)pyrrolidine**
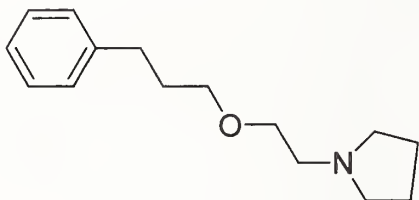
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3120 ± 430
δ-receptor: 29% inhibition at 10 μM
κ-receptor: 13% inhibition at 10 μM

SUMMARY

NIH 11294 has very low affinity at the μ opioid receptor and no affinity at δ or κ opioid receptors.

* * *

NIH 11296   **4-Phenyltetrahydro-2*H*-pyran-4-yl propionate**
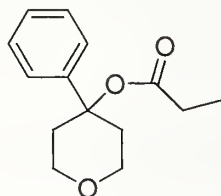
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 14% inhibition at 10 μM
δ-receptor: 24% inhibition at 10 μM
κ-receptor: 3% inhibition at 10 μM

SUMMARY

NIH 11296 has no affinity at μ, δ, or κ opioid receptors.

* * *

NIH 11304   **(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxopropyl)-6,7-benzomorphan.HCl**
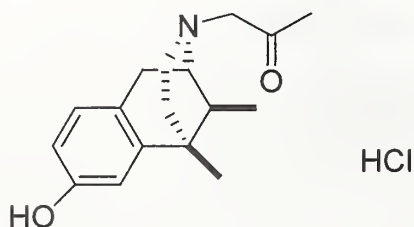
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 6300 ± 980
δ-receptor: 24% inhibition at 10 μM
κ-receptor: 21% inhibition at 10 μM

SUMMARY

NIH 11304 has very low affinity at the μ opioid receptor and no affinity at δ or κ opioid receptors.

NIH 11305   (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxopropyl)-6,7-benzomorphan.HCl

HCl
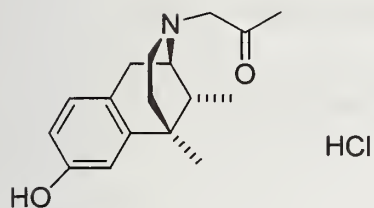
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 77.2 ± 30.7
δ-receptor: 893 ± 151
κ-receptor: 121 ± 9

SUMMARY

NIH 11305 has affinity at the μ opioid receptor, with similar affinity at the κ opioid receptor but and low affinity at the δ opioid receptor.

*   *   *

NIH 11306   (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(5-oxohexyl)-6,7-benzomorphan.HCl
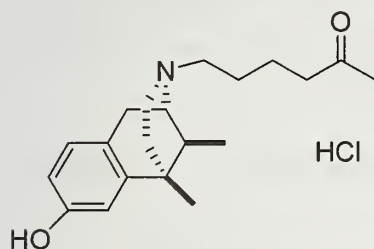
HCl

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3360 ± 760
δ-receptor: 14% inhibition at 10 μM
κ-receptor: 5110 ± 1390

SUMMARY

NIH 11306 has very low affinity at the μ and κ opioid receptors and no affinity at the δ opioid receptor.

*   *   *

NIH 11307   (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(5-oxohexyl)-6,7-benzomorphan.HCl

HCl
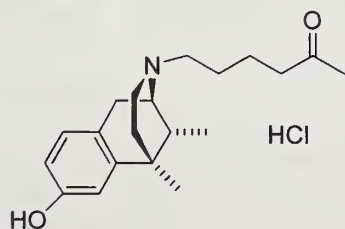
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 21.0 ± 1.5
δ-receptor: 372 ± 24
κ-receptor: 140 ± 40

SUMMARY

NIH 11307 has affinity at μ opioid receptors and low affinity at the δ and κ opioid receptors. The compound is 7 fold selective for μ over δ and 18-fold selective for μ over δ.

NIH 11308   (+)-(1*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxobutyl)-6,7-benzomorphan.HCl
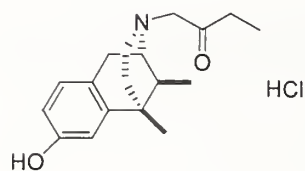
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 15% inhibition at 10 μM
δ-receptor: 28% inhibition at 10 μM
κ-receptor: 9490 ± 3900

SUMMARY

NIH 11308 has very low affinity at the κ opioid receptor and no affinity at δ or μ opioid receptors.

*   *   *

NIH 11309   (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxobutyl)-6,7-benzomorphan.HCl
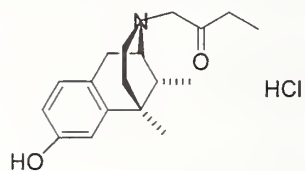
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 71.5 ± 11
δ-receptor: 848 ± 56
κ-receptor: 71.1 ± 10

SUMMARY

NIH 11309 has equal affinity at the μ and κ opioid receptors and low affinity at δ opioid receptors.

*   *   *

NIH 11310   Thienorphine.HCl
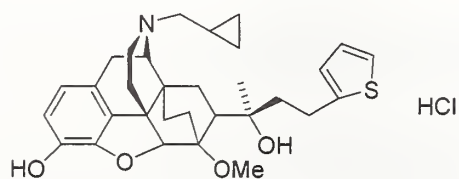
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.22 ± 0.07
δ-receptor: 0.69 ± 0.03
κ-receptor: 0.14 ± 0.06

GTPγS ASSAY (nM)

μ-receptor   19 ± 4 % of maximal stimulation; EC_{50} = 1.9 ± 0.4
δ-receptor: 2 ± 2 % of maximal stimulation; EC_{50} = not available
κ-receptor: 75 ± 5 % of maximal stimulation; EC_{50} = 0.3 ± 0.2

SUMMARY

NIH 11310 has very high affinity at μ, δ and κ opioid receptors. It is a partial agonist with very high potency at the κ opioid receptor and a very low efficacy partial agonist with high potency at the μ opioid receptor. NIH 11310 has no effect at the δ opioid receptor.

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NIH 11312   **5'-Fluorooxymorphindole.HCl**
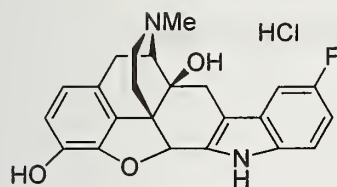
(structure)	**OPIOID RECEPTOR BINDING (nM)** μ-receptor: 21.4 ± 4.7 δ-receptor: 2.3 ± 0.1 κ-receptor: 307 ± 43

GTPγS ASSAY (nM)

μ-receptor   24 ± 4 % of maximal stimulation; $EC_{50} = 1730 ± 1080$
δ-receptor: 16 ± 1 % of maximal stimulation; $EC_{50} = 16 ± 10$
κ-receptor: not determined

SUMMARY

NIH 11312 has high affinity at the δ opioid receptor with 9-fold selectivity over μ and 130-fold selectivity over κ opioid receptors. NIH 11312 is a low efficacy partial agonist with very low potency at the μ opioid receptor, and a very low efficacy partial agonist with potency at the δ opioid receptor (100x more potent at δ than μ).

*   *   *

NIH 11313   **5'-Chlorooxymorphindole.HCl**
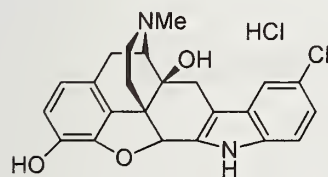
(structure)	**OPIOID RECEPTOR BINDING (nM)** μ-receptor: 46.6 ± 9.9 δ-receptor: 5.1 ± 1.2 κ-receptor: 361 ± 36

GTPγS ASSAY (nM)

μ-receptor: 25 ± 1 % of maximal stimulation; $EC_{50} = 630 ± 120$
δ-receptor: 9 ± 2 % of maximal stimulation; $EC_{50} = 20 ± 4$
κ-receptor: not determined

SUMMARY

NIH 11313 has high affinity at the δ opioid receptor with 9-fold selectivity over μ and 70-fold selectivity over κ opioid receptors. It is a low efficacy partial agonist at the μ opioid receptor and a very low efficacy partial agonist at the δ opioid receptor and is 30 times more potent at the δ opioid receptor than at the μ opioid receptor.

NIH 11314   **5'-Brorooxymorphindole.HCl**

NMe
HCl
OH
Br
HO
O
N
H
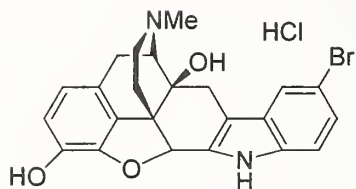
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 71.2 ± 22.6
δ-receptor: 8.6 ± 0.4
κ-receptor: 253 ± 45

GTPγS ASSAY

μ-receptor: 25 ± 1 % of maximal stimulation; $EC_{50} = 770 \pm 200$
δ-receptor: 12 ± 2 % of maximal stimulation: $EC_{50} = 13 \pm 6$
κ-receptor: not done

SUMMARY

NIH 11314 has high affinity at the δ opioid receptor with 8-fold selectivity over μ and 29-fold selectivity over the κ opioid receptor. The compound is a low efficacy partial agonist at the μ opioid receptor and a very low efficacy partial agonist at the δ opioid receptor and is 60 times more potent at the δ opioid receptor than at the μ opioid receptor.

*   *   *

NIH 11315   **5'-Iodooxymorphindole.HCl**

NMe
HCl
OH
I
HO
O
N
H
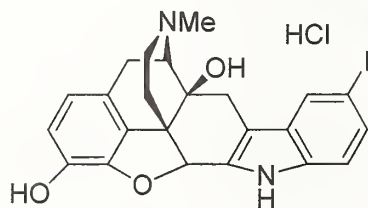
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 65.5 ± 12.6
δ-receptor: 3.8 ± 0.3
κ-receptor: 161 ± 46

GTPγS ASSAY (nM)

μ-receptor: 25 ± 2 % of maximal stimulation: $EC_{50} = 430 \pm 180$
δ-receptor: 14 ± 2 % of maximal stimulation: $EC_{50} = 19 \pm 1$
κ-receptor: not determined

SUMMARY

NIH 11315 has high affinity at the δ opioid receptor with at least 17-fold selectivity over μ and κ opioid receptors. It is a low efficacy partial agonist at the μ opioid receptor and a very low efficacy partial agonist at the δ opioid receptor and is 20 times more potent at the δ opioid receptor than at the μ opioid receptor.

NIH 11316   7'-Fluorooxymorphindole.HCl
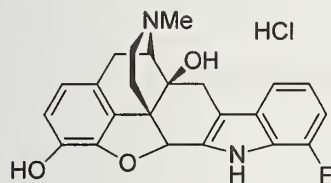
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 65.0 ± 13.1
δ-receptor: 0.5 ± 0.2
κ-receptor: 271 ± 50

GTPγS ASSAY (nM)

μ-receptor: 11 ± 3 % of maximal stimulation: $EC_{50} = 560 \pm 200$
δ-receptor: 10 ± 5 % of maximal stimulation: EC_{50} = not determined
κ-receptor: not determined

SUMMARY

NIH 11316 has very high affinity at the δ opioid receptor with at least 130-fold selectivity over μ and κ opioid receptors. NIH 11316 is likely to be a high affinity selective δ-antagonist.

* * *

NIH 11317   5',7'-Difluorooxymorphindole.HCl
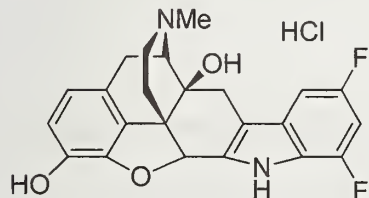
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 58.5 ± 3.8
δ-receptor: 1.1 ± 0.3
κ-receptor: 207 ± 44

GTPγS ASSAY (nM)

μ-receptor: 24 ± 4 % of maximal stimulation: $EC_{50} = 440 \pm 100$
δ-receptor: 13 ± 3 % of maximal stimulation: $EC_{50} = 19 \pm 7$
κ-receptor: not determined

SUMMARY

NIH 11317 has high affinity at the δ opioid receptor with at least 53 fold selectivity over μ and κ opioid receptors. The compound is a low efficacy partial agonist at the μ opioid receptor and a very low efficacy partial agonist at the δ opioid receptor and is 20 times more potent at the δ opioid receptor than at the μ opioid receptor.

NIH 11318   **5',7'-Dichlorooxymorphindole.HCl**
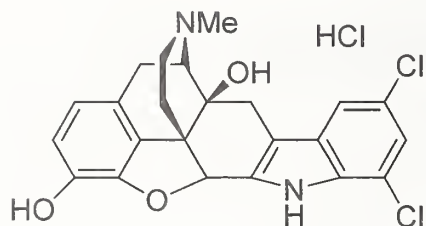
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 28.9 ± 4.6
δ-receptor: 6.7 ± 1.1
κ-receptor: 380 ± 45

GTPγS ASSAY (nM)

μ-receptor   67 ± 8 % of maximal stimulation; $EC_{50} = 416 ± 106$
δ-receptor: 24 ± 6 % of maximal stimulation; $EC_{50} = 29 ± 14$
κ-receptor: not determined

SUMMARY

NIH 11318 has high affinity at the δ opioid receptor with 4 fold selectivity over μ and 57 fold selectivity over κ opioid receptors. The compound is a partial agonist with low potency at the μ opioid receptor and a low efficacy partial agonist with potency at the δ opioid receptor (14x more potent at δ than μ).

*   *   *

NIH 11319   **Oxymorphindole.HCl**
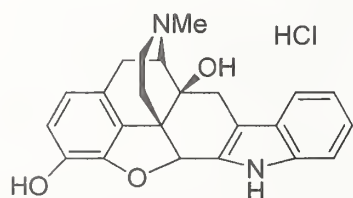
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 105 ± 23
δ-receptor: 0.9 ± 0.2
κ-receptor: 515 ± 35

GTPγS ASSAY (nM)

μ-receptor: 19 ± 1 % of maximal stimulation: $EC_{50} = 560 ± 100$
δ-receptor: 17 ± 3 % of maximal stimulation: $EC_{50} = 16 ± 6$
κ-receptor: not determined

SUMMARY

NIH 11319 has very high affinity at the delta opioid receptor with at least 117 fold selectivity over mu and kappa opioid receptors. NIH 11319 is a very low efficacy partial agonist at the mu and delta opioid receptors and is 35 times more potent at the delta opioid receptor than at the mu opioid receptor.

NIH 11323   (+)-(1S,5S,9S)-5,9-Dimethyl-2-(5-hexynyl)-2'-hydroxy-6,7-benzomorphan
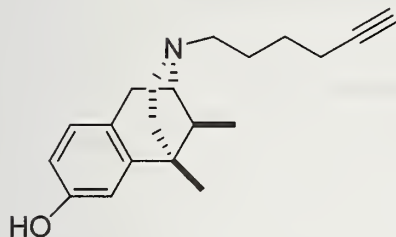
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 632 ± 40
δ-receptor: 13200 ± 4600
κ-receptor: 239 ± 2

SUMMARY

NIH 11323 has low affinity at the μ and κ opioid receptors and very low affinity at the δ opioid receptor.

*   *   *

NIH 11324   (-)-(1R,5R,9R)-5,9-Dimethyl-2-(5-hexynyl)-2'-hydroxy-6,7-benzomorphan
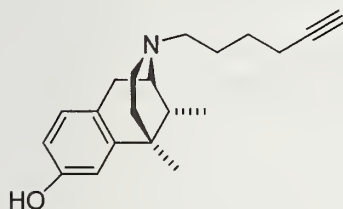
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 4.3 ± 1.1
δ-receptor: 54.5 ± 16.9
κ-receptor: 7.5 ± 0.4

SUMMARY

NIH 11324 has high affinity at the mu and kappa opioid receptors and affinity at the delta opioid receptor.

*   *   *

NIH 11325   (-)-(1R,5R,9R)-5,9-Dimethyl-2-(5-cyanopentyl)-2'-hydroxy-6,7-benzomorphan
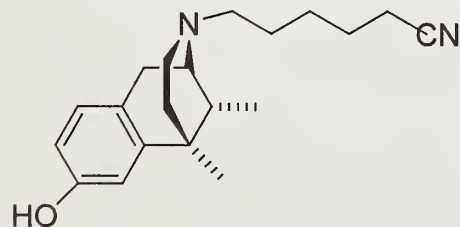
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 16.8 ± 2.2
δ-receptor: 212 ± 60
κ-receptor: 8.1 ± 2.1

SUMMARY

NIH 11325 has high affinity at the κ opioid receptor, affinity at the μ opioid receptor and low affinity at the δ opioid receptor.

NIH 11326   **(+)-(1S,5S,9S)-5,9-Dimethyl-2-(5-cyanopentyl)-2'-hydroxy-6,7-benzomorphan**
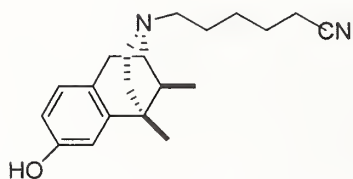
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 2240 ± 430
δ-receptor: 22% inhibition at 10 μM
κ-receptor: 302 ± 42

SUMMARY

NIH 11326 has low affinity at the κ opioid receptor, very low affinity at the μ opioid receptor and no affinity at the δ opioid receptor.

*   *   *

NIH 11327   ***N*-(4-Phenylbutyl)-4-phenylpiperidine-4-nitrile.oxalate**
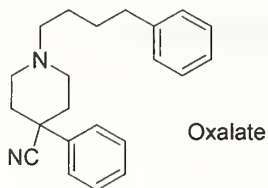
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 9760 ± 680
δ-receptor: 25% inhibition at 10 μM
κ-receptor: 27% inhibition at 10 μM

SUMMARY

NIH 11327 has very low affinity at the μ opioid receptor and no affinity at the δ and κ opioid receptors.

*   *   *

NIH 11328   ***N*-(Benzyl)-4-phenylpiperidine-4-nitrile.oxalate**
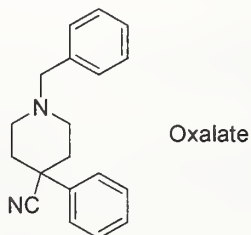
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 5850 ± 90
δ-receptor: 19 % inhibition at 10 μM
κ-receptor: 10,900 ± 2800

SUMMARY

NIH 11328 has very low affinity at the μ and κ opioid receptors and no affinity at the δ opioid receptor.

NIH 11329   *N*-Allyl-4-phenylpiperidine-4-nitrile.HCl
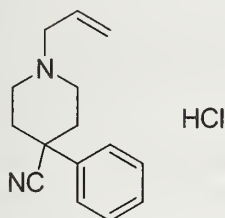
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 12% inhibition at 10 μM
δ-receptor: 10% inhibition at 10 μM
κ-receptor: 10% inhibition at 10 μM

SUMMARY

NIH 11329 has no affinity at μ, δ, or κ opioid receptors.

*   *   *

NIH 11330   *N*-Crotyl-4-phenylpiperidine-4-nitrile.HCl
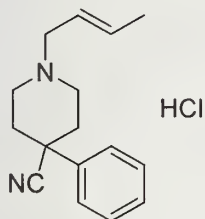
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 32% inhibition at 10 μM
δ-receptor: 26% inhibition at 10 μM
κ-receptor: 25% inhibition at 10 μM

SUMMARY

NIH 11330 has no affinity at μ, δ, or κ opioid receptors.

*   *   *

NIH 11331   *N*-(2-Methylallyl)-4-phenylpiperidine-4-nitrile.HCl
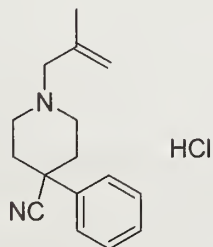
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 19% inhibition at 10 μM
δ-receptor: 25% inhibition at 10 μM
κ-receptor: 5040 ± 1310

SUMMARY

NIH 11331 has very low affinity at the κ opioid receptor and no affinity at μ and δ opioid receptors.

NIH 11332   *N*-Methyl-4-phenylpiperidine-4-nitrile. HCl

HCl
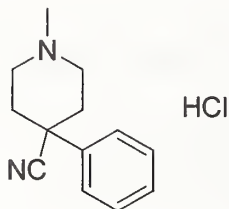
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 23% inhibition at 10 μM
δ-receptor: 16% inhibition at 10 μM
κ-receptor: 14%inhibition at 10 μM

SUMMARY

NIH 11332 has no affinity at μ, δ, or κ opioid receptors.

*   *   *

NIH 11333   **3-Desoxy-7,8-dihydromorphine.oxalate**
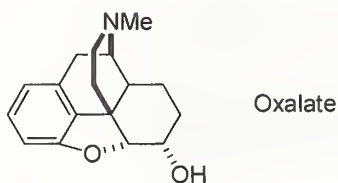
Oxalate

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 122 ± 37
δ-receptor: 4910 ± 320
κ-receptor: 5250 ± 2450

SUMMARY

NIH 11333 has low affinity at μ opioid receptor with very low affinity for δ and κ opioid receptors.

*   *   *

NIH 11334   **6-Desoxymorphine.oxalate**

Oxalate
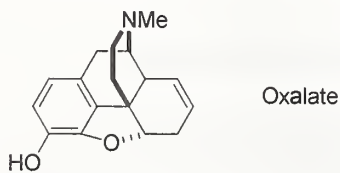
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 2.9 ± 1.1
δ-receptor: 45.5 ± 3.1
κ-receptor: 11.8 ± 3.1

SUMMARY

NIH 11334 has high affinity at the μ opioid receptor and affinity at δ and κ opioid receptors. It is 4 fold selective for μ over κ and 16-fold selective for μ over δ.

NIH 11335   3,6-Didesoxydihydromorphine.HCl

HCl
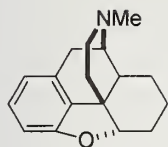
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 22.9 ± 2.9
δ-receptor: 589 ± 64
κ-receptor: 241 ± 27

SUMMARY

NIH 11335 has affinity at the μ opioid receptor with at least 10-fold selectivity over the δ and κ opioid receptors.

*   *   *

NIH 11345   (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-oxo-3,3-dimethylbutyl)-6,7-benzomorphan.oxalate
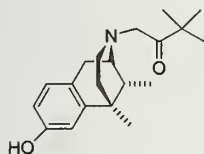
Oxalate

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 297 ± 95
δ-receptor: 2050 ± 210
κ-receptor: 200 ± 31

SUMMARY

NIH 11345 has low affinity at the μ and κ opioid receptors and very low affinity at the δ opioid receptor.

*   *   *

NIH 11346   (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-oxo-3,3-dimethylbutyl)-6,7-benzomorphan.HBr
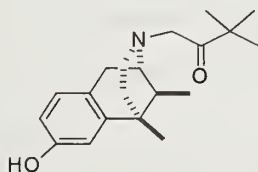
HBr

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 24% inhibition at 10 μM
δ-receptor: 26% inhibition at 10 μM
κ-receptor: 4900 ± 530

SUMMARY

NIH 11346 has very low affinity at the δ opioid receptor and no affinity for the μ and κ opioid receptors.

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NIH 11347   (-)-(1R,5R,9R)-5,9-Dimethyl-2-(2-(2-hydroxyethoxy)ethyl)-2'-hydroxy-6,7-benzomorphan.HCl
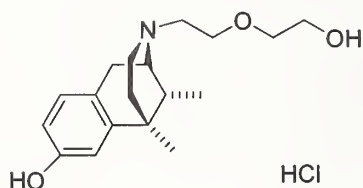
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 231 ± 40
δ-receptor: 1080 ± 47
κ-receptor: 64 ± 7

SUMMARY

NIH 11347 has affinity at the κ opioid receptor, low affinity at the μ opioid receptor, and very low affinity at the δ opioid receptor.

*   *   *

NIH 11348   (+)-(1S,5S,9S)-5,9-Dimethyl-2-(2-(2-hydroxyethoxy)ethyl)-2'-hydroxy-6,7-benzomorphan.HCl
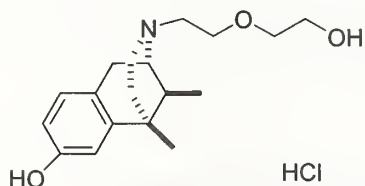
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1240 ± 245
δ-receptor: 39% inhibition at 10 μM
κ-receptor: 582 ± 12

SUMMARY

NIH 11348 has low affinity at the κ opioid receptor, very low affinity at μ opioid receptor, and no affinity at the δ opioid receptor.

*   *   *

NIH 11349   (-)-(1R,5R,9R)-2-(3-Cyanopropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl
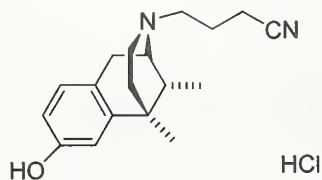
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3.1 ± 1.3
δ-receptor: 9.9 ± 2.7
κ-receptor: 0.32 ± 0.03

SUMMARY

NIH 11349 has very high affinity at the κ opioid receptor and high affinity at μ and δ opioid receptors. It is 10-fold selective for κ over μ and 31-fold selective for κ over δ.

NIH 11350 (+)-(1S,5S,9S)-2-(3-Cyanopropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl
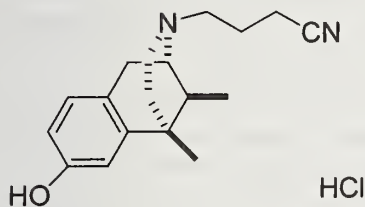
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1890 ± 580
δ-receptor: 7090 ± 720
κ-receptor: 181 ± 17

SUMMARY

NIH 11350 has low affinity for the κ opioid receptor with 10-fold selectivity for κ over μ and 39-fold selectivity for κ over δ.

*   *   *

NIH 11351 (+)-(1R,5R,9R)-2-(2-Methoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl
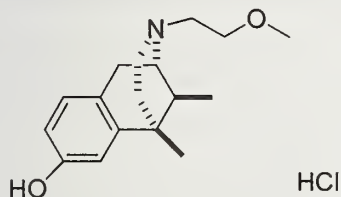
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 246 ± 62
δ-receptor: 1780 ± 140
κ-receptor: 123 ± 24

SUMMARY

NIH 11351 has low affinity at the κ and μ opioid receptors and very low affinity at the δ opioid receptor.

*   *   *

NIH 11352 (-)-(1S,5S,9S)-2-(2-Methoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl
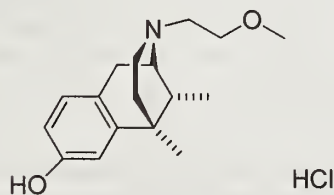
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.32 ± 0.10
δ-receptor: 2.1 ± 0.4
κ-receptor: 0.24 ± 0.04

SUMMARY

NIH 11352 has very high affinity at the κ and μ opioid receptors and high affinity at the δ opioid receptor.

NIH 11353   3-Isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine
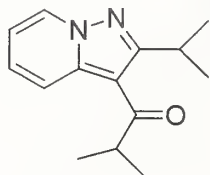
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3% inhibition at 10 μM
δ-receptor: 4% inhibition at 10 μM
κ-receptor: 1% inhibition at 10 μM

SUMMARY

NIH 11353 has no affinity at the μ, δ, or κ opioid receptors.

* * *

NIH 11211   9-(8-Azabicyclo[3.2.1]oct-3-ylidene)-15,5R-9H-xanthene-3-carboxylic acid diethylamide.HCl
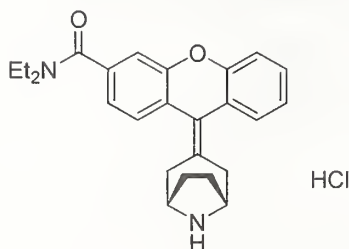
THE REINFORCING EFFECTS OF NIH 11211 IN RHESUS MONKEYS

The reinforcing effects of NIH 11211 were evaluated in three monkeys that were experienced with intravenous self-administration of alfentanil and saline. The subjects were given the opportunity to respond and receive alfentanil or saline infusions through intravenously implanted catheters during two 130 min sessions each day. At the beginning of each session, a red light was illuminated over one of two levers in the monkeys' cages. When the light was illuminated, 30 responses (for Biff) or 10 responses (for Hilda and Bonzo) on that lever resulted in an intravenous infusion of drug or saline. Each infusion was followed by a 45 sec timeout; during the infusion and the timeout, the red light was extinguished. There was a centrally located green light that was illuminated during the infusions. After each timeout, the red light was turned on again, and the fixed ratio schedule was again in effect.

Each session was divided into four components of 25 min or 20 injections, whichever came first. The components were separated from each other by 10 min blackout periods, during which time all stimulus lights were extinguished and lever responses had no programmed consequences. The duration of the intravenous infusion that served to reinforce behavior was different in each of the four components. This resulted in four different doses of alfentanil or the test drug being available to the monkeys during different components of each session. When saline was available, different infusion durations of saline were delivered as a consequence of responding.

On approximately half of the sessions, alfentanil was used to maintain behavior; response-contingent saline was available on the other baseline sessions. The doses of alfentanil that were available during single sessions were 0.00003, 0.0001, 0.0003, and 0.001 mg/kg/inj. These doses were presented in one of four orders: ascending, descending, and two mixed orders.

These doses were associated with infusion durations of 0.5, 1.7, 5, and 16.7 sec. When saline was available, these infusion durations were also used to deliver saline during a session. Prior to substitution of NIH 11211, each monkey was required to demonstrate a dose-related increase in behavior maintained by alfentanil, and consistently low rates of responding when saline was response-contingent.

A wide range of doses of NIH 11211 was tested in each monkey using this procedure. Because only four doses could be evaluated in a single session, a wider range of doses were evaluated by using different concentrations of NIH 11211 solutions. In these three monkeys, 0.0003, 0.001, 0.003, and 0.01 mg/kg/inj NIH 11211 were substituted for alfentanil on each of two sessions; 0.001, 0.003, 0.01, and 0.03 mg/kg/inj NIH 11211 were substituted on each of two sessions; 0.003, 0.01, 0.03, and 0.1 mg/kg/inj NIH 11211 were substituted on each of two sessions; and 0.01, 0.03, 0.1, and 0.3 mg/kg/inj NIH 11211 were substituted on each of two sessions. An ascending dose order was consistently used during substitution of NIH 11211. These data were averaged across doses per injection, and the mean and standard deviation are included on the accompanying graph.

The graph demonstrates that, for each monkey, increasing doses of alfentanil (squares) led to increasing rates of responding. Hilda and Bonzo responded at considerably lower rates than did Biff, perhaps because these monkeys were new to the procedure. Saline (triangles) did not maintain behavior in any monkey. Note: The abscissae [dose(mg/kg/inj)] does not refer to saline. NIH 11211 (inverted triangles) maintained rates of responding that were usually as low as those maintained by saline or by small doses of alfentanil. NIH 11211 did not appear to have reinforcing effects in these monkeys under these conditions.

NIH 11211
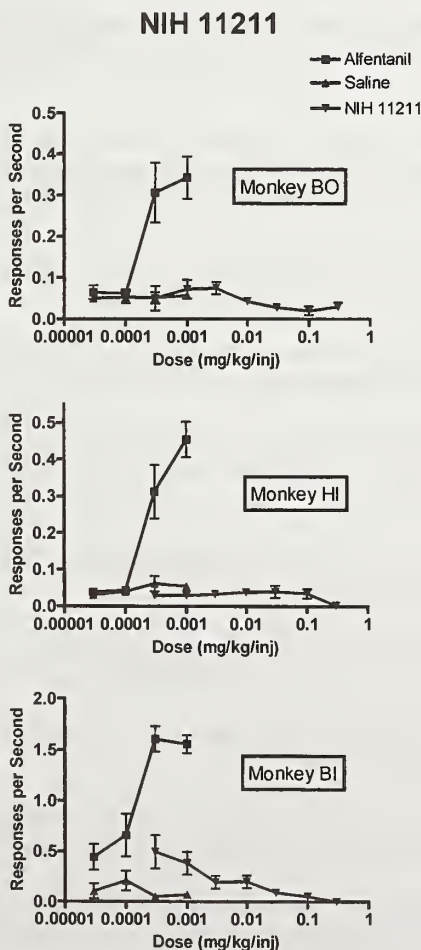
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AFFILIATION

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PROGRESS REPORT FROM THE TESTING PROGRAM FOR STIMULANT AND DEPRESSANT DRUGS (2007)

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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 23 years. The group currently includes laboratories at The University of Texas Health Science Center at San Antonio (UTHSCSA; CP France, LR McMahon), the University of Michigan (UM; WE Fantegrossi [current address: Emory University], G Winger, JH Woods), The University of Mississippi Medical Center (UMMC; WL Woolverton), and the University at Buffalo (UB; JC Winter). As part of the Drug Evaluation Committee (JH 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 (A 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, one compound was tested for its capacity to induce phencyclidine (PCP)-like discriminative stimulus effects in rats (UB). This report includes the results of evaluation of CPDD 0069 and CPDD 0070. All studies were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committees at UTHSCSA, UM, UMMC, UB and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health. In accordance with IACUC requirements, environmental enrichment toys were also provided to monkeys on a regular rotating basis.

METHODS

Reinforcing Effects in Rhesus Monkeys (UM)

Subjects and Apparatus

Three adult male rhesus monkeys (Macaca mulatta) experienced with self-administration of cocaine and saline served as subjects. Animals were surgically prepared with indwelling silicone rubber catheters using 10 mg/kg ketamine (i.m.) and 2 mg/kg xylazine (i.m.) as anesthetic. 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, Quebec, Canada) connected to a flexible stainless steel spring tether 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 lights (red-green-red) across the top, and two response levers (one mounted under each red light). Animals were fed between 10 and 12 Purina monkey chows twice per day, and water was continuously available. Daily fresh fruit and other treats supplemented this diet. Operation of the infusion pump delivered 1 ml of drug solution over 5 seconds.

Procedure

Two 60-minute experimental sessions were conducted each day: a morning session starting at about 10:00 AM and an afternoon session starting at about 4:00 PM. The onset of each session was signaled by illumination of a red stimulus light. In the presence of this light, completion of the response requirement (FR 10) on the lever beneath the light resulted in the operation of the infusion pump. During the 5-second infusion, the red stimulus light was extinguished and the center green light was illuminated; lever presses had no programmed consequence during the infusion. Immediately following each infusion, all stimulus lights were extinguished for a 1-minute timeout period, during which lever presses had no programmed consequence. Each timeout period counted toward the total 60-minute session time.

Under baseline conditions, animals were maintained on a cocaine dose of 0.01 mg/kg/injection. Saline was randomly substituted for cocaine approximately every third or fourth session, occasionally for two consecutive sessions. Substitutions of CPDD 0069 occurred two to three times each week, starting with the smallest dose. At least three sessions intervened between each substitution of CPDD 0069; during at least one of these sessions

cocaine was available, and during at least one of these intervening sessions, saline was available. The number of injections of cocaine or saline that were taken in the session most immediately before each substitution of CPDD 0069 was averaged for comparison with CPDD 0069. Each dose of CPDD 0069 was made available at least twice.

Drugs

Cocaine HCl and CPDD 0069 were dissolved in sterile 0.9% saline. Doses of 0.01, 0.03, and 0.1 mg/kg/injection of CPDD 0069 were tested in each of the three monkeys.

Discriminative Stimulus Effects in Rhesus Monkeys (amphetamine discrimination, UMMC)

Subjects and Apparatus

Three adult rhesus monkeys served as subjects and had received other drugs prior to this study. Monkeys were individually housed in stainless-steel cages with water available continuously. Feeding consisted of 110 to 200 g of Teklad Monkey Chow immediately after each session and a chewable vitamin tablet 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 and a white house light mounted on the ceiling. Above each lever was a set of white and red jeweled lights. Shoes were attached to the foot rest of 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

All monkeys previously had been trained in a discrete-trials paradigm to discriminate 1.0 mg/kg of amphetamine from saline. Each monkey was placed in the chair and moved to the test room. In the test room their feet were placed into shoes and held in place with a Velcro strap. Each monkey was given an infusion of either saline (0.25 ml/kg) or the training drug, followed by a 2.0 ml saline flush, i.g. via a nasogastric tube. Monkeys then remained in the chair in the test room. Fifty-five minutes after the infusion, monkeys were placed in the experimental chambers. The session then began with a 5-minute timeout, after which the house and lever lights were illuminated (trial) and responding on the correct lever avoided electric shock (8515 and Ou3) or delivered a 1-gram 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 (FR 2 or 3, 8515; FR 5, M163, Ou3) was not satisfied on the correct lever within 10 seconds of the onset of the lights, shock (250 msec duration, 5 mA intensity) was delivered (8515 and Ou3). If the response requirement was not met within 4 seconds of this shock, 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 ended when two shocks were delivered or no food was delivered in each of two consecutive trials. 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 and D denotes sessions preceded by drug. Testing began when at least 80% of the responses in the first trial, and at least 90% of the total trials (27/30), were completed on the correct lever for seven out of eight consecutive sessions; in addition, responding in the eighth of these consecutive sessions had to satisfy training criteria. During tests, sessions were conducted according to the following two-week schedule: SDTST, DSTDT, where T denotes a test session. If the criteria for stimulus control were not satisfied during the a training session, 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. For test sessions that involved s.c. injections, i.g. infusions of saline were also given at the usual pretreatment time (one hour pre-session), followed immediately by s.c. injection of the test drug.

Drugs

d-Amphetamine sulfate (Abbott Laboratories, N. Chicago, IL) and CPDD 0069 were dissolved in sterile 0.9% saline and administered in a volume of 0.25 ml/kg body weight. Injections (s.c.) were given in 1.0 ml/10 kg up to a dose of 1.0 mg/kg; for a dose of 3.0 mg/kg, injection volume was increased to 3.0 ml/kg because of solubility limitations. Doses of CPDD 0069 were tested at least twice, once the day after a saline training session and once the day after an amphetamine training session. When results were disparate in those two tests, the test sessions were generally repeated. CPDD 0070 was prepared in DMSO in a volume of 0.25 ml/kg. Each dose of CPDD 0070 was tested once.

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations, UTHSCSA)

METHODS

Subjects and Apparatus

The subjects were four female (LI, NI, SA, and JI) and three male (JE, LE, and RO) rhesus monkeys weighing between 6.3 and 9.1 kg. Monkeys were housed individually in stainless steel cages where water was continuously available and they 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 an array of 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 located adjacent to the chambers.

Procedures

Flumazenil Discrimination. Monkeys JI, JE, and LE consumed 5.6 mg/kg of diazepam 3 h prior to daily sessions in which they discriminated between s.c. injections of vehicle and either 0.1 mg/kg (JI) or 0.178 mg/kg (JE, LE) of flumazenil while responding under a fixed-ratio 5 schedule of food presentation. Training sessions consisted of several discrete, 15-minute cycles with each cycle comprising 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 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 0069, or CPDD 0070 were administered during the first min of the timeout and 5 consecutive responses on either lever resulted in the delivery of food. Test substances also were studied every 15 minutes for up to 2 hours after administration (i.e., 8, 15-min cycles) to determine their time course.

Midazolam Discrimination. Monkeys LI, NI, RO, and SA discriminated between s.c. injections of saline and 0.32 mg/kg of midazolam while responding under a fixed-ratio 10 schedule of stimulus-shock termination. Daily sessions consisted of several discrete, 15-minute cycles with each cycle comprising 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 0069, or CPDD 0070 were administered during the first minute of the timeout and 10 consecutive responses on either lever postponed the shock schedule. Test substances also were studied every 15 minutes for up to 2 hours after administration (i.e., 8, 15-min cycles) to determine their time course.

Drugs

Diazepam (Zenith Laboratories, Northvale, NJ) was suspended in 44 ml of fruit punch containing suspending Agent K (JI) or crushed with a mortar and pestle to yield a dose of 5.6 mg/kg/daily administration. 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 0069 was dissolved in saline and was studied up to a dose of 5.6 mg/kg s.c. CPDD 0070 was dissolved in DMSO and was studied up to a dose of 0.56 mg/kg s.c.

Discriminative Stimulus Effects in Rats (phencyclidine [PCP], UB)

METHODS

Subjects and Apparatus

Twelve male Fischer 344 rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN, USA) were housed in pairs under a 12/12 hr light/dark cycle with free access to water in the home cages. Training and testing occurred during the light cycle. Caloric intake was controlled to maintain a mean body weight of approximately 300 g with standard rat chow provided after sessions. Caloric control and decreased frequency of food availability have been shown to increase lifespan and decrease frequency of disease in rats.

Commercially available chambers (model ENV-008, MED Associates) were located in sound-attenuating boxes equipped with a house light and exhaust fan. Chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper that could deliver 0.1 ml of sweetened condensed mild diluted 2:1 with tap water. Sessions were controlled and data collected by a computer and commercially-available software and interface (MED-PC State Notation, Version IV).

Procedure

After learning to drink from the dipper, rats were trained to press one then the other lever with the number of responses required for reinforcer delivery systematically increased across sessions from 1 to 10. During this training the lever that resulted in reinforcer delivery was alternated randomly across sessions. Subsequently, subjects were trained to discriminate vehicle from 3.0 mg/kg PCP (i.p.), administered 30 minutes prior to the session. For half of the subjects the left lever was active after PCP and the right lever active after vehicle; lever designation were opposite for the remaining rats. Stimulus control was adequate for testing when, in five consecutive sessions, at least 83% of all responses prior to delivery of the first reinforcer were on the injection-appropriate lever (i.e., no more than 2 responses on the injection-inappropriate lever).

Tests with CPDD 0070 were conducted no more than once per week, with half of the subjects receiving saline on the day prior to testing and the other half receiving PCP. Test sessions ended after 10 responses were made on either lever; no reinforcer was delivered. The distribution of responses between the two levers was expressed as a percentage of total responses made on the PCP-associated lever. Response rate was calculated by dividing the total number of responses on both levers by elapsed time. Data for any rat that failed to make 10 responses within 10 minutes were not included in calculation of discrimination results and were included for calculation of response rate.

Drugs

Phencyclidine hydrochloride (PCP, National Institute on Drug Abuse) was dissolved in 0.9% saline and injected i.p. in a volume of 1 ml/kg body weight. CPDD 0070 was dissolved in a minimal volume of DMSO and diluted with water; injections were i.p. in a volume of 2 ml/kg body weight.

RESULTS

2 CH$_3$SO$_3$H
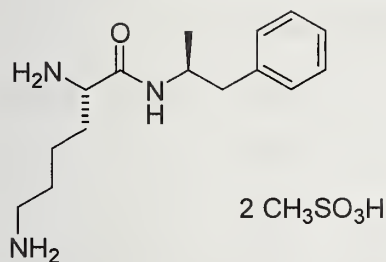
CPDD 0069: (2S,2'S)-2,6-Diamine-N-(1-phenylpropan-2-yl)hexanamide.dimesylate

Reinforcing Effects in Rhesus Monkeys (UM)

As shown in Table 1, monkeys received an average of between 36.4 and 48.7 injections of cocaine, and between 9.8 and 13.5 injections of saline, prior to tests with CPDD 0069. The smallest dose of CPDD 0069 (0.01 mg/kg/injection) maintained responding similar to what was observed with saline, with between 9.7 and 12.5 injections received per session. Increasing unit doses of CPDD 0069 maintained increasing self administration with between 19 and 31 injections received of 0.03 mg/kg/injection and between 23.2 and 49 injections received of 0.1 mg/kg/injection. Larger doses of CPDD 0069 were not tested because all of the monkeys showed marked behavioral changes, including nystagmus or increased irritability, following self-administration of the 0.1 mg/kg/injection of CPDD 0069.

Table 1. Self administration (i.v.) of cocaine, saline and CPDD 0069

			CPDD 0069 (mg/kg/injection)		
Subject	Cocaine	Saline	0.01	0.03	0.1
CA	36.4	9.8	9.7	19.0	23.2
ST	37.4	11.7	12.5	20.2	27.0
BI	48.7	13.5	12.3	31.0	49.0

Discriminative Stimulus Effects in Rhesus Monkeys (amphetamine discrimination, UMMC)

All three monkeys discriminated reliably between i.g. amphetamine and saline (Table 2). When given i.g. 60 minutes before the session, CPDD 0069 (1.0-10 mg/kg) had variable discriminative stimulus effects, both within and across monkeys (Table 2). For example, monkey 8515 showed dose-related generalization to amphetamine with a maximum of 95% drug-lever responding at a dose of 5.6 mg/kg (ED$_{50}$=2.65 mg/kg). Monkey M163 showed partial (maximum 50%) effect that was not clearly dose related from doses of 1.0 to 10 mg/kg. Monkey Ou3 responded exclusively on the amphetamine-associated lever after a dose of 1.0 mg/kg, and less so at larger doses of CPDD 0069. Rate of responding was not clearly affected by any dose of CPDD 0069.

When given s.c., amphetamine engendered a dose-related increase in responding on the drug-associated lever, with the maximum possible effect (100%) observed in all monkeys (Table 3). The mean ED$_{50}$ for amphetamine was 0.15 mg/kg (SEM=0.04). When administered s.c., CPDD 0069 also occasioned a dose-related increase in amphetamine-lever responding, with a near maximum possible effect (more than 98%) observed in all monkeys (Table 4). The mean ED$_{50}$ for CPDD 0069 was 1.73 mg/kg (SEM=0.42).

Table 2. Discriminative stimulus effects of amphetamine, saline and CPDD 0069 (i.g.) in monkeys discriminating amphetamine

			CPDD 0069 (mg/kg)				
Subject	Amphetamine	Saline	0.3	1.0	3.0	5.6	10.0
8515*	100/1.4**	1.5/1.8	0/1.4	0/1.5	78/1.5	95/1.4	n.t.
M163	100/1.8	5/1.4	n.t.	45/1.9	50/2.3	28/2.1	31/1.6
Ou3	100/2.3	0/2.7	0/2.0	100/2.3	47/2.0	48/2.3	0/1.6[1]

*The response requirement was FR 2 for 8515 and FR 5 for M163 and Ou3.
**Data represent the percent drug-appropriate trials/average response rate (responses/second).
CPDD 0069 was administered via nasogastric tube 60 minutes prior to testing.
 n.t.=not tested
10.0 mg/kg was tested only once in Ou3.

Table 3. Discriminative stimulus effects of amphetamine (s.c.) in monkeys discriminating amphetamine

	Amphetamine (mg/kg)			
Subject	0.03	0.1	0.3	1.0
8515	0/1.7	26.5/1.6	91.5/1.7	100/1.4
M163	1.5/2.0	49.5/1.4	40/1.1	100/1.5
Ou3	0/2.6	50/2.5	100/2.3	n.t.

See Table 2 for details. Monkeys received i.g. saline one hour before the first trial, followed by s.c. amphetamine.

Table 4. Discriminative stimulus effects of CPDD 0069 (s.c.) in monkeys discriminating amphetamine

	CPDD 0069 (mg/kg)			
Subject	0.1	0.3	1.0	3.0
8515	0/1.6[1]	10/1.6[1]	0/1.8	98/1.8
M163	0/1.8	73/1.1	24.5/1.8	98/1.3
Ou3	0/2.6[1]	0/2.6	50/2.3	100/2.6

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations, UTHSCSA)

Flumazenil Discrimination.   In monkeys receiving 5.6 mg/kg/day of diazepam, 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 5). Over the doses studied, flumazenil decreased response rate in JI and increased response rate in JE.

Table 5. Discriminative stimulus effects of flumazenil (s.c.) in diazepam-treated monkeys discriminating flumazenil

Flumazenil (mg/kg)

Subject	Vehicle	0.01	0.032	0.1
JI	0/1.41*	11/1.65	53/1.29	98/0.79
JE	0/0.46	0/0.38	74/0.90	88/1.04

*Data represent the percent responding on the drug-associated lever for the entire session/average response rate (responses/second).

CPDD 0069 did not substitute for the flumazenil discriminative stimulus (Table 6) up to a dose (1.0 mg/kg) that suppressed responding in both monkeys. Data shown are from 45 minutes after administration of CPDD 0069 (peak onset for rate-decreasing effects). At the largest dose studied (1.0 mg/kg), the onset of action for CPDD 0069 to suppress responding was 45 minutes in JI and 30 minutes in NI and the duration of action was at least 75 minutes (Table 7).

Table 6. Discriminative stimulus effects of CPDD 0069 (s.c.) in diazepam-treated monkeys discriminating flumazenil

CPDD 0069 (mg/kg)

Subject	Vehicle	0.1	0.32	1.0
JI	0/1.62	n.t.	0/1.66	*/0
JE	0/0.42	0/0.27	0/0.76	*/0

*Discrimination data are not presented when response rate was <20% of control response rate
See Tables 2 and 5 for details

Table 7. Time course of rate-decreasing effects for CPDD 0069 in diazepam-treated monkeys discriminating flumazenil

Minutes after 1.0 mg/kg (s.c.) CPDD 0069

Subject	15	30	45	60	75	90	105	120
JI	0/1.59	0/1.42	*/0	*/0	*/0.25	*/0	*/0	*/0
JE	0/0.13	*/0	*/0	*/0	*/0.25	*/0	4/0.39	0/1.02

See Tables 2 and 5 for details

Midazolam Discrimination. In other monkeys, midazolam dose-dependently increased responding on the drug (midazolam)-associated lever with a dose of 0.1 mg/kg occasioning greater than 80% drug-lever responding in each monkey (Table 8). The largest dose of midazolam (0.1 mg/kg) slightly increased response rate in LI and decreased response rate in NI.

Table 8. Discriminative stimulus effects of midazolam (s.c.) in monkeys discriminating midazolam.

	Midazolam (mg/kg)			
Subject	Vehicle	0.01	0.032	0.1
LI	0/1.59	0/1.39	0/1.47	89/2.05
NI	0/3.08	0/3.01	0/2.71	86/0.78

See Tables 2 and 5 for details

CPDD 0069 did not substitute for the midazolam discriminative stimulus and did not markedly alter response rates (Table 9) up to a dose of 5.6 mg/kg. Data shown are from 45 minutes after administration of CPDD 0069.

Table 9. Discriminative stimulus effects of midazolam (s.c.) in monkeys discriminating midazolam.

	CPDD 0069 (mg/kg)			
Subject	Vehicle	1.0	3.2	5.6
LI	0/1.07	0/1.40	0/1.34	0/1.04
NI	0/3.08	0/2.25	0/1.90	0/2.80

See Tables 2 and 5 for details
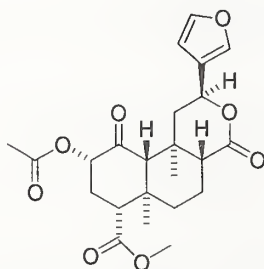
CPDD 0070: Salvinorin A

Discriminative Stimulus Effects in Rhesus Monkeys (amphetamine discrimination, UMMC)

When CPDD 0070 (0.01-1.0 mg/kg) was administered i.g. 60 minutes before the session, neither monkey completed any trials on the amphetamine-associated lever (Table 10). These doses of CPDD 0070 did not affect rate of lever pressing. Larger doses could not be tested because of limited solubility.

Table 10. Discriminative stimulus effects of CPDD 0070 (i.g.) in monkeys discriminating amphetamine

CPDD 0070 (mg/kg)

Subject	Amphetamine	Saline	0.01	0.03	0.3	1.0
8515	100/1.4	1.5/1.8	n.t.	n.t.	0/1.9	0/1.6
Ou3	100/2.3	0/2.7	0/2.6	0/2.1	0/2.5	0/2.65

The response requirement was FR 3 for 8515 and FR5 for Ou3.
See Tables 2 and 3 for details

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations, UTHSCSA)

Flumazenil Discrimination. In monkeys receiving 5.6 mg/kg/day of diazepam p.o. and discriminating between 0.056 mg/kg of flumazenil and vehicle, flumazenil dose-dependently increased responding on the drug (flumazenil)-associated lever with doses of 0.032 mg/kg (JI) and 0.1 mg/kg (LE) occasioning greater than 80% drug-lever responding (Table 11). Over the doses studied, flumazenil slightly decreased response rate in JI and had relatively little effect on response rate in LE.

Table 11. Discriminative stimulus effects of flumazenil (s.c.) in diazepam-treated monkeys discriminating flumazenil

Flumazenil (mg/kg)

Subject	Vehicle	0.0032	0.01	0.032	0.1
JI	0/1.92	0/1.91	0/2.16	100/1.44	n.t.
LE	2/1.05	2/1.23	7/1.22	10/1.25	98/1.10

See Tables 2 and 5 for details

CPDD 0070 did not substitute for the flumazenil discriminative stimulus (Table 12) up to doses (0.1 mg/kg in LE and 0.32 mg/kg in JI) that suppressed responding. Data shown are from 30 minutes after administration of CPDD 0070 (peak onset for rate-decreasing effects).   At the largest doses studied (0.32 mg/kg in JI and 0.1 mg/kg in JE), the onset of action for CPDD 0070 to suppress responding was 15-30 minutes and the duration of action was at least 105 minutes (Table 13).

Table 12. Discriminative stimulus effects of CPDD 0070 (s.c.) in diazepam-treated monkeys discriminating flumazenil

CPDD 0070 (mg/kg)

Subject	Vehicle	0.032	0.1	0.32
JI	0/1.98	n.t.	0/2.05	*/0.
LE	4/1.07	2/0.93	*/0	n.t.

See Tables 2 and 5 for details

Table 13. Time course of rate-decreasing effects for CPDD 0070 in diazepam-treated monkeys discriminating flumazenil

Minutes after 0.1 (LE) or 0.32 (JI) mg/kg (s.c.) CPDD 0070

Subject	15	30	45	60	75	90	105	120
JI	*/0	*/0	*/0	*/0	*/0	*/0	*/0	1/0.5
LE	7/0.85	*/0	*/0	*/0	*/0	*/0	*/0	*/0

See Tables 2 and 5 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 doses of 0.1 mg/kg (LI) and 0.32 mg/kg (RO and SA) occasioning greater than 80% drug-lever responding (Table 14). The largest dose of midazolam (0.32 mg/kg) slightly decreased response rate. At a dose of 0.56 mg/kg, CPDD 0070 substituted for the midazolam discriminative stimulus (Table 16) in one (SA) of three monkeys and decreased response rate in two monkeys (RO and SA). Data shown are from 30 minutes after administration of CPDD 0070. At the largest dose (0.56 mg/kg) studied, the onset of action of CPDD 0070 to decrease (RO and SA) or to increase (LI) response rate was 15-30 minutes. One monkey (SA) responded predominantly on the midazolam-lever 15-60 minutes after administration of CPDD 0070 (Table 16).

Table 14. Discriminative stimulus effects of midazolam (s.c.) in monkeys discriminating midazolam

Midazolam (mg/kg)

Subject	Vehicle	0.01	0.032	0.1	0.32
RO	0/2.56	0/2.61	0/3.01	56/2.39	100/1.89
SA	0/3.06	0/2.74	0/2.80	67/2.42	100/2.43
LI	0/1.76	0/1.63	11/1.58	100/1.86	100/1.35

See Tables 2 and 5 for details

Table 15. Discriminative stimulus effects of CPDD 0070 (s.c.) in monkeys discriminating midazolam

CPDD 0070 (mg/kg)

Subject	Vehicle	0.32	0.56
RO	0/1.87	0/2.66	0/0.94
SA	0/2.97	0/3.31	88/2.04
LI	0/1.49	22/1.94	0/1.62

See Tables 2 and 5 for details

Table 16. Time course of rate-decreasing effects for CPDD 0070 in monkeys discriminating midazolam

Minutes after 0.56 mg/kg (s.c.) CPDD 0070

Subject	15	30	45	60	75	90	105	120
RO	21/1.62	0/0.94	0/2.30	0/2.23	0/2.19	0/2.33	0/2.39	0/2.43
SA	68/1.80	88/2.04	94/2.10	99/1.95	33/2.82	0/3.46	0/3.07	0/3.06
LI	11/2.40	0/1.62	0/1.83	0/2.03	0/2.14	0/1.70	0/2.03	0/1.97

See Tables 2 and 5 for details

Discriminative Stimulus Effects in Rats (phencyclidine [PCP], UB)

Rats reliably discriminated between PCP and vehicle as indicated by more than 95% responding on the PCP-associated lever after the administration of the training dose (3.0 mg/kg) and 4% responding on the PCP-associated lever after the administration of vehicle (Table 17). Up to a dose of 1.0 mg/kg, CPDD 0070 occasioned predominantly vehicle-lever responding without markedly affecting rate of responding (Table 17).

Table 17. Discriminative stimulus effects of PCP, vehicle, and CPDD 0070 in rats discriminating PCP

	PCP-lever responding	Response rate
Vehicle (14)*	4 ± 2**	25 ± 3***
3.0 mg/kg PCP (14)	95 ± 2	25 ± 3
CPDD 0070		
0.2 mg/kg (14)	9 ± 4	17 ± 3
0.4 mg/kg (4)	27 ± 19	29 ± 4
1.0 mg/kg (3)	0	19 ± 7

*Number in parentheses indicates the number of rats studied
**Average (± SEM) percentage of responses on the PCP lever prior to completion of 10 responses on either lever
***Average response rate (± SEM) in responses/minute

CONCLUSIONS

CPDD 0069

CPDD 0069 maintained reliable i.v. self administration responding in monkeys with a history of responding for cocaine. When administered i.g., CPDD 0069 had variable effects in monkeys discriminating amphetamine; however, when administered s.c. it occasioned complete or near complete amphetamine-lever responding in all three monkeys. CPDD 0069 did not substitute either for midazolam or for flumazenil in monkeys receiving diazepam daily, although it decreased response rate for more than 2 hours after s.c. administration. Collectively these data suggest that CPDD 0069 has positive reinforcing effects and that it shares discriminative stimulus effects with amphetamine, a known drug of abuse. Given the strong predictive validity of these procedures in non-human primates to the effects of drugs in humans, these data indicate that CPDD 0069 is likely to have abuse liability in humans and that it might exert amphetamine-like subjective effects.

CPDD 0070

Among several different drug discrimination procedures in monkeys and in rats, CPDD 0070 did not clearly share discriminative stimulus effects with amphetamine, midazolam, flumazenil (in diazepam-treated subjects), or with PCP. Notwithstanding one monkey trained to discriminate midazolam that responded predominantly on the midazolam lever after receiving the largest dose of CPDD 0070, this compound does not appear to have effects in common with any of the training drugs used among these procedures. The generality of these largely negative data are limited insofar as other discriminations and other procedures (e.g,. self administration) could be sensitive to effects of CPDD 0070 that might be predictive of abuse liability.

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EVALUATION OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (2007)

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The identity of compounds submitted by the Biological Coordinator, Dr. Andrew Coop, of the University of Maryland 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). Supported by NIDA Contract DA 1-7725.

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. Beginning with NIH 11256, the dose regimen of morphine sulfate was changed from 3 mg/kg s.c. daily every six hours at 6 AM, 12 noon, 6 PM and midnight to 4 mg/kg, s.c. daily at 6 AM, 12 noon and 6 PM. 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, 4.0 mg/kg; and c) vehicle control, 1 ml/kg. Withdrawal signs were scored, absent or present, once during each of five consecutive 30 min observation periods. Withdrawal signs included: slowing of movement, drowsiness (sitting with eyed closed and lethargic or being indifferent to surroundings), fighting, vocalizing, rigidity of abdominal muscles, vocalization during palpation of abdominal muscles, restlessness (pacing), tremors, coughing, retching, vomiting, wet-dog shakes and masturbation. The observer was "blind" regarding the assignment of treatments. The mean cumulative score ± SEM was calculated for each observation period 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 (0.06 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
11199	Peptide	T	T	T	T		
11200	Peptide	T	T	T	T		
11201	Peptide	T	T	T	T		
11202	Peptide	T	T	T	T		
11203	Peptide	T	T	T	T		

Table 1. (continued)

NIH #	CHEMICAL NAME OR GENERIC CLASS	MOUSE DATA				MONKEY DATA	
		TF	TF vs M	PPQ	HP	SDS	PPT-W
11209	Peptide	T	T	T	T		
11205	Peptide	T	T	T	T		
11206	Peptide	T	T	T	T		
11207	Peptide	T	T	T	T		
11209	Peptide	T	T	T	T		
11209	6,7-Benzomorphan	T	T	T	T	T	
11210	6,7-Benzomorphan	T	T	T	T	T	
11228	Morphinan	T	T	T	T		
11222	Morphinan	T	T	T	T		
11223	Morphinan	T	T	T	T		
11224	Morphinan	T	T	T	T		
11225	Morphinan	T	T	T	T		
11228	Morphinan	T	T	T	T		
11227	Morphine	T	T	T	T		
11228	Salvinorin	T	T	T	T		
11285	6,7-Benzomorphan	T	T	T	T		
11286	6,7-Benzomorphan	T	T	T	T		
11287	6,7-Benzomorphan	T	T	T	T		
11288	6,7-Benzomorphan	T	T	T	T	T	
11209	Phenylmorphinan	T	T	T	T	T	
11290	Phenylmorphinan	T	T	T	T	T	
11292	Phenylpyran	T	T	T	T		
11293	Phenylamine	T	T	T	T		
11285	Phenylpyran	T	T	T	T		
11296	Phenylpyran	T	T	T	T		
11304	6,7-Benzomorphan	T	T	T	T		
11305	6,7-Benzomorphan	T	T	T	T		T
11307	6,7-Benzomorphan	T	T	T	T		
11308	6,7-Benzomorphan	T	T	T	T		
11304	6,7-Benzomorphan	T	T	T	T		T
11312	5-Flurooxymorphendole	T	T	T	T		
11314	5'-Chlorooxymorphindole	T	T	T	T		
11314	5'-Bromooxymorphindole	T	T	T	T		
11315	5'-Iodooxymorphindole	T	T	T	T		
11316	7'-Fluorooxymorphindole	T	T	T	T		
11317	5',7'-Difluorooxymorphindole	T	T	T	T		
11318	5',7'-Dichlorooxymorphindole	T	T	T	T		
11319	Oxymorphindole	T	T	T	T		
11320	Oripavine	T	T	T	T		

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Table 1. (continued)

NIH #	CHEMICAL NAME OR GENERIC CLASS	MOUSE DATA				MONKEY DATA	
		TF	TF vs M	PPQ	HP	SDS	PPT-W
11321	Oripavine	T	T	T	T		
11322	Morphine	T	T	T	T		
11323	6,7-Benzomorphan	T	T	T	T		
11324	6,7-Benzomorphan	T	T	T	T	T	
11325	6,7-Benzomorphan	T	T	T	T	T	
11326	6,7-Benzomorphan	T	T	T	T		
11334	6-Desoxymorphine	T	T	T	T		
11345	6,7-Benzomorphan	T	T	T	T		
11346	6,7-Benzomorphan	T	T	T	T		
11347	6,7-Benzomorphan	T	T	T	T		
11348	6,7-Benzomorphan	T	T	T	T		
11349	6,7-Benzomorphan	T	T	T	T		
11350	6,7-Benzomorphan	T	T	T	T		
11351	6,7-Benzomorphan	T	T	T	T		
11352	6,7-Benzomorphan	T	T	T	T	T	

T = Tested

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 that allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe that was attached to a syringe pump. The animals received 4-8 ml of solution every 24 hr. During withdrawal, the following signs were noted: irritability; front-paw shakes; wet-dog shakes; facial rubbings with front paws; eyelid ptosis and immobility.

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 the test compound, at appropriate doses, as specified above, for 4-6 days and then, were placed in abrupt withdrawal and observed for overt behavioral signs.

Mouse-Antinociception Tests

Male ICR mice, weighing 20-30 g, were used. All drugs were dissolved in sterile water or in a suitable vehicle and usually injected by the subcutaneous (s.c.) route of administration. Other routes of administration, when employed, are indicated in the report. 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.), intravenously (i.v.), or 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 light 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 (0.2 mg/ml), 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.

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 - 1) 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 2. Comparative Data (ED50, mg/kg, s.c. and 95% C.L. of Selected Standards in 4 Mouse Agonist-Antagonist Assays

Drug	Assays ED50 (95% C.L.) or % change, mg/kg/ s.c			
	TF	TF Antagonist	Phenylquinone	Hot -Plate
Pentazocine	15% at 10	18 (12 - 26)	1.7 (1.0 – 2.5)	13% at 30
Cyclazocine	17% at 1	0.03 (0.02 – 0.78)	0.01 (0.005 – 0.03)	25% at 9
Naloxone HCl	None at 10	0.04 (0.02 – 0.09)	Inactive	---
Naltrexone HCl	None at 10	0.007 (0.002 – 0.02)	Inactive	---
Morphine SO$_4$	1.92 (0.89 – 4.14)	Inactive	0.4 (0.2 – 0.8)	0.85 (0.39 – 1.86)
Codeine PO$_4$	17.5 (15.4 – 19.9)	Inactive	8.25 (5.12 – 13.29)	6.4 (0.39 – 16.8)
Enadoline HCl Kappa agonist NIH 10672	0.015 (0.003 – 0.059)	Inactive	0.0015 (0.004 – 0.006)	0.01 (0.004 – 0.04)
(+)-SNC80 NIH 10815 Delta agonist	Inactive	Inactive	3.8 (1.6 – 9.3)	Inactive
Sufentanil citrate NIH 9726 Mu agonist	0.004 (0.002 – 0.009)	---	---	---

Table 3. Apparent pA_2 values 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	-

pA_2: 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 test 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 opioids, special subtype testing is conducted. Results obtained with selective opioid antagonists vs standard mu-, kappa- and delta agonists are presented in Table 4.

Table 4. AD50s of selective opioid antagonists versus opioid agonist ED80s

Selective Antagonist	Antagonist Pretreatment time	Agonist	Agonist ED80 Pretreatment time	Assay	Antagonist AD50 95% C.L.
beta-FNA i.c.v. mu	4 hr	Sufentanil NIH 9726 s.c.	20 min	TF	3.98 (1.24 – 12.89) µg/brain
		Morphine s.c.			1.25 (0.56 – 2.78) µg/brain
Naltrindole NIH 10589 s.c. delta	30 min	SNC 80 NIH 10815 s.c.	20 min	PPQ	5.48 (2.97 – 10.11) mg/kg
Naltrindole i.c.v. delta		DPDPE NIH 10892 i.c.v.	10 min	PPQ	1.38 0.41 – 4.68 µg/brain
nor-BNI NIH 10588 s.c. kappa	2 hr	Enadoline NIH10672 s.c.	20 min	TF	10.26 (4.14 – 25.38) mg/kg
		(-)-U-50488 NIH 10533 s.c.			1.72 (0.57 – 5.16) mg/kg

NIH 11199 Acetyl-Arg-Phe(4-COOH)-Tyr-Arg-Trp-Arg-NH$_2$

MOUSE DATA - ED50 OR AD50
(95 % C.L) or % change
Drug was administered i.c.v., ug/brain

1) **TF** – 20% at 1, inactive at 1 and 3, and 30% at 30
2) **TF vs. M** – 18% at 1; 0% at 10 and 30% at 30
3) **PPQ** – 1.84 (0.69 – 4.84)
4) **HP** – Inactive at 1, 10 and 30

Comment: NIH 11199 was active in the PPQ assay. It may have delta-opioid agonist activity. Opioid subtype testing using naltrindole would help settle this issue. It also displayed erratic and weak effects in the tail-flick and tail-flick vs morphine assays.

NIH 11200 Acetyl-Arg-Phe(4-F)-Tyr-Arg-Trp-Arg-NH$_2$

> **MOUSE DATA - ED50 OR AD50**
> (95 % C.L.) or % change
> Drug was administered i.c.v., ug/brain
>
> 1) **TF** – 7% at 1, 11% at 10 and 12% at 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

Varying degrees of convulsive behavior and loss of righting reflex noted.

Comment: Antinociceptively speaking, NIH 11200 lacks activity. However, overt convulsive behavior and loss of righting reflex were noted.

NIH 11201 Acetyl-Arg-Phe(4-F)-Tyr-Arg-Trp-Arg-NH$_2$

> **MOUSE DATA - ED50 OR AD50**
> (95 % C.L) or % change
> Drug was administered i.c.v., ug/brain
>
> 1) **TF** – Inactive at 1, 33% at 10 and inactive at 30
> 2) **TF vs. M** – Inactive at 1 and 10 and 30% at 30
> 3) **PPQ** – 54% at 1, 3, and 10 and 27% at 30
> 4) **HP** – Inactive at 1, 10 and 30

Varying degrees of ataxia, convulsions and impaired righting were noted.

Comment: Pronounced CNS effects and no opioid agonist activity characterized NIH 11201.

NIH 11202 Acetyl-Arg-Phe(4-CN)-Tyr-Arg-Trp-Arg-NH$_2$

> **MOUSE DATA - ED50 OR AD50**
> (95 % C.L) or % change
> Drug was administered i.c.v., ug/brain
>
> 1) **TF** – Inactive at 1 and 10 and 22% at 30
> 2) **TF vs. M** – Inactive at 1, 10 and 30
> 3) **PPQ** – Inactive at 1 and 10 and 26% at 30
> 4) **HP** – Inactive at 1 and 10

Impaired righting reflex, ataxia and/or sedation were observed in all tests.

Comment: Pronounced CNS effects noted. Opioid agonist activity was not evident.

NIH 11203 Acetyl-Arg-Phe(4-CN)-Tyr-Arg-Trp-Arg-NH$_2$

> **MOUSE DATA -** ED50 OR AD50
> (95 % C.L.) or % change
> Drug was administered i.c.v., ug/brain
>
> 1) **TF** – Inactive at 1 and 10 and 17% at 30
> 2) **TF vs. M** – Not tested
> 3) **PPQ** – Inactive at 0.3, 48% at 1, 35% at 3 and inactive at 10
> 4) **HP** – Not tested. N = 4 at 10.

Drug supply was exhausted due to accidental loss of sample.

Comment: Impaired righting reflex and ataxia were noted and erratic results were obtained in the PPQ test.

NIH 11204 Acetyl-Arg-Tyr-Phe(4-F)-Arg-Trp-Arg-NH$_2$

> **MOUSE DATA -** ED50 OR AD50
> (95 % C.L) or % change
> Drug was administered i.c.v., µg/brain
>
> 1) **TF** – Inactive at 1, 10 and 30
> 2) **TF vs. M** – 37% at 1, 25% at 10 and 30
> 3) **PPQ** – Inactive at 0.3, 45% at 1, 42% at 3, 52% at 10 and 23% at 30
> 4) **HP** – Inactive at 1, 10 and 30

Varying degrees of ataxia, convulsions and loss of loss of righting reflex were noted.

Comment: Discernable opioid properties were not evident.

NIH 11205 Acetyl-Arg-Tyr-Phe(4-NHAc)-Arg-Trp-Arg-NH$_2$

> **MOUSE DATA -** ED50 OR AD50
> (95 % C.L.) or % change
> Drug was administered i.c.v., ug/brain
>
> 1) **TF** – Inactive at 1, 32% at 10 and inactive at 30
> 2) **TF vs. M** – 32% at 1, 44% at 10 and 27% at 30
> 3) **PPQ** – Inactive at 1, 10 and 30
> 4) **HP** – Inactive at 1, 10 and 30

Impaired righting reflex, muscle twitching and ataxia were noted.

Comment: NIH 11125 has prominent CNS effects and unremarkable opioid agonist properties.

NIH 11206 Acetyl-Arg-Tyr(3-Cl)-Tyr-Arg-Trp-Arg-NH$_2$

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change
Drug was administered i.c.v., ug/brain

1) **TF** – Inactive at 1 and 10
2) **TF vs. M** – 26% at 1 and inactive at 10
3) **PPQ** – Inactive at 1, 29% at 3, 35% at 10 and 29% at 30
4) **HP** – Inactive at 1, 10 and 30

Note: 4/6 died at 30 ug/brain before testing in the tail- flick and morphine antinociceptive tests, respectively. Varying degrees of convulsions, loss of righting, impaired righting reflex, convulsions and sedation, in the PPQ test, were noted.

Comment: Dramatic CNS effects, erratic dose response in the PPQ test, and weak morphine antagonism activity were noted with this compound.

NIH 11207 Acetyl-Arg-Tyr-Phe(4-benzyl)-Arg-Trp-Arg-NH$_2$

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change
Drug was administered i.c.v., ug/brain

1) **TF** – Inactive at 1 and 10, 34% at 30
2) **TF vs. M** – Inactive at 1,10 and 30
3) **PPQ** – 26% at 1, 32% at 10 and 42% at 30
4) **HP** – Inactive at 1, 10 and 30

Varying degrees of ataxia, convulsive behavior and tremors were observed.

Comment: Dramatic CNS manifestations and unremarkable antinociceptive activity were noted.

NIH 11208 Heptanoyl-Arg-Tyr-Phe-Arg-Trp-Arg-NH$_2$

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change
Drug was administered i.c.v.,ug/brain

1) **TF** – 27% at 1, 15% at 10 and 20% at 30
2) **TF vs. M** – Inactive at 1, and 10
3) **PPQ** – 46% at 1, 14% at 10 and 26% at 30
4) **HP** – Inactive at 1, 10 and 30

At 30 µg/brain, 2/6 died, 1/6 sedated and 1/6 vocalized. Loss of righting reflex in some animals.

Comment: The data do not portend opioid agonist or mu-opioid antagonist properties.

NIH 11209, (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl
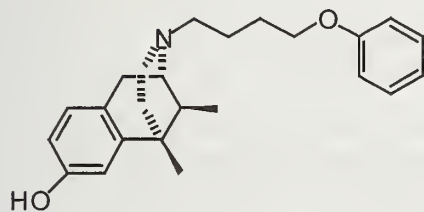
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** –Inactive at 1, 10 and 30
3) **PPQ** - 12.6 (4.9 – 32.6)
4) **HP** - Inactive at 1, 10 and 30

Vehicle was 20% Hydroxypropyl-beta- cyclodextrin in water.
Insufficient supply for testing higher doses.

MONKEY DATA – As illustrated in the accompanying figure, at doses of 2 and 8 mg/kg, NIH 11209 is without effect in withdrawn morphine-dependent monkeys.
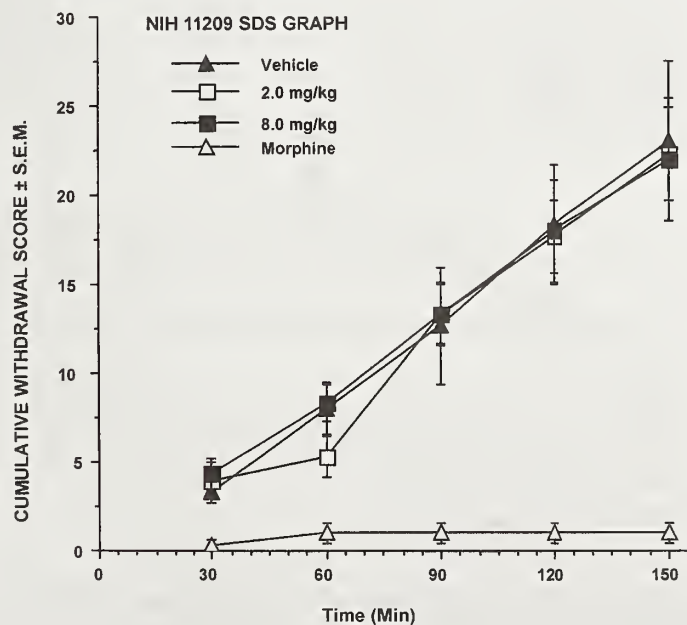
Fig NIH 11209 SDS: Results of a study in which single doses of NIH 11209 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: All the data indicates that NIH 11209 is devoid of mu-and kappa-opioid agonist and antagonist properties.

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NIH 11210 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl
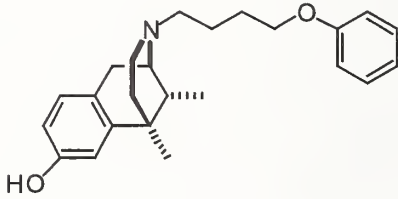
MOUSE DATA - ED50 OR AD50
 (95 % C.L.) or % change, mg/kg. s.c.

1) **TF** – 5% at 1, 24% at 19 and inactive at 30
2) **TF vs. M** – 8% at 1, 20% at 10 and 8% at 30
3) **PPQ** – 6.28 (2.14 – 18.4)
4) **HP** – 12.5% at 1, inactive at 10 and 25% at 30

Vehicle was 20% Hydroxypropyl-β-cyclodextrin in warm sterile water

MONKEY DATA - (SDS)   The results in the accompanying figure clearly illustrate that NIH 11210 neither substituted for morphine nor attenuated or exacerbated withdrawal signs at doses of 2.5 and 10 mg/kg..
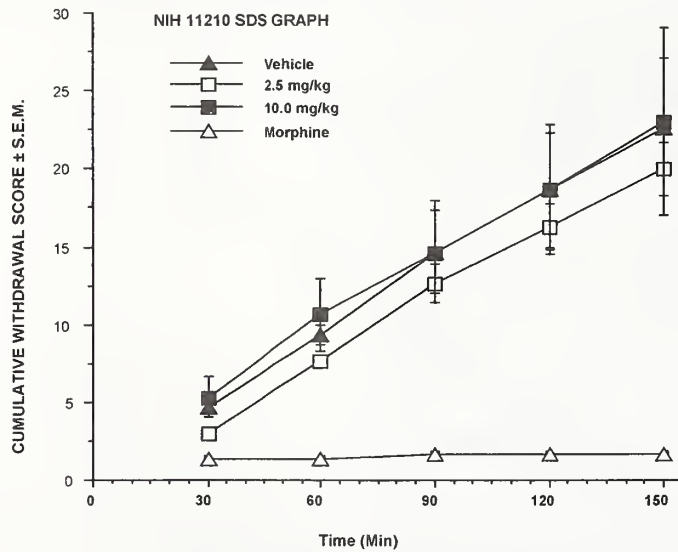
Fig NIH 11210-SDS: Results of a study in which single doses of NIH 11210 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results in two species indicate that NIH 11210 is unlikely to have mu- and/or kappa-opioid agonist or antagonist activity.

NIH 11221 5,6-Didehydro-4,14-dihydroxy-3-methoxy-17-methyl-7-(4-phenylbutyl)morphinan-6-carbonitrile
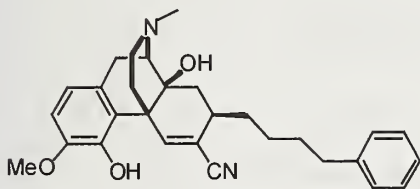
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – 5% at 1 and 13% at 10
2) **TF vs. M** – 17% at 1 and 16% at 10
3) **PPQ** – 4.0 (2.7 – 5.9)
4) **HP** – 18% at 1 and 43% at 10[a]

Not enough drug for higher doses. Vehicle was 20% Hydroxypropyl-beta-cyclodextrin in water.

Comment: Potent mu- and kappa-agonist and antagonist are not prominent properties of NIH 11221.

NIH 11222 5,6-Didehydro-4,14-dihydroxy-3-methoxy-17-methyl-7-(5-phenylpentyl)morphinan-6-carbonitrile
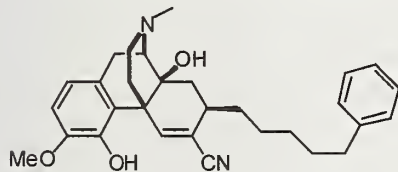
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – Inactive at 1, 45% at 10 and 57% at 30
2) **TF vs. M** – Inactive at 1 and 10
3) **PPQ** – 3.0 (0,95 – 9,46)
4) **HP** – 12% at 1 and 50% at 10

Not enough drug for testing higher doses.
Vehicle was 20% Hydroxypropyl-beta-cyclodextrin and 0.05N HCl, (Solution was cloudy)

Comment: Remarkable mu- and kappa-opioid agonist and antagonist properties were not observed.

NIH 11223 5,6-Didehydro-4,14-dihydroxy-3-methoxy-17-methyl-7-(6-phenylhexyl)morphinan-6-carbonitrile
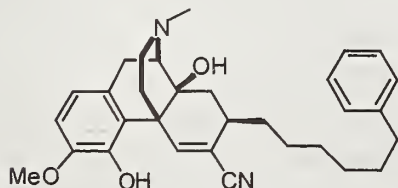
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – Inactive at 0.33 and 10
2) **TF vs. M** – 28% at 1 and 15% at 10
3) **PPQ** – Inactive at 1 and 44% at 10
4) **HP** – Inactive at 0.33, 37% at 1 and 20% at 10

Not enough drug was availiable for testing higher doses. Vehicle was 20% Hydroxypropyl-beta-cyclodextrin and 0,05N HCl.

Comment: At the doses tested, remarkable opioid activity was not evident with NIH 11223.

NIH 11224 7-Benzyl-5,6-didehydro-4,14-dihydroxy-3-methoxy-17-methyl-morphinan-6-carbonitrile
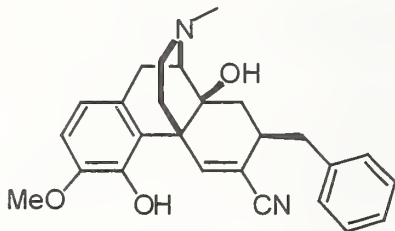
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – 6% at 1 and 5% at 10
2) **TF vs. M** – Inactive at 1 and 10
3) **PPQ** – Inactive at 1 and 60% at 10
5) **HP** – Inactive at 1 and 10

Vehicle was Hydroxypropyl-beta-cyclodextrin and 0.05N HCl.

Comment:. At the doses tested, NIH 11224 does not display opioid activity.

NIH 11225 6,7-Didehydro-4,5-epoxy-6-idimazolyl-3-methoxy-17-methyl-14-(3-phenylpropyloxy)morphinan
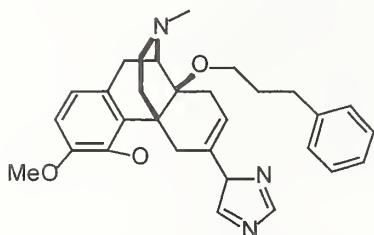
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – 7% at 1 and 54% at 10
2) **TF vs. M** – Inactive at 1 and 10
3) **PPQ** – 0.66 (0,028 – 1.60)
4) **HP** – 2.68 (1.6 – 4.4)

Vehicle was 20% Hydroxypropyl-beta-cyclodextrin and 0.05N HCl.

Comment: This profile of activity suggests that NIH 11225 has mu- and/or kappa-opioid agonist activity. Subtype studies could resolve this question.

NIH 11226 4-Cinnamyloxy-5,6,7,8-tetradehydro-14-hydroxy-3-methoxy-17-methyl-morphinan-6-carbonitrile
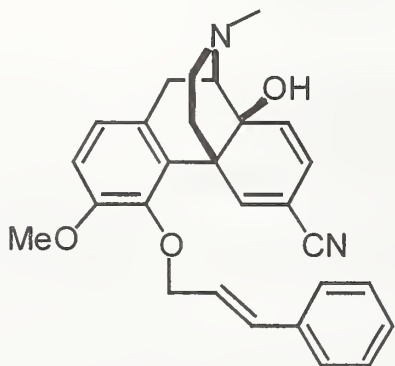
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – 11.7 (7.0 – 19.70)
2) **TF vs. M** – 16% at 1 and Inactive at 10
3) **PPQ** – 2.77 (1.5 – 5.0)
4) **HP** – 20% at 1 and 59% at 10

Vehicle was 0.05N HCl.

Comment: These data indicate that NIH 11226 may have mu- and kappa-opioid-agonist activity. Opioid subtype testing would resolve this matter.

NIH 11227 Tyr-Tyr-Phe-Phe-Ile-(6-O)-hydrocodone.HCl
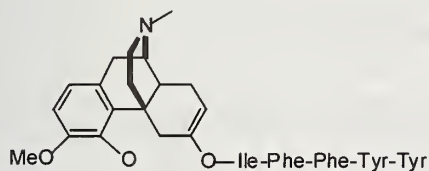
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – Inactive at 1 and 10 and 33% at 30
2) **TF vs. M** – 12% at 1, 22% at 10 and inactive at 30
3) **PPQ** – 3.42 (1.46 – 8.0)
4) **HP** – 24% at 1, 30% at 10 and 44% at 30

Comment: NIH 11227 shows weak antinociceptive activity in tests designed to predict mu- and kappa-opioid agonist properties.

NIH 11228 Salvinorin A
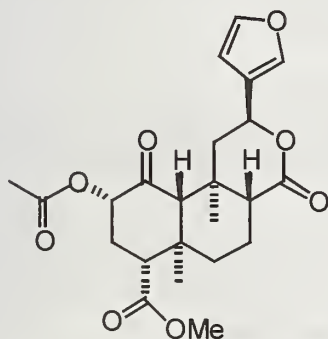
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – 1.98 (1.02 – 3.82)
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 0.59 (0,024 – 1.43)
4) **HP** – Inactive at 1, 28% at 10 and inactive at 30

Straub tail noted in the HP test at 30 mg/kg. Vehicle was 50% Hydroxypropyl-beta-cyclodextrin in 0.05N HCl. Very poor solubility. At times, it was in suspension.

Comment:. In the TF and PPQ tests potent opioid agonist activity was evident. Curiously, significant HP activity was not manifested, The HP test was run twice and different technicians independently tested the compound.

NIH 11285 (+)-(1S,5S,9S)- 2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl
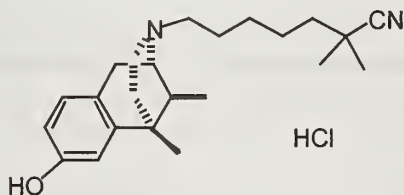
MOUSE DATA – ED50 OR AD50
(95 % C.L.) or % change, mg/kg. S.c.

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – Inactive at 1 and 10 and 14% at 30
3) **PPQ** – Inactive at 1 and 10, 34% at 30
4) **HP** – 15% at 1, 14% at 10 and inactive at 30

Comment: Opioid-wise, activity with this compound was not remarkable.

NIH 11286 (-)-(1R,5R,9R)-2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl
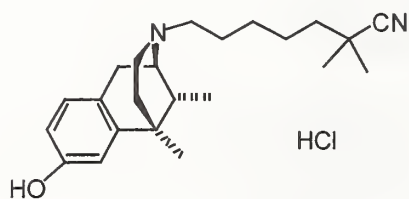
MOUSE DATA – ED50 OR AD50
(95 % C.L. or % change, mg/kg, s.c.

1) **TF** – Inactive at 1 and 10, 13% at 30
2) **TF vs. M** – 9% at 1, 17% at 10 and 18% at 30
3) **PPQ** – 5% at 1, inactive at 10 and 30
4) **HP** – 30% at 1, 36% at 10 and 37% at 30

Comment: Remarkable opioid activity was not noted.

NIH 11287 (+)-(1S,5S,9S)-2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.Oxalate
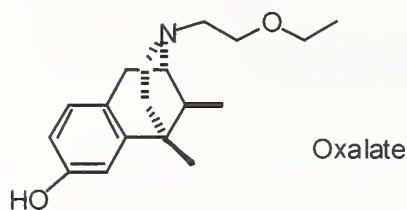
MOUSE DATA – ED50 OR AD50
(95 % C.L.) or % change mg/kg, s.c.

1) **TF** – Inactive at 1,10 and 30
2) **TF vs. M** – Inactive at 1 and 10 and 9% at   30
3) **PPQ** – Inactive at 1 and 10, 42% at 30
4) **HP** – Inactive at 1 and 10, 37% at 30

Comment: With NIH 11287, opioid activity was not evident in the mouse.

NIH 11288 (-)-(1R,5R,9R)-2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.Oxalate
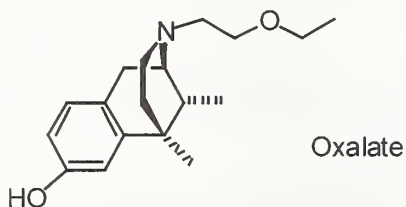
MOUSE DATA – ED50 OR AD50
(95 % C.L.) or % change, mg/kg, s.c.

1) **TF** – 0.86 (0.67 – 1.11)
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 0.18 (0.10 – 0.32)
4) **HP** – 1.33 (0.70 – 2.55)

One mouse displayed Straub tail.

MONKEY DATA – SDS As shown in the accompanying figure, NIH 11288 substituted completely for morphine at the highest dose tested (3 mg/kg). At this dose the signs slowing, salivation, drowsiness, jaw and body sag and eyelid ptosis were noted.
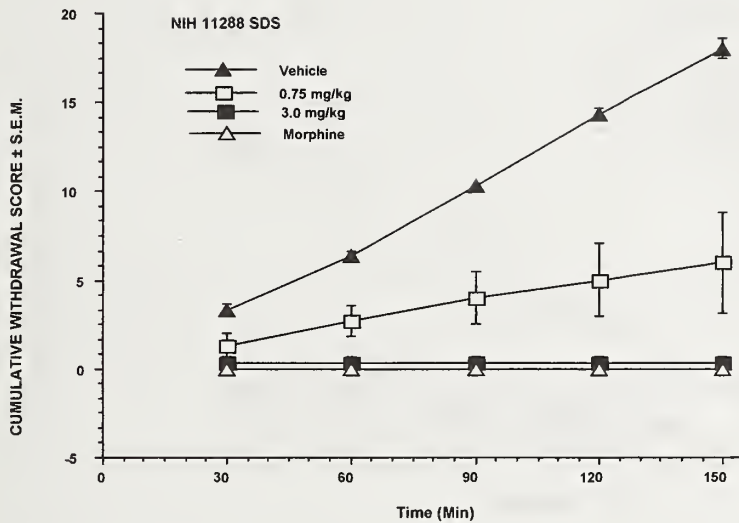
Fig NIH 11288-SDS: Results of a study in which single doses of NIH 11288 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity in the mouse and monkeys is that of a classical mu-opioid agonist. However, the behavioral signs noted in the monkey at 3 mg/kg also suggest kappa-opioid agonist activity. A more definitive conclusion requires opioid agonist subtying tests.

NIH 11289 (1R,5R,9R)-5-(3-Hydroxyphenyl)-2-phenethyl-2-aza-bicyclo[3.3.1]nonan-9-ol.HCl

HCl
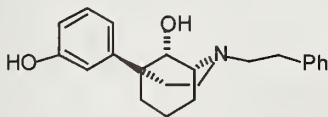
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – 0.0043 (0.003 – 0.0061)
2) **TF vs. M** – Not tested
3) **PPQ** – 0.0023 (0.0015 – 0.0036)
4) **HP** – 0.0018 (0.001 – 0.0032)

Straub tails, ataxia, quick onset convulsions, and increased locomotor activity were noted

MONKEY DATA – SDS As shown in the figure, NIH 11289 substituted completly for morphine at doses of 0.005 and 0.03 mg.kg. The drug acted promtly and its duration of action was at least 2.5 hours. The potency estimate is at least 1000 times that of morphine.
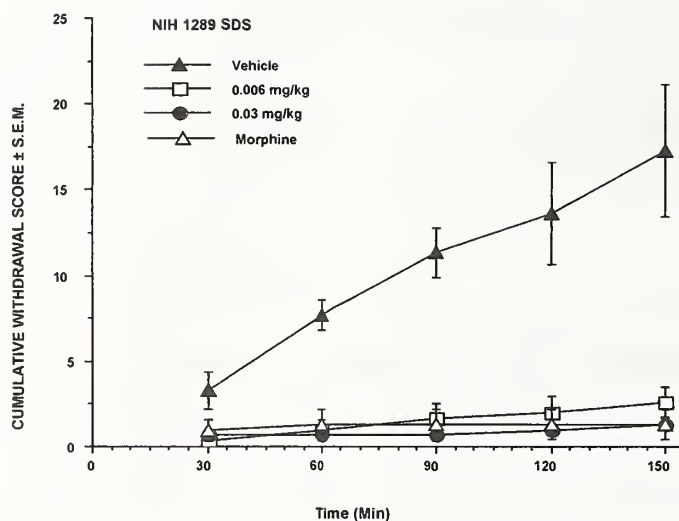
Fig NIH 11289-SDS: Results of study in which single doses of NIH 11289 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment:. In the mouse and monkey, NIH 11289 has a profile of activity associated with potent mu-opioid agonists.

NIH 11290 (1R,5R)-3-(9-Methylene-2-phenethyl-2-aza-bicyclo[3.3.1]nonan-5-yl.]-phenol.Oxalate
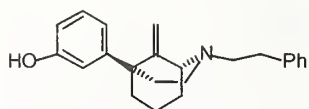
Oxalate

MOUSE DATA – ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** – 0.030 (0.022 – 0.041)
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 0.023 (0.016 – 0.033)
4) **HP** – 0.017 - (0.008 – 0.035)

Straub tails an increased locomotor activity were noted.

MONKEY DATA - SDS   NIH 11290 substituted completely for morphine (see figure). Activity was dose related. This compound is approximately 3 times as potent as morphine.
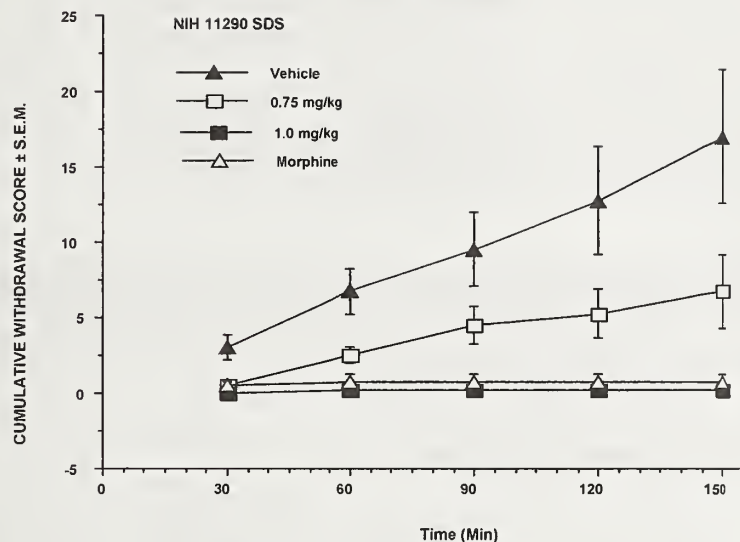
Fig NIH 11290-SDS: Results of study in which single doses of NIH 11290 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 11290 appears to be more potent in mice that in morphine-dependent monkeys. The profile is typically that of a mu-opioid agonist.

NIH 11292 4-Phenyltetrahydro-2H-pyran-4-ol
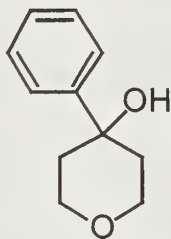
MOUSE DATA – ED50 OR AD50
(95 % C.L.) or % change, mg/kg s.c.

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – 3% at 0.3, 36% at 1, 3% at 3, 22% at 10 and 15% at 30
3) **PPQ** –Inactive at 1, 18% at 10 and 20% at 30
4) **HP** – 18% at 1, 41% at 10 and 4% at 30

Vehicle was 20% Hydroxypropyl-beta-cyclodextrin in water for injection.

Comment: The biological effects of NIH 11292 do not predict remarkable opioid activity in mice.

NIH 11293 N,N-Dimethyl-2-(3-phenylpropoxy)ethylamine
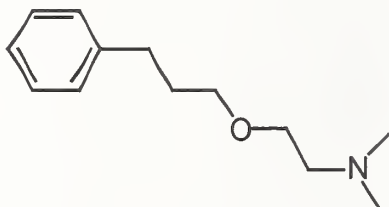
MOUSE DATA – ED50 OR AD50
(95 % C.L.) or % change, mg/kg, s.c.

1) **TF** – Inactive at 1 and 10
2) **TF vs. M** – Inactive at 1 and 10
3) **PPQ** –38% at 11 and 20% at 10
4) **HP** – Inactive at 1 and 10

Drug supply was limited. Vehicle was 20% Hydroxypropyl-beta-cyclodextrin in water for injection.

Comment: The data in mice do not indicate remarkable opioid activity.

NIH 11296 4-Phenyltetrahydro-2H-pyran-4-yl propionate
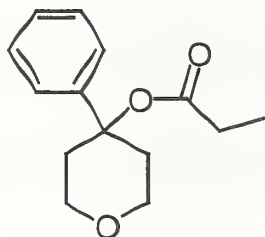
MOUSE DATA – ED50 OR AD50
(95 % C.L) % change, mg/kg, s.c.

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** – 21% at 1, 31% 10 and 20% at 30

Comment: The data derived from the mouse tests is not supportive of opioid activity for NIH 11296.

NIH 11304 (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-oxopropyl)-6,7-benzomorphan.HCl
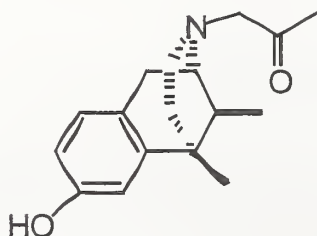
MOUSE DATA – ED50 OR AD50
(95 % C.L. or % change, mg/kg. s.c.

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – 16% at 1, Inactive at 10 and 30
3) **PPQ** – 3.4 (1.30 – 8.87
4) **HP** – 14% at 1, 19% at 10 and inactive at 30

HCl

Comment: Although NIH 11304 was inactive in tests that characterize mu- and kappa-opioid agonists, delta–opioid agonist activity was not ruled out.

NIH 11305 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-oxopropyl)-6,7-benzomorphan.HCl
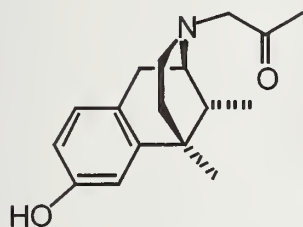
MOUSE DATA - ED50 OR AD50
% C.L.) or % change, mg/kg, s.c.)

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – 1.32 (0.60 – 2.90)
3) **PPQ** – 8.03 (4.40 – 14.67)
4) **HP** – 3% at 1, 25% at 10 and inactive at 30

MONKEY DATA – PPt-W: At doses of 1.5 and 6.0 mg/kg, NIH 11305 precipitated withdrawal signs. The effect was prompt, dose related and its duration of action was at least 2/12 hr. Potency estimate was 1/100 that of the reference standard naloxone hydrochloride.
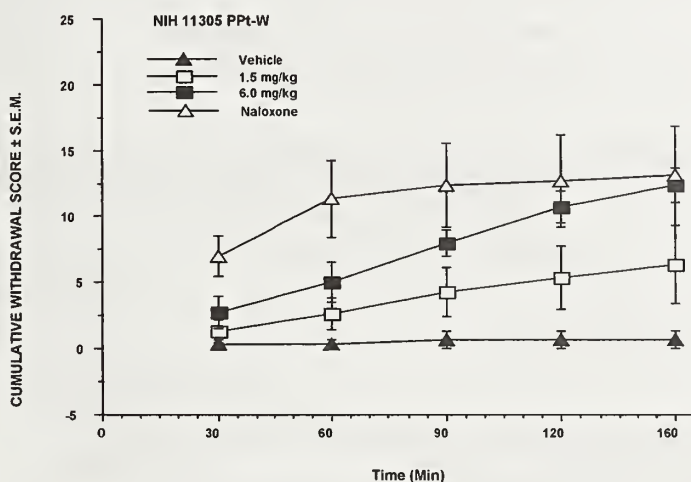
Fig NIH 11305-PPt-W: Results of a study in which single doses of NIH 11305 were given to morphine dependent monkeys.

Comment: NIH 11305 has mu and kappa-opioid antagonist properties and uncharacterized antinociceptive action.

NIH 11306 (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(5-oxohexyl)-6,7-benzomorphan.HCl
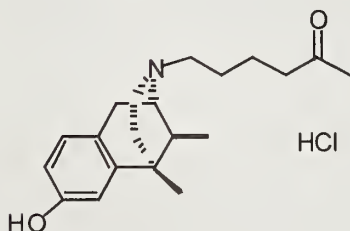
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.)

1) **TF** – Inactive at 1 and 10, 7% at 30
2) **TF vs. M** –Inactive at 1, 10 and 30
3) **PPQ** – Inactive at 1, 21% at 10 and 38% at 30
4) **HP** – 5 % at 24% at 10 and 5% at 30

Comment: Inactive in all four mouse tests.

NIH 11307 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(5-oxohexyl)-6,7-benzomorphan.HCl
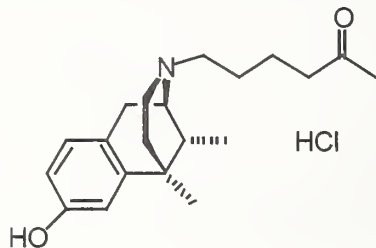
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – 3% at 1, 7% at 10 and 18% at 30
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 13.3 (4.5 – 39.3)
4) **HP** Inactive at 1, 10 and 30

Comment:. It is unlikely that NIH 11307 has mu- or kappa-opioid properties. Many possible mechanisms of action suggest themselves when a drug is active in the PPQ test.

NIH 11308 (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-oxobutyl)-6,7-benzomorphan.HCl
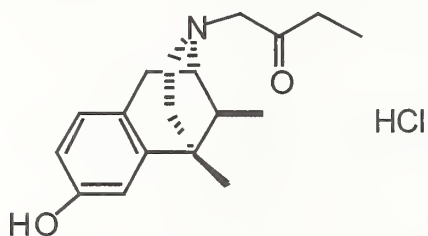
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.)

1) **TF** – 13% at 1, inactive at 10 and 30
2) **TF vs. M** – 39 % at 1, inactive at 10 and 14% at 30
3) **PPQ** – Inactive at 1, 8% at 10 and inactive at 30
4) **HP** – 5% at 1 and 10, 11% at 30

Comment: NIH 11308 did not express opioid activity.

NIH 11309 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-oxobutyl)-6,7-benzomorphan.HCl
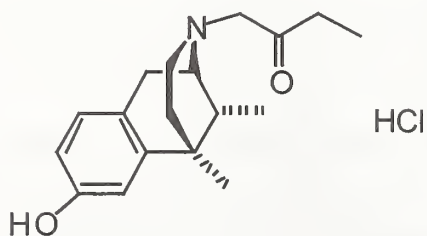
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – 13% at 1, inactive at 10 and 30
2) **TF vs. M** – 5.33 (3.42 – 8.3)
3) **PPQ** – 14% at 1, inactive at 10 and 29% at 30
4) **HP** – 11% at 1, 23% at 10 and inactive at 30

MONKEY DATA – PPT-W At doses of 2.75 and 10 mg/kg. NIH 11309 failed to precipitate withdrawal in morphine–dependent monkeys. (See accompanying figure).

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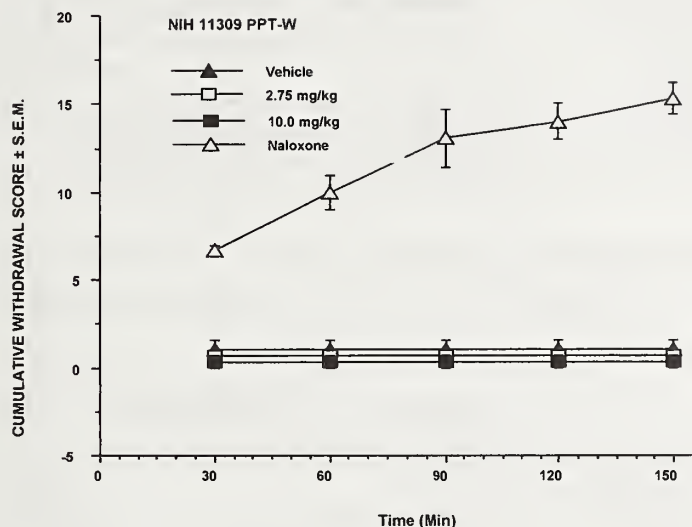
Fig NIH 11309-PPt-W: Results of study in which single doses of NIH 11309 were given to morphine-dependent monkeys.

Comment: Although some weak opioid-antagonist activity was found in mice, in the dose range tested, this activity was not expressed in monkeys.

NIH 11312 5'-Fluorooxymorphindole.HCl
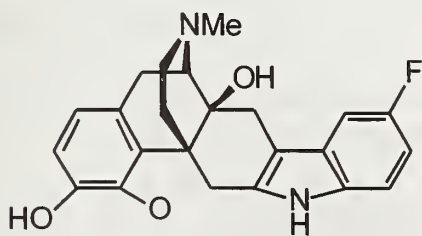
MOUSE DATA – ED50 OR AD50
(95 % C.L) or % change, mg/kg, s.c.

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – 7% at 1, 21% at 10 and inactive at 30
3)   **PPQ** – 7% at 1, 14% at 10 and 5% at 30
4) **HP** – 31% at 1 and 8% at 10

Vehicle was 10% Hydroxypropyl-beta-cyclodextrin in water for injection.

Comment: Regarding opioid properties, inactivity best describes NIH 11312

NIH 11313 5'-Chlorooxymorphindole.HCl
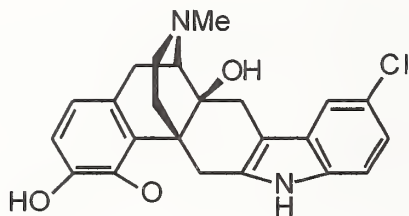
MOUSE DATA – ED50 OR AD50
(95 % C.L. or % change mg/kg, s.c.

1) TF – Inactive at 1 and 10
2) TF vs. M – 13% at 1 and 20% at 10
3) PPQ – 51%at 1, 53% and 53% at 30
4) HP – 16% at 1 and inactive at 10

Comment: Remarkable antinociceptive activity was not evident.

NIH 11314 5'-Bromooxymorphindole.HCl
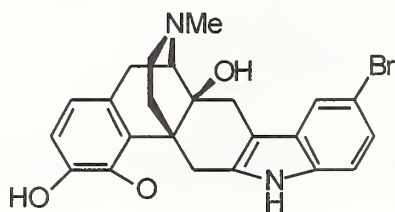
MOUSE DATA – ED50 OR AD50
(95 % C.L.) or % change, mg/kg, s.c.

1) TF – Inactive at 1
2) TF vs. M – 11% at 1
3) PPQ – 30% at 1
4) HP – 13% at 1

Vehicle was 0.02 N HCl in water for injection.

Comment: Limited supplies precluded a full evaluation of NIH 11314. The preliminary data do not signify opioid activity.

NIH 11315 5'-Iodooxymorphindole.HCl
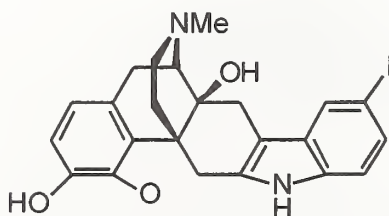
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

1) TF – Inactive at 1 and 10
2) TF vs. M – 35% at1 and inactive at 10
3) PPQ – 33% at 1, 47% at 3, 10 and 30
4) **HP – 10% at1 and 28% at 10**

Drug supply was exhausted.

Vehicle was 5% Hydroxypropyl-beta-cyclodextrin in water for injection.

Comment: Regarding antinociceptive and/or opioid activity, the results are not encouraging.

NIH 11316 7'-Fluorooxymorphindole.HCl
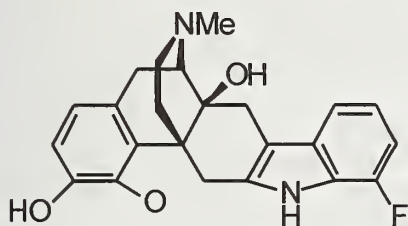
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/k, s.c.

1) **TF** – Inactive at 1 and 10
2) **TF vs. M** – Inactive at 1 and 10 amd 12% at 30
3) **PPQ** – Inactive at 1, 23% at 10 and inactive at 30
4) **HP** – 7% at 1, 18% at 10

Drug supply was exhausted. Vehicle was 0.01N HCl.

Comment: At the doses tested, antinociceptive activity was not remarkable.

NIH 11317 5',7'-Difluorooxymorphindole.HCl
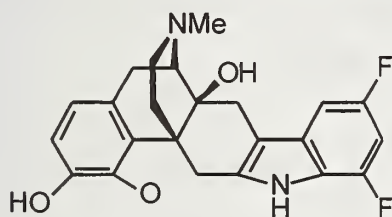
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** -Inactive at 1 and 3, 45% at 10 and 10% at 30
4) **HP** - 15% at 1 and 18% at 10

Vehicle was 0.01N HCl. Drug supply was exhausted.

Comment:. Opioid and/or antinociceptive properties do not characterize NIH 11317.

NIH 11318 5',7'-Dichlorooxymorphindole.HCl
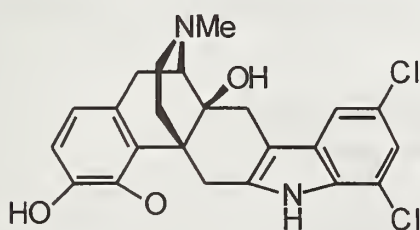
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – Inactive at 1 and 49% at 10
2) **TF vs. M** – 49% at 1 and 23% at 10
3) **PPQ** – 2.36 (1.5 – 3.7)
4) **HP** – 19% at 1 and 49% at 10

Vehicle was 10% Hydroxypropyl-beta-cyclodextrin in sterile water. Drug supply was exhausted.

Comment: This profile of activity suggests weak mu-opioid agonist and antagonist properties.

NIH 11319 Oxymorphindole.HCl
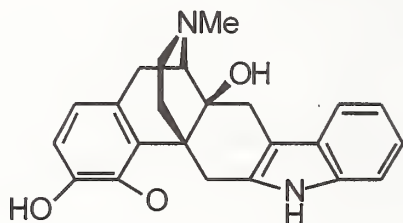
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – Inactive at 1 and 10
2) **TF vs. M** – Inactive at 1 and 10
3) **PPQ** – 33% at 1 and 10
4) **HP** – 13% at 1 and 47% at 10

Vehicle was 5% hydroxypropyl-beta-cyclodextrin. Drug supply was exhausted.

Comment:. Testing at doses of 1 and 10 mg/kg did not reveal substantial antinociceptive activity in the mouse tests.

NIH 11320 7☐-(o-Methylcinnamoylaminomethyl)-6,14-endoethanotetrahydrooripavine.HCl **(which symbol)**
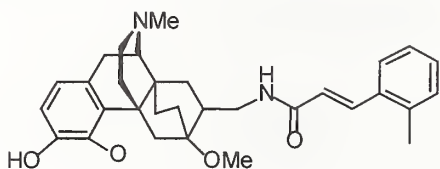
MOUSE DATA - ED50 OR AD50
(95%C.L.) or % change, mg/kg, s.c.

1) **TF** – 1.76 (1.48 – 2.11)
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 0.63 (0.44 – 0.90)
4) **HP** – 1.00 (0.58 – 1.75)

Vehicle was 5% Hydroxypropyl-beta-cyclodextrin in 0.02N HCl.

Comment:. This profile of activity is typical of that of a mu-opioid agonist. However, kappa-opioid agonist activity has not been ruled out. Subtying could resolve this issue.

NIH 11321 7☐-(p-Methylcinnamoylaminomethyl)-6,14 endoethano-tetrahydrooripavine.HCl **(which symbol)**
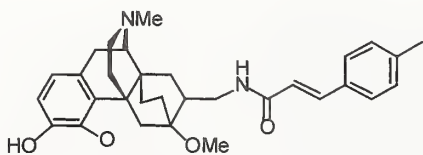
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – 6.37 (2.57 – 15.80)
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 2.70 (1.74 – 4.20)
4) **HP** – 2.28 (1.34 – 3.88)

Straub tails and increased locomotor activity were noted. Drug supply was exhausted.

Comment: The behavioral manifestations and antinociceptive profile suggest mu-opioid agonist activity. However, usually, potency in the PPQ test is an order of magnitude greater than that calculated in the TF test.

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NIH 11322 6□-o-Nitrocinnamoylnaltrexamine.Oxalate **(which symbol)**
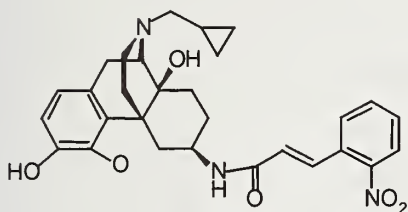
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/k, s.c.

1) **TF** – Not tested
2) **TF vs. M** – Not tested
3) **PPQ** - 18.5 (13.2 – 26.1)
4) **HP** – Not tested

Submitter requested that we test only PPQ analgesia. Vehicle was 10% Hydroxypropyl-beta-cyclodextrin in 0.01N HCl.

Comment:. NIH 11322 is active in the PPQ assay. Further testing could reveal its mode of action.

NIH 11323 (+)-(1S,5S,9S)-5,9-dimethyl-2-(5-hexynyl)-2'-hydroxy-6,7-benzomorphan.
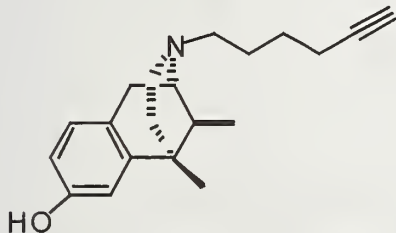
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – Inactive at 1 and 10 and 40% at 30
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 15.47 (12.53 – 19.11)
4) **HP** – 27% at 1, inactive at 10 and 13% at 30

Vehicle was 0.02N HCl.

Comment: Activity on the PPQ test requires additional testing to ascertain the mechanism(s) involved.

NIH 11324 (-)-(1R,5R,9R)-5,9-dimethyl-2-(5-hexynyl)-2'-hydroxy-6,7-benzomorphan.
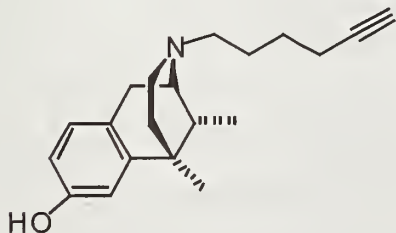
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.)

1) **TF** – 4.61 (3.76 – 5.66)
2) **TF vs. M** – Inactive at 1 and 19 and 34% at 30
3) **PPQ** – 0.76 – 0.65 – 0.90)
4) **HP** – 1.51 (0.86 – 2.63)

Vehicle was 0.02N HCl.

MONKEY DATA – SDS At doses of 2.5 and 10, NIH 11324 produced a dose-related attenuation of withdrawal signs in morphine-dependent monkeys in withdrawal. At the high dose the signs ataxia and slowing were noted.

NIH 11324 SDS

— ▲ — Vehicle
— ☐ — 2.5 mg/kg
— ■ — 10.0 mg/kg
— △ — Morphine
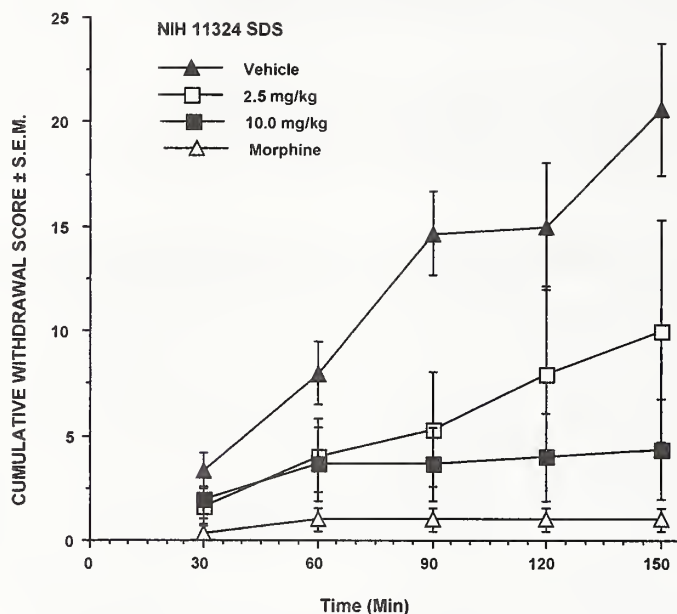
Fig NIH 11324-SDS: Results of study in which single doses of NIH 11324 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment : Results in mice and monkeys suggest that NIH 11324 is an opioid with uncharacterized central nervous system properties.

NIH 11325 (-)-(1R,5R,9R)-5,9-Dimethyl-2-(5-cyanopentyl)-2'-hydroxy-6,7-benzomorphan.
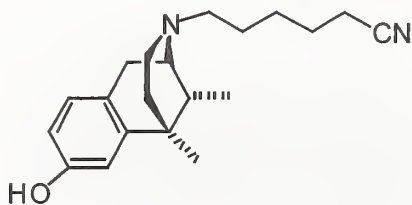
MOUSE DATA – ED50 OR AD50
(95 % C.L.) or % change, mg/kg, s.c.

1) **TF** – 8.67 (5.03 – 14.94)
2) **TF vs. M** – 14% at 1, inactive at 10 and 30
3) **PPQ** – 2.80 (1.37 – 5.70)
4) **HP** – Inactive at 1, 41% st 10 and 52% at 30

MONKEY DATA - SDS

In the dose range of 2.5 - 10 mg/kg, NIH 11325 attenuated withdrawal and substituted completely for morphine sulfate. The drug acted promptly and had a duration of action of at least 2 1/2 hours. Potency estimate is 1/3 that of morphine sulfate. No overt behavioral effects were noted.
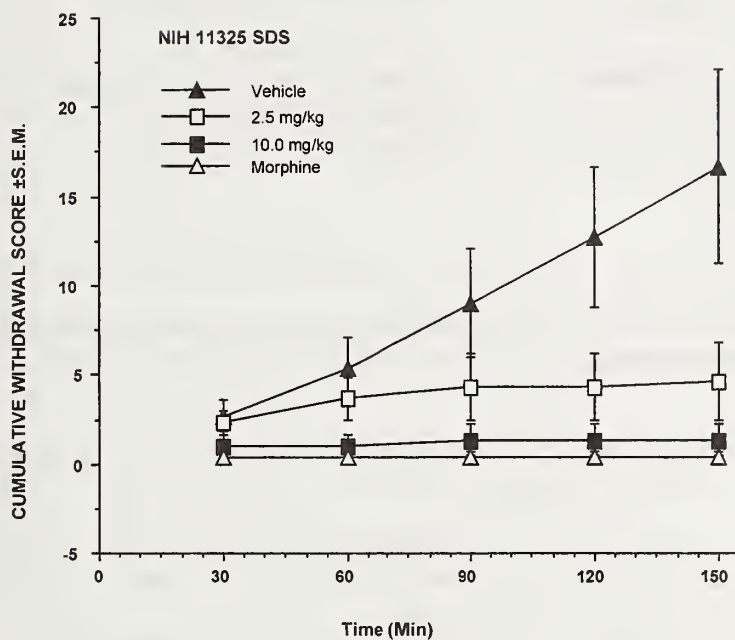
Fig NIH 11325-SDS. Results of study in which single doses of NIH11325 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The data indicate that NIH 11325 is a mu-opioid agonist

NIH 11326 (+)-(1S,5S,9S)-5,9-Dimethyl-2-(5-cyanopentyl)-2'-hydroxy-6,7-benzomorphan
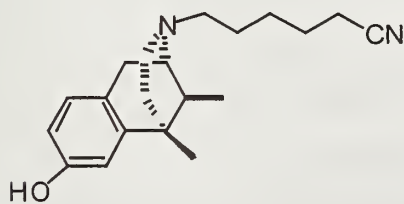
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg, s.c.

1) **TF** – Inactive at 1, 6% at 10 and 30% at 30
2) **TF vs. M** – 21% at 1, 3% at 10 and inactive at 30
3) **PPQ** – 3% at 1, 11% at 10 and 34% at 30
4) **HP** – 13% at 1, 20% at 10 and inactive at 30

Comment: These results do not predict opioid antinociceptive properties.

NIH 11334 6-Desoxymorphine.Oxalate
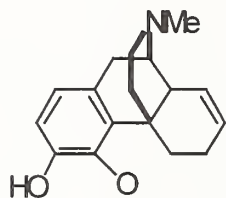
Oxalate

MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/k, /s.c.

1) **TF** – 0.2 (0.1 - 0.3)
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 0.03 (0.018 – 0.055
4) **HP** – 0.33 (0.15 – 0.72)

Straub Tail was noted at the high dose.

Comment: This antinociceptive profile of activity is reminiscent of that of a potent mu-opioid agonist. Potency estimate is 10x that of morphine sulfate.

NIH 11345 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-oxo-3,3-dimethylbutyll)-6,7-benzomorphan.Oxalate
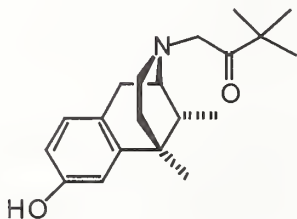
Oxalate

MOUSE DATA – ED50 OR AD50
(95 % C.L.) mg/kg or % change)

1) **TF** – 6% at 1, 3% at 10 and 30% at 30
2) **TF vs. M** – Inactive at 1 and 30, 41% at 10
   Repeat -15% at 1, 4% at 10 and 64% at 30
3) **PPQ** – 7.9 (3.8 – 16.5)
4) **HP** – 22% at 1, 5% at 10 and inactive at 30

Comment: NIH 11345 does not possess mu- and kappa-opioid agonist properties. Antinociception in the PPQ test was not characterized.

NIH 11346 (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-oxo-3,3-dimethylbutyl)-6,7-benzomorphan.HBr
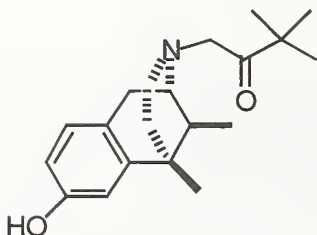
HBr

MOUSE DATA – ED50 OR AD50
(95 % C.L.) mg/kg or % change)

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 29 % at 1, 27% at 3, 38% at 10 and 23% at 30
4) **HP** – Inactive at 1, 10 and 30

Comment: These results do not indicate opioid activity.

NIH 11347   (-)-(1R,5R,9R)-5,9-Dimethyl-2-(2-(2-hydroxyethoxy)ethyl)-2'-hydroxy-6,7-benzomorphan.HCl
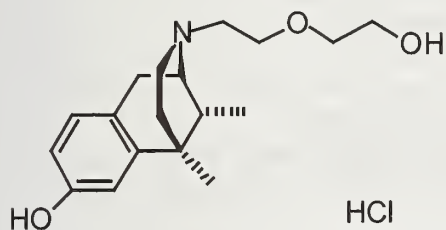
MOUSE DATA – ED50 OR AD50
(95 % C.L.) mg/kg or % change)

1) **TF** – Inactive at 1,10 and 30
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 13% at 1, inactive at 10 and 47% at 30
4) **HP** – 18% at 1, 5% at 10 and 18% at 30

Comment: Little evidence for opioid activity is indicated for NIH 11347.

NIH 11348   (+)-(1S,5S,9S)-5,9-Dimethyl-2-(2-(2-hydroxyethoxy)ethyl)-2'-hydroxy-6,7-benzomorphan.HCl
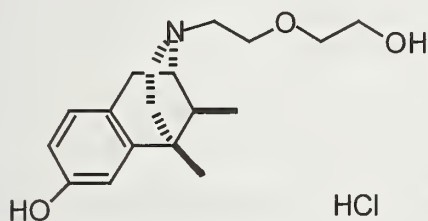
MOUSE DATA – ED50 OR AD50
(95 % C.L.) mg/kg or % change)

1) **TF** – Inactive at 1, 10 and 30
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 28% at 1, 26% at 10 and 6% at 30
4) **HP** – 9% at 1, 35% at 10 and 28% at 30

Comment: This profile of activity in the mouse does not indicate opioid activity.

NIH 11349   (-)-(1R,5R,9R)-2-(3-Cyanopropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl
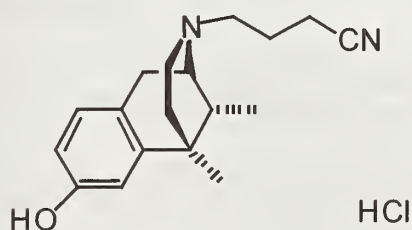
MOUSE DATA – ED50 OR AD50
(95 % C.L.) mg/kg or % change)

1) **TF** – 0.3 (0.2 – 0.5)
2) **TF vs. M** – Inactive at 1, 10 and 30
3)   **PPQ** – 0.14 (0.10 – 0.18)
4) **HP** – 5.1 (2.0 – 12.6)

Sedation and Straub tail of 30 min duration observed in HP at 1, 3, 10 and 30 mg/kg.

Comment: Indications are that NIH 11349 is a mu-opioid agonist.

NIH 11350   (+)-(1S,5S,9S)-2-(3-Cyanopropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl
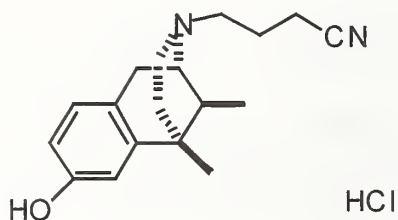
MOUSE DATA – ED50 OR AD50
(95 % C.L.) mg/kg or % change)

1) **TF** – Inactive at 1 and 10, 10% at 30
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 3% at 1, 25% at 10 and inactive at 30
4) **HP** – 25% at 1, 14% at 10 and inactive at 30

Comment: There is little, if any, indication for opioid activity with NIH 11350

NIH 11351   (+)-(1R,5R,9R)-2-(2-Methoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl
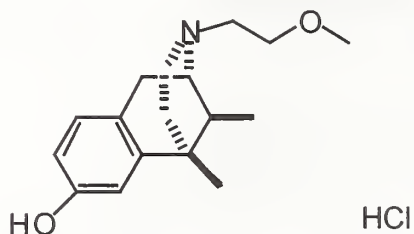
MOUSE DATA – ED50 OR AD50
(95 % C.L.) mg/kg or % change)

1) **TF** – Inactive at 1, 6% at 10 and 38% at 30
2) **TF vs. M** – 6% at 1, inactive at 10 and 12% at 30
3) **PPQ** – 2.63 (1.86 – 3.72)
4) **HP** – Inactive at 1, 28% at 10 and inactive at 30

Comment: Opioid antagonist and mu- and kappa-opioid agonist properties can be ruled out with NIH 11351.

NIH 11352   (-)-(1S,5S,9S)-2-(2-Methoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl
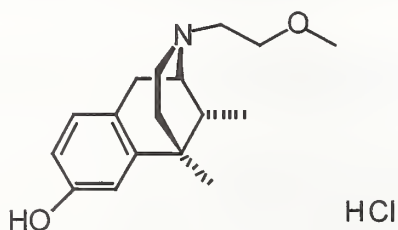
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.)

1) **TF** – 0.0306 (0.0177 0.0531)
2) **TF vs. M** – Inactive at 1, 10 and 30
3) **PPQ** – 0.0066 (0.0040 – 0.0011
4) **HP** – 0.26 (0.18 – 0.41)

Straub tail was noted at 1 and 10 mg/kg in the TF vs M test before morphine was given.

MONKEY DATA – (SDS)

As shown in the figure, NIH 11352 dose dependently attenuated but did not completely block at the doses tested in morphine-dependent monkeys in which morphine had been withdrawn 15 hr earlier.
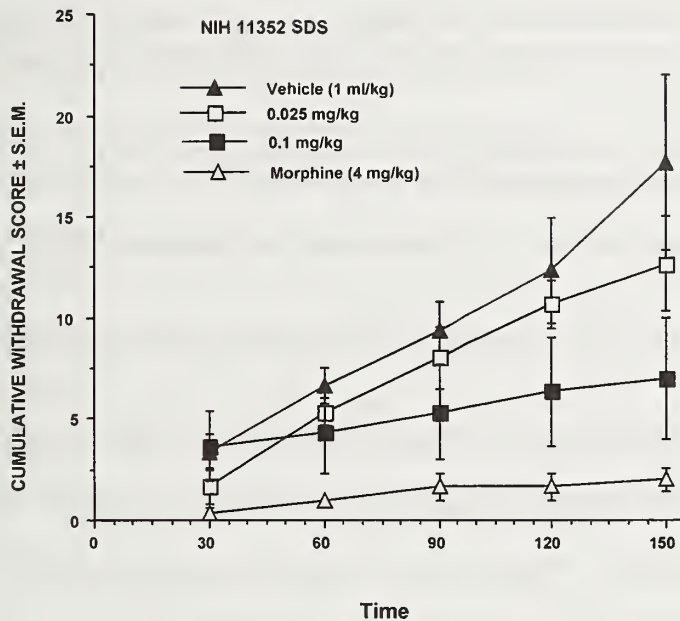
Fig NIH 11352-SDS.   Results of study in which single doses of NIH11352 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results in two species indicate that NIH 11352 is a potent mu-opioid agonist. It is approximately 30 times more potent than morphine sulfate. Its onset of action is rapid. Duration of action is at least as long as that of morphine.

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SUBJECT INDEX

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