

# Director's Report

to the  
**NATIONAL ADVISORY COUNCIL  
ON DRUG ABUSE**

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**Nora D. Volkow, M.D.**  
**Director**  
**National Institute on Drug Abuse**





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*\* These sections contain select information. More comprehensive information will be posted in the [September 2014 Staff Report to the Director](#).*



## RESEARCH HIGHLIGHTS

### **BASIC AND BEHAVIORAL RESEARCH**

#### ***DCNBR***

**Separate GABA Afferents to Dopamine Neurons Mediate Acute Action of Opioids, Development of Tolerance, and Expression of Withdrawal** Matsui A, Jarvie BC, Robinson BG, Hentges ST, Williams JT. *Neuron*. 2014 Jun 18; 82(6): 1346-56. doi: 10.1016/j.neuron.2014.04.030. Epub 2014 May 22.

GABA release from interneurons in VTA, projections from the nucleus accumbens (NAc), and rostromedial tegmental nucleus (RMTg) was selectively activated in rat brain slices. The inhibition induced by  $\mu$ -opioid agonists was pathway dependent. Morphine induced a 46% inhibition of IPSCs evoked from the RMTg, 18% from NAc, and IPSCs evoked from VTA interneurons were almost insensitive (11% inhibition). In vivo morphine treatment resulted in tolerance to the inhibition of RMTg, but not local interneurons or NAc, inputs. One common sign of opioid withdrawal is an increase in adenosine-dependent inhibition. IPSCs evoked from the NAc were potently inhibited by activation of presynaptic adenosine receptors, whereas IPSCs evoked from RMTg were not changed. Blockade of adenosine receptors selectively increased IPSCs evoked from the NAc during morphine withdrawal. Thus, the acute action of opioids, the development of tolerance, and the expression of withdrawal are mediated by separate GABA afferents to dopamine neurons.

**Chronic Cannabinoid Receptor 2 Activation Reverses Paclitaxel Neuropathy Without Tolerance or Cannabinoid Receptor 1-Dependent Withdrawal** Deng L, Guindon J, Cornett BL, Makriyannis A, Mackie K, Hohmann AG. *Biol Psychiatry*. 2014 Apr 25. Pii: S0006-3223(14)00274-1. Doi: 10.1016/j.biopsych.2014.04.009. [Epub ahead of print].

Mixed cannabinoid receptor 1 and 2 (CB<sub>1</sub> and CB<sub>2</sub>) agonists such as  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) can produce tolerance, physical withdrawal, and unwanted CB<sub>1</sub>-mediated central nervous system side effects. Whether repeated systemic administration of a CB<sub>2</sub>-preferring agonist engages CB<sub>1</sub> receptors or produces CB<sub>1</sub>-mediated side effects is unknown. The authors evaluated antiallodynic efficacy, possible tolerance, and cannabimimetic side effects of repeated dosing with a CB<sub>2</sub>-preferring agonist AM1710 in a model of chemotherapy-induced neuropathy produced by paclitaxel using CB<sub>1</sub>knockout (CB<sub>1</sub>KO), CB<sub>2</sub> knockout (CB<sub>2</sub>KO), and wild-type (WT) mice. Comparisons were made with the prototypic classiccannabinoid  $\Delta^9$ -THC. The authors also explored the site and possible mechanism of action of AM1710. Paclitaxel-induced mechanical and cold allodynia developed to an equivalent degree in CB<sub>1</sub>KO, CB<sub>2</sub>KO, and WT mice. Both AM1710 and  $\Delta^9$ -THC suppressed established paclitaxel-induced allodynia in WT mice. In contrast to  $\Delta^9$ -THC, chronic administration of AM1710 did not engage CB<sub>1</sub> activity or produce antinociceptive tolerance, CB<sub>1</sub>-mediatedcannabinoid withdrawal, hypothermia, or motor dysfunction. Antiallodynic efficacy of systemic administration of AM1710 was absent in CB<sub>2</sub>KO mice and WT mice receiving the CB<sub>2</sub> antagonist AM630, administered either systemically or intrathecally. Intrathecal administration of AM1710 also attenuated paclitaxel-induced allodynia in WT mice, but not CB<sub>2</sub>KO mice, implicating a possible role for spinal CB<sub>2</sub> receptors in AM1710 antiallodynic efficacy. Finally, both acute andchronic administration of AM1710 decreased messenger RNA levels of tumor necrosis factor- $\alpha$  and monocyte chemoattractant protein 1 in lumbar spinal cord

of paclitaxel-treated WT mice. These results highlight the potential of prolonged use of CB<sub>2</sub> agonists for managing chemotherapy-induced allodynia with a favorable therapeutic ratio marked by sustained efficacy and absence of tolerance, physical withdrawal, or CB<sub>1</sub>-mediated side effects.

**G9a Influences Neuronal Subtype Specification In Striatum** Maze I, Chaudhury D, Dietz DM, Von Schimmelmann M, Kennedy PJ, Lobo MK, Sullivan SE, Miller ML, Bagot RC, Sun H, Turecki G, Neve RL, Hurd YL, Shen L, Han MH, Schaefer A, Nestler EJ. *Nat Neurosci.* 2014 Apr; 17(4): 533-9. doi: 10.1038/nn.3670. Epub 2014 Mar 2.

Cocaine-mediated repression of the histone methyltransferase (HMT) G9a has recently been implicated in transcriptional, morphological and behavioral responses to chronic cocaine administration. Here, using a ribosomal affinity purification approach, the authors found that G9a repression by cocaine occurred in both Drd1-expressing (striatonigral) and Drd2-expressing (striatopallidal) medium spiny neurons. Conditional knockout and overexpression of G9a within these distinct cell types, however, revealed divergent behavioral phenotypes in response to repeated cocaine treatment. These studies further indicated that such developmental deletion of G9a selectively in Drd2 neurons resulted in the unsilencing of transcriptional programs normally specific to striatonigral neurons and in the acquisition of Drd1-associated projection and electrophysiological properties. This partial striatopallidal to striatonigral 'switching' phenotype in mice indicates a new role for G9a in contributing to neuronal subtype identity and suggests a critical function for cell type-specific histone methylation patterns in the regulation of behavioral responses to environmental stimuli.

**The Effects Of Social Learning on the Acquisition Of Cocaine Self-Administration** Smith MA, Lacy RT, Strickland JC. *Drug Alcohol Depend.* 2014 Aug 1; 141: 1-8. doi: 10.1016/j.drugalcdep.2014.04.025. Epub 2014 May 14.

Social learning models of substance use propose that drug-use behaviors are learned by observing and mimicking the behavior of others. The aim of this study was to examine the acquisition of cocaine self-administration in three groups of experimentally naïve rats: rats that were tested in isolation, rats that were tested in the presence of another rat that had access to cocaine and had previously been trained to self-administer cocaine, and rats that were tested in the presence of another rat that did not have access to cocaine. Male rats were reared in isolated or pair-housed conditions and implanted with intravenous catheters. Pair-housed rats were then assigned to drug-experienced or drug-naïve conditions. In the drug-experienced condition, one rat of each pair was trained to self-administer cocaine in isolation before the reintroduction of its partner. In the drug-naïve condition, one rat of each pair did not have access to cocaine for the duration of the study. For each group, the acquisition of cocaine self-administration was measured over 15 days in rats with access to cocaine but no prior operant training. Rats tested with a drug-experienced partner were faster to acquire cocaine self-administration and emitted more active lever presses than rats tested with a cocaine-naïve partner. Data for the isolated control group fell between the other two groups on these measures. These data indicate that the acquisition of cocaine self-administration can either be facilitated or inhibited by social contact. Collectively, these results support a social learning model of substance use.

**Excessive Cocaine Use Results From Decreased Phasic Dopamine Signaling In The Striatum** Willuhn I, Burgeno LM, Groblewski PA, Phillips PE. *Nat Neurosci.* 2014 May; 17(5): 704-9. doi: 10.1038/nn.3694. Epub 2014 Apr 6.

Drug addiction is a neuropsychiatric disorder marked by escalating drug use. Dopamine neurotransmission in the ventromedial striatum (VMS) mediates acute reinforcing effects of abused drugs, but with protracted use the dorsolateral striatum is thought to assume control over drug seeking. The authors measured striatal dopamine release during a cocaine self-administration regimen that produced escalation of drug taking in rats. Surprisingly, they found that phasic dopamine decreased in both regions as the rate of cocaine intake increased, with the decrement in dopamine in the VMS significantly correlated with the rate of escalation. Administration of the dopamine precursor L-DOPA at a dose that replenished dopamine signaling in the VMS reversed escalation, thereby demonstrating a causal relationship between diminished dopamine transmission and excessive drug use. Together these data provide mechanistic and therapeutic insight into the excessive drug intake that emerges following protracted use.

**Post-Retrieval Extinction Attenuates Cocaine Memories** Sartor GC, Aston-Jones G. *Neuropsychopharmacology.* 2014 Apr; 39(5): 1059-65. doi: 10.1038/npp.2013.323. Epub 2013 Nov 21.

Recent studies have shown that post-retrieval extinction training attenuates fear and reward-related memories in both humans and rodents. This noninvasive, behavioral approach has the potential to be used in clinical settings to treat maladaptive memories that underlie several psychiatric disorders, including drug addiction. However, few studies to date have used a post-retrieval extinction approach to attenuate addiction-related memories. In the current study, the authors attempted to disrupt cocaine-related memories by using the post-retrieval extinction paradigm in male Sprague Dawley rats. Results revealed that starting extinction training 1 h after cocaine contextual memory was retrieved significantly attenuated cocaine-primed reinstatement of conditioned place preference (CPP) and relapse of cocaine CPP (drug-free and cocaine-primed) following 30 days of abstinence. However, animals that did not retrieve the contextual cocaine memory before extinction training, or animals that began extinction training 24 h after retrieval (outside of the reconsolidation window), demonstrated normal cocaine CPP. Conversely, animals that received additional CPP conditioning, rather than extinction training, 1 h after reactivation of cocaine memory showed enhanced cocaine CPP compared with animals that did not reactivate the cocaine memory before conditioning. These results reveal that a behavioral manipulation that takes advantage of reconsolidation and extinction of drug memories may be useful in decreasing preference for, and abuse of, cocaine.

**Persistent Pain Facilitates Response To Morphine Reward By Downregulation Of Central Amygdala Gabaergic Function** Zhang Z, Tao W, Hou YY, Wang W, Lu YG, Pan ZZ. *Neuropsychopharmacology.* 2014 Aug;39(9): 2263-71. doi:10.1038/npp.2014.77. Epub 2014 Apr 1.

Opioid-based analgesics are widely used for treating chronic pain, but opioids are highly addictive when repeatedly used because of their strong rewarding effects. In recent years, abuse of prescription opioids has dramatically increased, including incidences of misuse of opioid drugs prescribed for pain control. Despite this issue in current clinical pain management, it remains unknown how pain influences the abuse liability of prescription opioids. Pain as aversive experience may affect opioid reward of positive emotion through common brain sites involved in emotion processing. In this study, on a rat model of chronic pain, the authors determined how persistent pain altered behavioral responses to morphine reward measured by the paradigm of

unbiased conditioned place preference (CPP), focusing on GABAergic synaptic activity in neurons of the central nucleus of the amygdala (CeA), an important brain region for emotional processing of both pain and reward. The authors found that pain reduced the minimum number of morphine-conditioning sessions required for inducing CPP behavior. Both pain and morphine conditioning that elicited CPP inhibited GABA synaptic transmission in CeA neurons. Pharmacological activation of CeA GABA receptors reduced the pain and inhibited CPP induced both by an effective dose of morphine and by a sub-threshold dose of morphine under pain condition. Furthermore, inhibition of CeA GABA receptors mimicked the pain effect, rendering the sub-threshold dose of morphine effective in CPP induction. These findings suggest that pain facilitates behavioral responses to morphine reward by predisposing the inhibitory GABA function in the CeA circuitry involved in the behavior of opioid reward.

**Environmental Enrichment Reduces Methamphetamine Cue-Induced Reinstatement But Does Not Alter Methamphetamine Reward Or VMAT2 Function**

Hofford RS, Darna M, Wilmoth CE, Dvoskin LP, Bardo MT. Behav Brain Res. 2014 Aug 15; 270: 151-8. doi: 10.1016/j.bbr.2014.05.007. Epub 2014 May 10.

Environmental factors influence a variety of health-related outcomes. In general, being raised in an environment possessing social, sensory, and motor enrichment reduces the rewarding effects of various drugs, thus protecting against abuse vulnerability. However, in the case of methamphetamine (METH), which acts at the vesicular monoamine transporter 2 (VMAT2) to enhance dopamine release from the cytosol, previous evidence suggests that METH reward may not be altered by environmental enrichment. This study examined the influence of an enriched environment on measures of METH reward, METH seeking, and VMAT2 function. Rats were raised from weaning to adulthood in either an enriched environment (presence of social cohorts and novel objects) or an isolated environment (no cohorts or novel objects). Rats in these two conditions were subsequently tested for their acquisition of conditioned place preference (CPP), METH self-administration, maintenance of self-administration at various unit doses of METH (0.001-0.5mg/kg/infusion), and cue-induced reinstatement. VMAT2 function in striatum from these two groups also was assessed. No significant environment effects were found in CPP or METH self-administration, which paralleled a lack of effect in VMAT2 function between groups. However, cue-induced reinstatement was reduced by environmental enrichment. Together, these results suggest that environmental enrichment does not alter VMAT2 function involved in METH reward. However, the enrichment-induced decrease in cue-induced reinstatement indicates that enrichment may have a beneficial effect against relapse following a period of extinction via a neural mechanism other than striatal VMAT2 function.

**Mutation of Putative GRK Phosphorylation Sites In The Cannabinoid Receptor 1(CB1R) Confers Resistance To Cannabinoid Tolerance And Hypersensitivity To Cannabinoids In Mice**

Morgan DJ, Davis BJ, Kearns CS, Marcus D, Cook AJ, Wager-Miller J, Straiker A, Myoga MH, Karduck J, Leishman E, Sim-Selley LJ, Czyzyk TA, Bradshaw HB, Selley DE, Mackie K. J Neurosci. 2014 Apr 9; 34(15): 5152-63. doi: 10.1523/JNEUROSCI.3445-12.2014.

For many G-protein-coupled receptors (GPCRs), including cannabinoid receptor 1 (CB1R), desensitization has been proposed as a principal mechanism driving initial tolerance to agonists. GPCR desensitization typically requires phosphorylation by a G-protein-coupled receptor kinase (GRK) and interaction of the phosphorylated receptor with an arrestin. In simple model systems, CB1R is desensitized by GRK phosphorylation at two serine residues (S426 and S430). However,

the role of these serine residues in tolerance and dependence for cannabinoids in vivo was unclear. Therefore, the authors generated mice where S426 and S430 were mutated to nonphosphorylatable alanines (S426A/S430A). S426A/S430A mutant mice were more sensitive to acutely administered delta-9-tetrahydrocannabinol ( $\Delta(9)$ -THC), have delayed tolerance to  $\Delta(9)$ -THC, and showed increased dependence for  $\Delta(9)$ -THC. S426A/S430A mutants also showed increased responses to elevated levels of endogenous cannabinoids. CB1R desensitization in the periaqueductal gray and spinal cord following 7 d of treatment with  $\Delta(9)$ -THC was absent in S426A/S430A mutants.  $\Delta(9)$ -THC-induced downregulation of CB1R in the spinal cord was also absent in S426A/S430A mutants. Cultured autaptic hippocampal neurons from S426A/S430A mice showed enhanced endocannabinoid-mediated depolarization-induced suppression of excitation (DSE) and reduced agonist-mediated desensitization of DSE. These results indicate that S426 and S430 play major roles in the acute response to, tolerance to, and dependence on cannabinoids. Additionally, S426A/S430A mice are a novel model for studying pathophysiological processes thought to involve excessive endocannabinoid signaling such as drug addiction and metabolic disease. These mice also validate the approach of mutating GRK phosphorylation sites involved in desensitization as a general means to confer exaggerated signaling to GPCRs in vivo.

**[Loss of BDNF Signaling in D1R-Expressing NAc Neurons Enhances Morphine Reward by Reducing GABA Inhibition](#)** Koo JW, Lobo MK, Chaudhury D, Labonté B, Friedman A, Heller E, Peña CJ, Han MH, Nestler EJ. *Neuropsychopharmacology*. 2014 May 23. doi: 10.1038/npp.2014.118. [Epub ahead of print].

The nucleus accumbens (NAc) has a central role in the mechanism of action of drugs of abuse. The major neuronal type within the NAc is the GABAergic medium spiny neuron (MSN), with two major subpopulations defined—termed D1-type and D2-type MSNs—based on the predominant dopamine receptor expressed. However, very little is known about the contribution of altered GABAergic function in NAc MSNs to the neural and behavioral plasticity that contributes to the lasting actions of drugs of abuse. In the present study, the authors show that GABAergic activity is selectively modulated in D1-type MSNs of the NAc by signaling of brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine receptor kinase B (TrkB), and that such adaptations control rewarding responses to morphine. Optical activation of D1-type MSNs, or the knockout of TrkB from D1-type MSNs (D1-TrkB KO), enhances morphine reward, effects not seen for D2-type MSNs. In addition, D1-TrkB KO mice, but not D2-TrkB KO mice, display decreased GABA<sub>A</sub> receptor (GABAAR) subunit expression and reduced spontaneous inhibitory postsynaptic currents (sIPSCs) in D1-type, but not D2-type, MSNs in the NAc. Furthermore, the authors found that GABAAR antagonism in the NAc enhances morphine reward and that morphine exposure decreases TrkB expression as well as GABAergic activity in D1-type MSNs. Together, these data provide evidence for the enhancement of morphine reward through reduction of inhibitory GABAAR responses, an adaptation mediated by morphine-induced reduction of BDNF-TrkB signaling in D1-type MSNs.

**[Natural Neural Projection Dynamics Underlying Social Behavior](#)** Gunaydin LA, Grosenick L, Finkelstein JC, Kauvar IV, Fenno LE, Adhikari A, Lammel S, Mirzabekov JJ, Airan RD, Zalocusky KA, Tye KM, Anikeeva P, Malenka RC, Deisseroth K. *Cell*. 2014 Jun 19; 157(7): 1535-51. doi: 10.1016/j.cell.2014.05.017.

Social interaction is a complex behavior essential for many species and is impaired in major neuropsychiatric disorders. Pharmacological studies have implicated certain neurotransmitter

systems in social behavior, but circuit-level understanding of endogenous neural activity during social interaction is lacking. The authors therefore developed and applied a new methodology, termed fiber photometry, to optically record natural neural activity in genetically and connectivity-defined projections to elucidate the real-time role of specified pathways in mammalian behavior. Fiber photometry revealed that activity dynamics of a ventral tegmental area (VTA)-to-nucleus accumbens (NAc) projection could encode and predict key features of social, but not novel object, interaction. Consistent with this observation, optogenetic control of cells specifically contributing to this projection was sufficient to modulate social behavior, which was mediated by type 1 dopamine receptor signaling downstream in the NAc. Direct observation of deep projection-specific activity in this way captures a fundamental and previously inaccessible dimension of mammalian circuit dynamics.

**[Social Stress and CRF-Dopamine Interactions in the VTA: Role In Long-Term Escalation Of Cocaine Self-Administration](#)** Boyson CO, Holly EN, Shimamoto A, Albrechet-Souza L, Weiner LA, DeBold JF, Miczek KA. *J Neurosci.* 2014 May 7; 34(19): 6659-67. doi: 10.1523/JNEUROSCI.3942-13.2014.

The nature of neuroadaptations in the genesis of escalated cocaine taking remains a topic of considerable interest. Intermittent social defeat stress induces both locomotor and dopaminergic cross-sensitization to cocaine, as well as escalated cocaine self-administration. The current study examines the role of corticotropin releasing factor receptor subtypes 1 and 2 (CRFR1, CRFR2) within the ventral tegmental area (VTA) during social defeat stress. This study investigated whether injecting either a CRFR1 or CRFR2 antagonist directly into the VTA before each social defeat would prevent the development of later (1) locomotor sensitization, (2) dopaminergic sensitization, and (3) escalated cocaine self-administration in rats. CRFR1 antagonist CP376395 (50 or 500 ng/side), CRFR2 antagonist Astressin2-B (100 or 1000 ng/side), or vehicle (aCSF) was microinjected into the VTA 20 min before social defeat stress (or handling) on days 1, 4, 7, and 10. Ten days later, rats were injected with cocaine (10 mg/kg, i.p.) and assessed for either locomotor sensitization, measured by walking activity, or dopaminergic sensitization, measured by extracellular dopamine (DA) in the nucleus accumbens shell (NAcSh) through in vivo microdialysis. Locomotor sensitization testing was followed by intravenous cocaine self-administration. Intra-VTA antagonism of CRFR1, but not CRFR2, inhibited the induction of locomotor cross-sensitization to cocaine, whereas both prevented dopaminergic cross-sensitization and escalated cocaine self-administration during a 24 h "binge." This may suggest dissociation between locomotor sensitization and cocaine taking. These data also suggest that interactions between CRF and VTA DA neurons projecting to the NAcSh are essential for the development of dopaminergic cross-sensitization to cocaine.

**[Kappa Opioid Receptor-Mediated Antinociception Is Blocked By A Delta Opioid Receptor Agonist](#)** Taylor AM1, Roberts KW, Pradhan AA, Akbari HA, Walwyn W, Lutfy K, Carroll FI, Cahill CM, Evans CJ. *Br J Pharmacol.* 2014 Jun 12. doi: 10.1111/bph.12810. [Epub ahead of print]. The opioid receptor family is made up of four structurally homologous but functionally distinct receptors, the mu (MOP), delta (DOP), kappa (KOP), and nociceptin (NOP). Given that most opioid agonists are selective but not specific, a broad spectrum of behaviors due to activation of different opioid receptors is expected. In this study, the authors examine whether other opioid receptor systems influence KOP-mediated antinociception. They use a tail withdrawal assay in C57Bl/6 mice to assay the antinociceptive effect of systemically administered opioid agonists with varying

selectivity at the KOP. Pharmacological and genetic approaches were used to dissect out the interaction of the other opioid receptors in modulating KOP mediated antinociception. Etorphine, a potent agonist at all 4 opioid receptors, was not antinociceptive in MOP knock out (KO) mice. This result was unexpected since etorphine is an efficacious KOP agonist and specific KOP agonists remain analgesic in MOP KO mice. Given that KOP agonists are aversive, we considered KOP-mediated antinociception might be a form of stress-induced analgesia that is blocked by the anxiolytic effects of DOP. In support of this hypothesis, pretreatment with the DOP antagonist, naltrindole (10mg/kg), unmasked etorphine (3mg/kg) antinociception in MOP KO mice. Further, in wildtype (WT) mice, KOP-mediated antinociception by systemic U50,488H (10mg/kg) was blocked by pretreatment with the DOP agonist SNC80 (5mg/kg) and diazepam(1mg/kg). The authors conclude that systemic DOP agonists block systemic KOP antinociception, and these results identify DOP agonists as potential therapeutics for reversing stress-driven addictive and depressive behaviors mediated through KOP activation.

### **Acid-Sensing Ion Channels Contribute To Synaptic Transmission and Inhibit Cocaine-Evoked Plasticity**

Kreple CJ, Lu Y, Taugher RJ, Schwager-Gutman AL, Du J, Stump M, Wang Y, Ghobbeh A, Fan R, Cosme CV, Sowers LP, Welsh MJ, Radley JJ, LaLumiere RT, Wemmie JA. Nat Neurosci. 2014 Jun 22. doi: 10.1038/nn.3750. [Epub ahead of print].

Acid-sensing ion channel 1A (ASIC1A) is abundant in the nucleus accumbens (NAc), a region known for its role in addiction. Because ASIC1A has been suggested to promote associative learning, the authors hypothesized that disrupting ASIC1A in the NAc would reduce drug-associated learning and memory. However, contrary to this hypothesis, they found that disrupting ASIC1A in the mouse NAc increased cocaine-conditioned place preference, suggesting an unexpected role for ASIC1A in addiction-related behavior. Moreover, overexpressing ASIC1A in rat NAc reduced cocaine self-administration. Investigating the underlying mechanisms, the authors identified a previously unknown postsynaptic current during neurotransmission that was mediated by ASIC1A and ASIC2 and thus well positioned to regulate synapse structure and function. Consistent with this possibility, disrupting ASIC1A altered dendritic spine density and glutamate receptor function, and increased cocaine-evoked plasticity, which resemble changes previously associated with cocaine-induced behavior. Together, these data suggest that ASIC1A inhibits the plasticity underlying addiction-related behavior and raise the possibility of developing therapies for drug addiction by targeting ASIC-dependent neurotransmission.

### **Executive Control Processes Underlying Multi-Item Working Memory**

Lara AH, Wallis JD. Nat Neurosci. 2014 Jun; 17(6): 876-83. doi: 10.1038/nn.3702. Epub 2014 Apr 20.

A dominant view of prefrontal cortex (PFC) function is that it stores task-relevant information in working memory. To examine this and determine how it applies when multiple pieces of information must be stored, the authors trained two subjects to perform a multi-item color change detection task and recorded activity of neurons in PFC. Few neurons encoded the color of the items. Instead, the predominant encoding was spatial: a static signal reflecting the item's position and a dynamic signal reflecting the subject's covert attention. These findings challenge the notion that PFC stores task-relevant information. Instead, the authors suggest that the contribution of PFC is in controlling the allocation of resources to support working memory. In support of this, they found that increased power in the alpha and theta bands of PFC local field potentials, which are thought to reflect long-range communication with other brain areas, was correlated with more precise color representations.

### **Symbol Addition By Monkeys Provides Evidence For Normalized Quantity Coding**

Livingstone MS, Pettine WW, Srihasam K, Moore B, Morocz IA, Lee D. Proc Natl Acad Sci U S A. 2014 May 6; 111(18): 6822-7. doi: 10.1073/pnas.1404208111. Epub 2014 Apr 21.

Weber's law can be explained either by a compressive scaling of sensory response with stimulus magnitude or by a proportional scaling of response variability. These two mechanisms can be distinguished by asking how quantities are added or subtracted. The authors trained Rhesus monkeys to associate 26 distinct symbols with 0-25 drops of reward, and then tested how they combine, or add, symbolically represented reward magnitude. They found that they could combine symbolically represented magnitudes, and they transferred this ability to a novel symbol set, indicating that they were performing a calculation, not just memorizing the value of each combination. The way they combined pairs of symbols indicated neither a linear nor a compressed scale, but rather a dynamically shifting, relative scaling.

### **Hypocretin (Orexin) Facilitates Reward By Attenuating the Antireward Effects Of Its Cotransmitter Dynorphin In Ventral Tegmental Area**

Muschamp JW, Hollander JA, Thompson JL, Voren G, Hassinger LC, Onvani S, Kamenecka TM, Borgland SL, Kenny PJ, Carlezon WA Jr. 60. Proc Natl Acad Sci U S A. 2014 Apr 22; 111(16): E1648-55. doi: 10.1073/pnas.1315542111. Epub 2014 Mar 24.

Hypocretin (orexin) and dynorphin are neuropeptides with opposing actions on motivated behavior. Orexin is implicated in states of arousal and reward, whereas dynorphin is implicated in depressive-like states. The authors show that, despite their opposing actions, these peptides are packaged in the same synaptic vesicles within the hypothalamus. Disruption of orexin function blunts the rewarding effects of lateral hypothalamic (LH) stimulation, eliminates cocaine-induced impulsivity, and reduces cocaine self-administration. Concomitant disruption of dynorphin function reverses these behavioral changes. The authors also show that orexin and dynorphin have opposing actions on excitability of ventral tegmental area (VTA) dopamine neurons, a prominent target of orexin-containing neurons, and that intra-VTA orexin antagonism causes decreases in cocaine self-administration and LH self-stimulation that are reversed by dynorphin antagonism. These findings identify a unique cellular process by which orexin can occlude the reward threshold-elevating effects of coreleased dynorphin and thereby act in a permissive fashion to facilitate reward.

### **Dopamine Transporter Deficiency Syndrome: Phenotypic Spectrum From Infancy To Adulthood**

Ng J, Zhen J, Meyer E, Erreger K, Li Y, Kakar N, Ahmad J, Thiele H, Kubisch C, Rider NL, Morton DH, Strauss KA, Puffenberger EG, D'Agnano D, Anikster Y, Carducci C, Hyland K, Rotstein M, Leuzzi V, Borck G, Reith ME, Kurian MA. Brain. 2014 Apr; 137(Pt 4): 1107-19. doi: 10.1093/brain/awu022. Epub 2014 Mar 10.

Dopamine transporter deficiency syndrome due to SLC6A3 mutations is the first inherited dopamine 'transportopathy' to be described, with a classical presentation of early infantile-onset progressive parkinsonism dystonia. In this study the authors have identified a new cohort of patients with dopamine transporter deficiency syndrome, including, most significantly, atypical presentation later in childhood with a milder disease course. They report the detailed clinical features, molecular genetic findings and in vitro functional investigations undertaken for adult and paediatric cases. Patients presenting with parkinsonism dystonia or a neurotransmitter profile characteristic of dopamine transporter deficiency syndrome were recruited for study. SLC6A3 mutational analysis was undertaken in all patients. The functional consequences of missense variants on the dopamine transporter were evaluated by determining the effect of mutant dopamine transporter on dopamine

uptake, protein expression and amphetamine-mediated dopamine efflux using an in vitro cellular heterologous expression system. The authors identified eight new patients from five unrelated families with dopamine transporter deficiency syndrome. The median age at diagnosis was 13 years (range 1.5-34 years). Most significantly, the case series included three adolescent males with atypical dopamine transporter deficiency syndrome of juvenile onset (outside infancy) and progressive parkinsonism dystonia. The other five patients in the cohort presented with classical infantile-onset parkinsonism dystonia, with one surviving into adulthood (currently aged 34 years) and labelled as having 'juvenile parkinsonism'. All eight patients harboured homozygous or compound heterozygous mutations in SLC6A3, of which the majority are previously unreported variants. In vitro studies of mutant dopamine transporter demonstrated multifaceted loss of dopamine transporter function. Impaired dopamine uptake was universally present, and more severely impacted in dopamine transporter mutants causing infantile-onset rather than juvenile-onset disease. Dopamine transporter mutants also showed diminished dopamine binding affinity, reduced cell surface transporter, loss of post-translational dopamine transporter glycosylation and failure of amphetamine-mediated dopamine efflux. The authors' data series expands the clinical phenotypic continuum of dopamine transporter deficiency syndrome and indicates that there is a phenotypic spectrum from infancy (early onset, rapidly progressive disease) to childhood/adolescence and adulthood (later onset, slower disease progression). Genotype-phenotype analysis in this cohort suggests that higher residual dopamine transporter activity is likely to contribute to postponing disease presentation in these later-onset adult cases. Dopamine transporter deficiency syndrome remains under-recognized and these data highlights that dopamine transporter deficiency syndrome should be considered as a differential diagnosis for both infantile- and juvenile-onset movement disorders, including cerebral palsy and juvenile parkinsonism.

### **Cannabinoid Receptor Activation Shifts Temporally Engendered Patterns Of Dopamine Release**

Oleson EB, Cachope R, Fitoussi A, Tsutsui K, Wu S, Gallegos JA, Cheer JF. *Neuropsychopharmacology*. 2014 May; 39(6): 1441-52. doi: 10.1038/npp.2013.340. Epub 2013 Dec 18.

The ability to discern temporally pertinent environmental events is essential for the generation of adaptive behavior in conventional tasks, and our overall survival. Cannabinoids are thought to disrupt temporally controlled behaviors by interfering with dedicated brain timing networks. Cannabinoids also increase dopamine release within the mesolimbic system, a neural pathway generally implicated in timing behavior. Timing can be assessed using fixed-interval (FI) schedules, which reinforce behavior on the basis of time. To date, it remains unknown how cannabinoids modulate dopamine release when responding under FI conditions, and for that matter, how subsecond dopamine release is related to time in these tasks. In the present study, the authors hypothesized that cannabinoids would accelerate timing behavior in an FI task while concurrently augmenting a temporally relevant pattern of dopamine release. To assess this possibility, they measured subsecond dopamine concentrations in the nucleus accumbens while mice responded for food under the influence of the cannabinoid agonist WIN 55,212-2 in an FI task. Their data reveal that accumbal dopamine concentrations decrease proportionally to interval duration--suggesting that dopamine encodes time in FI tasks. The authors further demonstrate that WIN 55,212-2 dose-dependently increases dopamine release and accelerates a temporal behavioral response pattern in a CB1 receptor-dependent manner--suggesting that cannabinoid receptor activation modifies timing behavior, in part, by augmenting time-engendered patterns of dopamine release. Additional investigation uncovered a specific role for endogenous cannabinoid tone in timing behavior, as

elevations in 2-arachidonoylglycerol, but not anandamide, significantly accelerated the temporal response pattern in a manner akin to WIN 55,212-2.

**Reward Value Comparison via Mutual Inhibition in Ventromedial Prefrontal Cortex** Strait CE, Blanchard TC, Hayden BY. *Neuron*. 2014 Jun 18; 82(6): 1357-66. doi: 10.1016/j.neuron.2014.04.032. Epub 2014 May 29.

Recent theories suggest that reward-based choice reflects competition between value signals in the ventromedial prefrontal cortex (vmPFC). The authors tested this idea by recording vmPFC neurons while macaques performed a gambling task with asynchronous offer presentation. They found that neuronal activity shows four patterns consistent with selection via mutual inhibition: (1) correlated tuning for probability and reward size, suggesting that vmPFC carries an integrated value signal; (2) anti-correlated tuning curves for the two options, suggesting mutual inhibition; (3) neurons rapidly come to signal the value of the chosen offer, suggesting the circuit serves to produce a choice; and (4) after regressing out the effects of option values, firing rates still could predict choice—a choice probability signal. In addition, neurons signaled gamble outcomes, suggesting that vmPFC contributes to both monitoring and choice processes. These data suggest a possible mechanism for reward-based choice and endorse the centrality of vmPFC in that process.

**Ghrelin Acts As An Interface Between Physiological State and Phasic Dopamine Signaling**

Cone JJ, McCutcheon JE, Roitman MF. *J Neurosci*. 2014 Apr 2; 34(14): 4905-13. doi: 10.1523/JNEUROSCI.4404-13.2014.

Brief, high-concentration (phasic) spikes in nucleus accumbens dopamine critically participate in aspects of food reward. Although physiological state (e.g., hunger, satiety) and associated hormones are known to affect dopamine tone in general, whether they modulate food-evoked, phasic dopamine specifically is unknown. Here, the authors used fast-scan cyclic voltammetry in awake, behaving rats to record dopamine spikes evoked by delivery of sugar pellets while pharmacologically manipulating central receptors for the gut "hunger" hormone ghrelin. Lateral ventricular (LV) ghrelin increased, while LV ghrelin receptor antagonism suppressed the magnitude of dopamine spikes evoked by food. Ghrelin was effective when infused directly into the lateral hypothalamus (LH), but not the ventral tegmental area (VTA). LH infusions were made in close proximity to orexin neurons, which are regulated by ghrelin and project to the VTA. Thus, we also investigated and found potentiation of food-evoked dopamine spikes by intra-VTA orexin-A. Importantly, intra-VTA blockade of orexin receptors attenuated food intake induced by LV ghrelin, thus establishing a behaviorally relevant connection between central ghrelin and VTA orexin. Further analysis revealed that food restriction increased the magnitude of dopamine spikes evoked by food independent of any pharmacological manipulations. The results support the regulation of food-evoked dopamine spikes by physiological state with endogenous fluctuations in ghrelin as a key contributor. These data highlight a novel mechanism by which signals relating physiological state could influence food reinforcement and food-directed behavior.

## **BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH**

*DCNBR*

### **Inhibition during Early Adolescence Predicts Alcohol and Marijuana Use by Late**

**Adolescence** Squeglia LM, Jacobus J, Nguyen-Louie TT, Tapert SF. *Neuropsychology*. 2014 Apr 21. [Epub ahead of print].

Adolescent substance use has been associated with poorer neuropsychological functioning, but it is unclear if deficits predate or follow the onset of use. The goal of this prospective study was to understand how neuropsychological functioning during early adolescence could predict substance use by late adolescence. At baseline, participants were 175 substance-use-naïve healthy 12- to 14-year-olds (41% female) recruited from local schools. Participants completed extensive interviews and neuropsychological tests. Each year, participants' substance use was assessed. By late adolescence (ages 17 to 18), 105 participants transitioned into substance use and 75 remained substance-naïve. Hierarchical linear regressions examined how baseline cognitive performance predicted subsequent substance use, controlling for common substance use risk factors (i.e., family history, externalizing behaviors, gender, pubertal development, and age). Poorer baseline performance on tests of cognitive inhibition-interference predicted higher follow-up peak drinks on an occasion ( $\beta = -.15$ ;  $p < .001$ ), more days of drinking ( $\beta = -.15$ ;  $p < .001$ ), and more marijuana use days ( $\beta = -.17$ ;  $p < .001$ ) by ages 17 to 18, above and beyond covariates. Performances on short-term memory, sustained attention, verbal learning and memory, visuospatial functioning and spatial planning did not predict subsequent substance involvement ( $ps > .05$ ). Compromised inhibitory functioning during early adolescence prior to the onset of substance use was related to more frequent and intense alcohol and marijuana use by late adolescence. Inhibition performance could help identify teens at risk for initiating heavy substance use during adolescence, and potentially could be modified to improve outcome.

### **Intellectual, Neurocognitive, and Academic Achievement in Abstinent Adolescents with Cannabis Use Disorder**

Hooper SR, Woolley D, De Bellis MD. *Psychopharmacology (Berl)*. 2014 Apr; 231(8): 1467-77.

The active component of cannabis, delta-9 tetrahydrocannabinol (THC), has a long half-life and widespread neurocognitive effects. There are inconsistent reports of neurocognitive deficits in adults and adolescents with cannabis use disorders (CUD), particularly after a period of abstinence. This study aims to examine neurocognitive measures (IQ, academic achievement, attention, memory, executive functions) in abstinent adolescents with CUD, while controlling for demographic, psychopathology, and poly-substance confounders. The authors investigated neurocognitive performance in three groups: adolescents with CUD after successful first treatment and in full remission ( $n=33$ ); controls with psychiatric disorders without substance use disorder history ( $n=37$ ); and healthy adolescents ( $n=43$ ). Adolescents with psychiatric disorders, regardless of CUD status, performed significantly worse than the healthy adolescents in academic achievement. No group differences were seen in IQ, attention, memory, or executive functions. Lower academic achievement was positively associated with younger age of CUD onset, regular cannabis use, and maximum daily use. In the CUD group, lifetime nicotine use episodes were negatively associated with IQ. Lower overall neurocognitive function was associated with younger age of onset of regular cannabis use and relapse within the 1 year follow-up. Verifiably, abstinent adolescents with CUD history did not differ from the two comparison groups, suggesting that previously reported neurocognitive deficits may be related to other factors, including residual drug

effects, preexisting cognitive deficits, concurrent use of other substances (e.g., nicotine), or psychopathology. Adolescents with CUD may not be vulnerable to THC neuropsychological deficits once they achieve remission from all drugs for at least 30 days.

**[Left Middle Frontal Gyrus Response to Inhibitory Errors in Children Prospectively Predicts Early Problem Substance Use](#)** Heitzeg MM, Nigg JT, Hardee JE, Soules M, Steinberg D, Zubieta J, Zucker RA. *Drug Alcohol Depend.* 2014 Aug 1; 141: 51-7.

A core vulnerability trait for substance use disorder (SUD) is behavioral disinhibition. Error processing is a central aspect of inhibitory control that determines adaptive adjustment of performance; yet it is a largely overlooked aspect of disinhibition as it relates to risk for SUD. The authors investigated whether differences in brain activation during both successful and failed inhibition predicts early problem substance use. Forty-five 9-12 year olds underwent a functional MRI scan during a go/no-go task. They were then followed over approximately 4 years, completing assessments of substance use. Externalizing behavior was measured at ages 3-8, 9-12 and 11-13. Participants with drug use or problem alcohol use by ages 13-16 (n=13; problem-user group) were individually matched by gender, age, and family history of alcoholism with non-substance-using children (n=13; non-user group). The remaining 19 participants provided an independent sample from which to generate unbiased regions-of-interest for hypothesis testing in the problem-user and non-user groups. No differences were observed between groups in activation during correct inhibition compared with baseline. A significant difference arose in left middle frontal gyrus (LMFG) activation during failed inhibition compared with correct inhibition, with the problem-user group demonstrating blunted activation. The problem-user group also had more externalizing problems at ages 11-13. Logistic regression found that activation of LMFG significantly predicted group membership over and above externalizing problems. Blunted LMFG activation during performance errors may underlie problems adapting behavior appropriately, leading to undercontrolled behavior, early problem substance use and increased risk for SUD.

## **CLINICAL NEUROSCIENCE RESEARCH**

### ***DCNBR***

**[Worth the Wait: Effects of Age of Onset of Marijuana Use on White Matter and Impulsivity](#)**

Gruber SA, Dahlgren MK, Sagar KA, Gönenç A, Lukas SE. *Psychopharmacology.* 2014; 231(8):1455–1465.

Marijuana (MJ) use continues to rise, and as the perceived risk of using MJ approaches an all-time historic low, initiation of MJ use is occurring at even younger ages. As adolescence is a critical period of neuromaturation, teens and emerging adults are at greater risk for experiencing the negative effects of MJ on the brain. In particular, MJ use has been shown to be associated with alterations in frontal white matter microstructure, which may be related to reports of increased levels of impulsivity in this population. The aim of this study was to examine the relationship between age of onset of MJ use, white matter microstructure, and reported impulsivity in chronic, heavy MJ smokers. Twenty-five MJ smokers and 18 healthy controls underwent diffusion tensor imaging and completed the Barratt Impulsiveness Scale. MJ smokers were also divided into early onset (regular use prior to age 16) and late onset (age 16 or later) groups in order to clarify the impact of age of onset of MJ use on these variables. MJ smokers exhibited significantly reduced

fractional anisotropy (FA) relative to controls, as well as higher levels of impulsivity. Earlier MJ onset was also associated with lower levels of FA. Interestingly, within the early onset group, higher impulsivity scores were correlated with lower FA, a relationship that was not observed in the late onset smokers. MJ use is associated with white matter development and reported impulsivity, particularly in early onset smokers.

**Effects of APOE  $\epsilon$ 4, Age, and HIV on Glial Metabolites and Cognitive Deficits** Chang L, Jiang C, Cunningham E, Buchthal S, Douet V, Andres M, Ernst T. *Neurology*. 2014 Jun 17; 82(24): 2213-2222.

The authors aimed to evaluate the combined effects of HIV and APOE  $\epsilon$ 4 allele(s) on glial metabolite levels, and on known cognitive deficits associated with either condition, across the ages. One hundred seventy-seven participants, primarily of white and mixed race (97 seronegative subjects: aged  $44.7 \pm 1.3$  years, 85 [87.6%] men, 28 [28.9%] APOE  $\epsilon$ 4+; 80 HIV+ subjects: aged  $47.3 \pm 1.1$  years, 73 [91.3%] men, 23 [28.8%] APOE  $\epsilon$ 4+), were assessed cross-sectionally for metabolite concentrations using proton magnetic resonance spectroscopy in 4 brain regions and for neuropsychological performance. Frontal white matter myo-inositol was elevated in subjects with HIV across the age span but showed age-dependent increase in seronegative subjects, especially in APOE  $\epsilon$ 4+ carriers. In contrast, only seronegative APOE  $\epsilon$ 4+ subjects showed elevated myo-inositol in parietal cortex. All APOE  $\epsilon$ 4+ subjects had lower total creatine in basal ganglia. While all HIV subjects showed greater cognitive deficits, HIV+ APOE  $\epsilon$ 4+ subjects had the poorest executive function, fluency memory, and attention/working memory. Higher myo-inositol levels were associated with poorer fine motor function across all subjects, slower speed of information processing in APOE  $\epsilon$ 4+ subjects, and worse fluency in HIV+ APOE  $\epsilon$ 4+ subjects. In frontal white matter of subjects with HIV, the persistent elevation and lack of normal age-dependent increase in myo-inositol suggest that persistent glial activation attenuated the typical antagonistic pleiotropic effects of APOE  $\epsilon$ 4 on neuroinflammation. APOE  $\epsilon$ 4 negatively affects energy metabolism in brain regions rich in dopaminergic synapses. The combined effects of HIV infection and APOE  $\epsilon$ 4 may lead to greater cognitive deficits, especially in those with greater neuroinflammation. APOE  $\epsilon$ 4 allele(s) may be a useful genetic marker to identify white and mixed-race HIV subjects at risk for cognitive decline.

**Risky Decision Making, Prefrontal Cortex, and Mesocorticolimbic Functional Connectivity in Methamphetamine Dependence** Kohno M, Morales AM, Ghahremani DG, Helleman G, London ED. *JAMA Psychiatry*. 2014 Jul 1; 71(7): 812-820.

Various neuropsychiatric disorders, especially addictions, feature impairments in risky decision making; clarifying the neural mechanisms underlying this problem can inform treatment. The objective of this study was to determine how methamphetamine-dependent and control participants differ in brain activation during a risky decision-making task, resting-state functional connectivity within mesolimbic and executive control circuits, and the relationships between these measures. This was a case-control, functional magnetic resonance imaging study of methamphetamine-dependent and healthy comparison participants at rest and when performing the Balloon Analogue Risk Task, which involves the choice to pump a balloon or to cash out in the context of uncertain risk. The study was conducted at a clinical research center at an academic institution, and involved 25 methamphetamine-dependent and 27 control participants. Parametric modulation of activation in the striatum and right dorsolateral prefrontal cortex (rDLPFC; ie, the degree to which activation changed as a linear function of risk and potential reward), both indexed by pump number, and

resting-state functional connectivity, were measured in the whole brain with seeds in the midbrain and rDLPFC. Relationships between these outcomes were also tested. Parametric modulation of cortical and striatal activation by pump number during risk taking differed with group. It was stronger in the ventral striatum but weaker in the rDLPFC in methamphetamine-dependent participants than control individuals. Methamphetamine-dependent participants also exhibited greater resting-state functional connectivity of the midbrain with the putamen, amygdala, and hippocampus ( $P < .05$ , whole brain, cluster corrected). This connectivity was negatively related to modulation of rDLPFC activation by risk level during risky decision making. In control participants, parametric modulation of rDLPFC activation by risk during decision making was positively related to resting-state functional connectivity of the rDLPFC with the striatum. Maladaptive decision making by methamphetamine users may reflect circuit-level dysfunction, underlying deficits in task-based activation. Heightened resting-state connectivity within the mesocorticolimbic system, coupled with reduced prefrontal cortical connectivity, may create a bias toward reward-driven behavior over cognitive control in methamphetamine users. Interventions to improve this balance may enhance treatments for stimulant dependence and other disorders that involve maladaptive decision making.

**[A Window into the Intoxicated Mind? Speech as an Index of Psychoactive Drug Effects](#)** Bedi G, Cecchi GA, Slezak DF, Carrillo F, Sigman M, de Wit H. *Neuropsychopharmacology*. 2014 April. [Epub ahead of print].

Abused drugs can profoundly alter mental states in ways that may motivate drug use. These effects are usually assessed with self-report, an approach that is vulnerable to biases. Analyzing speech during intoxication may present a more direct, objective measure, offering a unique 'window' into the mind. Here, the authors employed computational analyses of speech semantic and topological structure after  $\pm$ 3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy') and methamphetamine in 13 ecstasy users. In 4 sessions, participants completed a 10-min speech task after MDMA (0.75 and 1.5mg/kg), methamphetamine (20 mg), or placebo. Latent Semantic Analyses identified the semantic proximity between speech content and concepts relevant to drug effects. Graph-based analyses identified topological speech characteristics. Group-level drug effects on semantic distances and topology were assessed. Machine-learning analyses (with leave-one-out cross-validation) assessed whether speech characteristics could predict drug condition in the individual subject. Speech after MDMA (1.5mg/kg) had greater semantic proximity than placebo to the concepts friend, support, intimacy, and rapport. Speech on MDMA (0.75mg/kg) had greater proximity to empathy than placebo. Conversely, speech on methamphetamine was further from compassion than placebo. Classifiers discriminated between MDMA (1.5mg/kg) and placebo with 88% accuracy, and MDMA (1.5mg/kg) and methamphetamine with 84% accuracy. For the two MDMA doses, the classifier performed at chance. These data suggest that automated semantic speech analyses can capture subtle alterations in mental state, accurately discriminating between drugs. The findings also illustrate the potential for automated speech-based approaches to characterize clinically relevant alterations to mental state, including those occurring in psychiatric illness.

## **EPIDEMIOLOGY RESEARCH**

### ***DESPR***

**Rates Of Substance Use Of American Indian Students In 8th, 10th, And 12th Grades Living On Or Near Reservations: Update, 2009-2012** Stanley LR, Harness SD, Swaim RC, Beauvais F. Public Health Rep. 2014 Mar-Apr; 129(2): 156-63.

Understanding the similarities and differences between substance use rates for American Indian (AI) young people and young people nationally can better inform prevention and treatment efforts. The authors compared substance use rates for a large sample of AI students living on or near reservations for the years 2009–2012 with national prevalence rates from Monitoring the Future (MTF). They identified and sampled schools on or near AI reservations by region; 1,399 students in sampled schools were administered the American Drug and Alcohol Survey. They computed lifetime, annual, and last-month prevalence measures by grade and compared them with MTF results for the same time period. Prevalence rates for AI students were significantly higher than national rates for nearly all substances, especially for 8th graders. Rates of marijuana use were very high, with lifetime use higher than 50% for all grade groups. Other findings of interest included higher binge drinking rates and OxyContin® use for AI students. The results from this study demonstrate that adolescent substance use is still a major problem among reservation-based AI adolescent students, especially 8th graders, where prevalence rates were sometimes dramatically higher than MTF rates. Given the high rates of substance userelated problems on reservations, such as academic failure, delinquency, violent criminal behavior, suicidality, and alcohol-related mortality, the costs to members of this population and to society will continue to be much too high until a comprehensive understanding of the root causes of substance use are established.

**Alcohol and Marijuana Use Patterns Associated With Unsafe Driving Among U.S. High School Seniors: High Use Frequency, Concurrent Use, and Simultaneous Use** Terry-McElrath YM, O'Malley PM, Johnston LD. Journal of Studies on Alcohol and Drugs, 75(3), 378–389.

This article examines noncausal associations between high school seniors' alcohol and marijuana use status and rates of self-reported unsafe driving in the past 12 months. Analyses used data from 72,053 students collected through annual surveys of nationally representative cross-sectional samples of U.S. 12th-grade students from 1976 to 2011. Two aspects of past-12-month alcohol and marijuana use were examined: (a) use frequency and (b) status as a nonuser, single substance user, concurrent user, or simultaneous user. Measures of past-12-month unsafe driving included any tickets/warnings or accidents, as well as tickets/warnings or accidents following alcohol or marijuana use. Analyses explored whether an individual's substance use frequency and simultaneous use status had differential associations with their rate of unsafe driving. Higher substance use frequency (primarily alcohol use frequency) was significantly and positively associated with unsafe driving. The rate of engaging in any unsafe driving was also significantly and positively associated with simultaneous use status, with the highest rate associated with simultaneous use, followed by concurrent use, followed by use of alcohol alone. Individuals who reported simultaneous use most or every time they used marijuana had the highest likelihood of reporting unsafe driving following either alcohol or marijuana use. This article expands the knowledge on individual risk factors associated with unsafe driving among teens. Efforts to educate U.S. high school students (especially substance users), parents, and individuals involved in

prevention programming and driver's education about the increased risks associated with various forms of drug use status may be useful.

**Accuracy Of Reports Of Lifetime Mental and Physical Disorders: Results From the Baltimore Epidemiological Catchment Area Study** Takayanagi Y, Spira AP, Roth KB, Gallo JJ, Eaton WW, Mojtabai R. *JAMA Psychiatry*. 2014; 71(3): 273-80.

Our understanding of how mental and physical disorders are associated and contribute to health outcomes in populations depends on accurate ascertainment of the history of these disorders. Recent studies have identified substantial discrepancies in the prevalence of mental disorders among adolescents and young adults depending on whether the estimates are based on retrospective reports or multiple assessments over time. It is unknown whether such discrepancies are also seen in midlife to late life. Furthermore, no previous studies have compared lifetime prevalence estimates of common physical disorders such as diabetes mellitus and hypertension ascertained by prospective cumulative estimates vs retrospective estimates. The objective of this study was to examine the lifetime prevalence estimates of mental and physical disorders during midlife to late life using both retrospective and cumulative evaluations. Prospective population-based survey (Baltimore Epidemiologic Catchment Area Survey) with 4 waves of interviews of 1071 community residents in Baltimore, Maryland, between 1981 and 2005. Lifetime prevalence of selected mental and physical disorders at wave 4 (2004-2005), according to both retrospective data and cumulative evaluations based on 4 interviews from wave 1 to wave 4. Retrospective evaluations substantially underestimated the lifetime prevalence of mental disorders as compared with cumulative evaluations. The respective lifetime prevalence estimates ascertained by retrospective and cumulative evaluations were 4.5% vs. 13.1% for major depressive disorder, 0.6% vs. 7.1% for obsessive-compulsive disorder, 2.5% vs. 6.7% for panic disorder, 12.6% vs. 25.3% for social phobia, 9.1% vs. 25.9% for alcohol abuse or dependence, and 6.7% vs. 17.6% for drug abuse or dependence. In contrast, retrospective lifetime prevalence estimates of physical disorders ascertained at wave 4 were much closer to those based on cumulative data from all 4 waves. The respective prevalence estimates ascertained by the 2 methods were 18.2% vs. 20.2% for diabetes, 48.4% vs. 55.4% for hypertension, 45.8% vs. 54.0% for arthritis, 5.5% vs. 7.2% for stroke, and 8.4% vs. 10.5% for cancer. One-time, cross-sectional population surveys may consistently underestimate the lifetime prevalence of mental disorders. The population burden of mental disorders may therefore be substantially higher than previously appreciated.

**Racial Susceptibility For QT Prolongation In Acute Drug Overdoses** Manini AF, Stimmel B, Vlahov D. *J Electrocardiol*. 2014; 47(2): 244-50.

QT prolongation independently predicts adverse cardiovascular events in suspected poisoning. The authors aimed to evaluate the association between race and drug-induced QT prolongation for patients with acute overdose. This was a cross-sectional observational study at two urban teaching hospitals. Consecutive adult ED patients with acute drug overdose were prospectively enrolled over a two year period. The primary outcome, long-QT, was defined using standard criteria: QTc > 470 ms in females and > 460 ms in males. The association between race and drug-induced QT prolongation was tested, considering several confounding variables. In 472 patients analyzed (46% female, mean age 42.3), QT prolongation occurred in 12.7%. Blacks had two-fold increased odds of drug-induced QT prolongation (OR 2.01, CI 1.03-3.91) and Hispanics had 48% decreased odds of drug-induced QT prolongation (OR 0.52, CI 0.29-0.94). The authors found significant racial susceptibility to drug-induced QT prolongation in this large urban study of acute overdoses.

**Associations Between DSM-IV Mental Disorders and Subsequent Self-reported Diagnosis Of Cancer** O'Neill S, Posada-Villa J, Medina-Mora ME, Al-Hamzawi AO, Piazza M, Tachimori H, Hu C, Lim C, Bruffaerts R, Lepine J-P, Matschinger H, de Girolamo G, de Jonge P, Alonso J, Caldas-de-Almeida JM, Florescu S, Kiejna A, Levinson D, Kessler RC, Scott KM. *J Psychosom Res.* 2014; 76(3): 207-12.

The associations between mental disorders and cancer remain unclear. It is also unknown whether any associations vary according to life stage or gender. This paper examines these research questions using data from the World Mental Health Survey Initiative. The World Health Organization Composite International Diagnostic Interview retrospectively assessed the lifetime prevalence of 16 DSM-IV mental disorders in face-to-face household population surveys in nineteen countries (n = 52,095). Cancer was indicated by self-report of diagnosis. Smoking was assessed in questions about current and past tobacco use. Survival analyses estimated associations between first onset of mental disorders and subsequently reported cancer. After adjustment for comorbidity, panic disorder, specific phobia and alcohol abuse were associated with a subsequently self-reported diagnosis of cancer. There was an association between number of mental disorders and the likelihood of reporting a cancer diagnosis following the onset of the mental disorder. This suggests that the associations between mental disorders and cancer risk may be generalized, rather than specific to a particular disorder. Depression is more strongly associated with self-reported cancers diagnosed early in life and in women. PTSD is also associated with cancers diagnosed early in life. This study reports the magnitude of the associations between mental disorders and a self-reported diagnosis of cancer and provides information about the relevance of comorbidity, gender and the impact at different stages of life. The findings point to a link between the two conditions and lend support to arguments for early identification and treatment of mental disorders.

**Dopamine Receptor Gene D4 Polymorphisms and Early Sexual Onset: Gender and Environmental Moderation In A Sample Of African-American Youth** Kogan SM, Lei M-K, Beach SRH, Brody GH, Windle M, Lee S, Mackillop J, Chen Y-F. *J Adolesc Health.* 2014. Early sexual onset and its consequences disproportionately affect African-American youth, particularly male youth. The dopamine receptor D4 gene (DRD4) has been linked to sexual activity and other forms of appetitive behavior, particularly for male youth and in combination with environmental factors (gene environment [GE] effects). The differential susceptibility perspective suggests that DRD4 may exert this effect by amplifying the effects of both positive and negative environments. The authors hypothesized that DRD4 status would amplify the influence of both positive and negative neighborhood environments on early sexual onset among male, but not female, African-Americans. Hypotheses were tested with self-report, bio specimen, and census data from five prospective studies of male and female African-American youth in rural Georgia communities, N=1,677. Early sexual onset was defined as intercourse before age 14. No significant GE findings emerged for female youth. Male youth with a DRD4 long allele were more likely than those with two DRD4 short alleles to report early sexual onset in negative community environments and not to report early onset in positive community environments. Dopaminergic regulation of adolescent sexual behaviors may operate differently by gender. DRD4 operated as an environmental amplification rather than a vulnerability factor.

## **PREVENTION RESEARCH**

### ***DESPR***

**Is Serotonin Transporter Genotype Associated With Epigenetic Susceptibility Or Vulnerability? Examination Of the Impact Of Socioeconomic Status Risk On African American Youth** Beach SRH, Brody GH, Lei MK, Kim S, Cui J, Philibert RA. *Dev Psychopathol.* 2014; 26(2): 289-304.

The authors hypothesized that presence of the short allele in the promoter region of the serotonin transporter would moderate the effect of early cumulative socioeconomic status (SES) risk on epigenetic change among African American youth. Contrasting hypotheses regarding the shape of the interaction effect were generated using vulnerability and susceptibility frameworks and applied to data from a sample of 388 African American youth. Early cumulative SES risk assessed at 11-13 years based on parent report interacted with presence of the short allele to predict differential methylation assessed at age 19. Across multiple tests, a differential susceptibility perspective rather than a diathesis-stress framework best fit the data for genes associated with depression, consistently demonstrating greater epigenetic response to early cumulative SES risk among short allele carriers. A pattern consistent with greater impact among short allele carriers also was observed using all cytosine nucleotide-phosphate-guanine nucleotide sites across the genome that was differentially affected by early cumulative SES risk. The authors conclude that the short allele is associated with increased responsiveness to early cumulative SES risk among African American youth, leading to epigenetic divergence for depression-related genes in response to exposure to heightened SES risk among short allele carriers in a "for better" or "for worse" pattern.

**Temporal Trends In Marijuana Attitudes, Availability and Use In Colorado Compared To Non-medical Marijuana States: 2003-11** Schuermeyer J, Salomonsen-Sautel S, Price RK, Balan S, Thurstone C, Min S-J, Sakai JT. *Drug Alcohol Depend.* 2014.

In 2009, policy changes were accompanied by a rapid increase in the number of medical marijuana cardholders in Colorado. Little published epidemiological work has tracked changes in the state around this time. Using the National Survey on Drug Use and Health, the authors tested for temporal changes in marijuana attitudes and marijuana-use-related outcomes in Colorado (2003-11) and differences within-year between Colorado and thirty-four non-medical-marijuana states (NMMS). Using regression analyses, the authors further tested whether patterns seen in Colorado prior to (2006-8) and during (2009-11) marijuana commercialization differed from patterns in NMMS while controlling for demographics. Within Colorado those reporting "great-risk" to using marijuana 1-2 times/week dropped significantly in all age groups studied between 2007-8 and 2010-11 (e.g. from 45% to 31% among those 26 years and older;  $p=0.0006$ ). By 2010-11 past-year marijuana abuse/dependence had become more prevalent in Colorado for 12-17 year olds (5% in Colorado, 3% in NMMS;  $p=0.03$ ) and 18-25 year olds (9% vs. 5%;  $p=0.02$ ). Regressions demonstrated significantly greater reductions in perceived risk (12-17 year olds,  $p=0.005$ ; those 26 years and older,  $p=0.01$ ), and trend for difference in changes in availability among those 26 years and older and marijuana abuse/dependence among 12-17 year olds in Colorado compared to NMMS in more recent years (2009-11 vs. 2006-8). These results show that commercialization of marijuana in Colorado has been associated with lower risk perception. Evidence is suggestive for marijuana abuse/dependence. Analyses including subsequent years 2012+ once available, will help determine whether such changes represent momentary vs. sustained effects.

## **BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH**

### ***DCNBR***

**Factors Predicting Development of Opioid Use Disorders among Individuals who Receive an Initial Opioid Prescription: Mathematical Modeling using a Database of Commercially-insured Individuals** Cochran BN, Flentje A, Heck NC, Van Den Bos J, Perlman D, Torres J, Valuck R, Carter J. *Drug Alcohol Depend.* 2014 May 1; 138: 202-8.

Prescription drug abuse in the United States and elsewhere in the world is increasing at an alarming rate with non-medical opioid use, in particular, increasing to epidemic proportions over the past two decades. It is imperative to identify individuals most likely to develop opioid abuse or dependence to inform large-scale, targeted prevention efforts. The present investigation utilized a large commercial insurance claims database to identify demographic, mental health, physical health, and healthcare service utilization variables that differentiate persons who receive an opioid abuse or dependence diagnosis within two years of filling an opioid prescription (OUDs) from those who do not receive such a diagnosis within the same time frame (non-OUDs). When compared to non-OUDs, OUDs were more likely to: (1) be male (59.9% vs. 44.2% for non-OUDs) and younger ( $M=37.9$  vs.  $47.7$ ); (2) have a prescription history of more opioids (1.7 vs. 1.2), and more days supply of opioids ( $M=272.5$ , vs.  $M=33.2$ ); (3) have prescriptions filled at more pharmacies ( $M=3.3$  per year vs.  $M=1.3$ ); (4) have greater rates of psychiatric disorders; (5) utilize more medical and psychiatric services; and (6) be prescribed more concomitant medications. A predictive model incorporating these findings was 79.5% concordant with actual OUDs in the data set. Understanding correlates of OUD development can help to predict risk and inform prevention efforts.

**Computerized versus In-person Brief Intervention for Drug Misuse: A Randomized Clinical Trial** Schwartz RP, Gryczynski J, Mitchell SG, Gonzales A, Moseley A, Peterson TR, Ondersma SJ, O'Grady KE. *Addiction.* 2014 Jan; 109: 1091-1098.

Several studies have found that brief interventions (BIs) for drug misuse have superior effectiveness to no-treatment controls. However, many health centers do not provide BIs for drug use consistently due to insufficient behavioral health staff capacity. Computerized BIs for drug use are a promising approach, but their effectiveness compared with in-person BIs has not been established. This study compared the effectiveness of a computerized brief intervention (CBI) to an in-person brief intervention (IBI) delivered by a behavioral health counselor. This was a two-arm randomized clinical trial, conducted in two health centers in New Mexico, United States. Participants were 360 adult primary care patients with moderate-risk drug scores on the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) who were randomly assigned on a 1: 1 basis to a computerized brief intervention (CBI) or to an in-person brief intervention (IBI) delivered by a behavioral health counselor. Assessments were conducted at baseline and 3-month follow-up, and included the ASSIST and drug testing on hair samples. The IBI and CBI conditions did not differ at 3 months on global ASSIST drug scores [ $b = -1.79$ ; 95% confidence interval (CI) =  $-4.37, 0.80$ ] or drug-positive hair tests [odds ratio (OR) = 0.97; 95% CI = 0.47, 2.02]. There was a statistically significant advantage of CBI over IBI in substance-specific ASSIST scores for marijuana ( $b = -1.73$ ; 95% CI =  $-2.91, -0.55$ ; Cohen's  $d = 0.26$ ;  $P = 0.004$ ) and cocaine ( $b = -4.48$ ; 95% CI =  $-8.26, -0.71$ ; Cohen's  $d = 0.50$ ;  $P = 0.021$ ) at 3 months. Computerized brief intervention can be an effective alternative to in-person brief intervention for addressing moderate drug use in primary care.

## **RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE**

### ***DPMCDA***

#### **Combination Treatment With Varenicline and Bupropion in an Adaptive Smoking Cessation Paradigm** Rose JE, Behm FM. Am J Psychiatry June 17 2014.

The authors assessed the efficacy and safety of combination treatment with varenicline and sustained-release bupropion for smokers who, based on an assessment of initial smoking reduction prior to the quit date, were deemed unlikely to achieve abstinence using nicotine patch treatment. In a randomized, double-blind, parallel-group adaptive treatment trial, the authors identified 222 cigarette smokers who failed to show a reduction of more than 50% in smoking after 1 week of nicotine patch treatment. Smokers were randomly assigned to receive 12 weeks of varenicline plus bupropion or varenicline plus placebo. The primary outcome measure was continuous smoking abstinence at weeks 8–11 after the target quit date. Both treatments were well tolerated. Participants who received the combination treatment had a significantly higher abstinence rate than those who received varenicline plus placebo (39.8% compared with 25.9%; odds ratio=1.89; 95% CI=1.07, 3.35). Combination treatment had a significantly greater effect on abstinence rate in male smokers (odds ratio=4.26; 95% CI=1.73, 10.49) than in female smokers (odds ratio=0.94; 95% CI=0.43, 2.05). It also had a significantly greater effect in highly nicotine-dependent smokers (odds ratio=3.51, 95% CI=1.64, 7.51) than in smokers with lower levels of dependence (odds ratio=0.71, 95% CI=0.28, 1.80). Among smokers who did not show a sufficient initial response to prequit nicotine patch treatment, combination treatment with varenicline and bupropion proved more efficacious than varenicline alone for male smokers and for smokers with a high degree of nicotine dependence.

#### **Nipping Cue Reactivity In the Bud: Baclofen Prevents Limbic Activation Elicited By Subliminal Drug Cues** Young KA, Franklin TR, Roberts DC, Jagannathan K, Suh JJ, Wetherill RR, Wang Z, Kampman KM, O'Brien CP, Childress AR. J Neurosci. 2014 Apr; 34(14): 5038-43.

Relapse is a widely recognized and difficult to treat feature of the addictions. Substantial evidence implicates cue-triggered activation of the mesolimbic dopamine system as an important contributing factor. Even drug cues presented outside of conscious awareness (i.e., subliminally) produce robust activation within this circuitry, indicating the sensitivity and vulnerability of the brain to potentially problematic reward signals. Because pharmacological agents that prevent these early cue-induced responses could play an important role in relapse prevention, the authors examined whether baclofen—a GABA<sub>B</sub> receptor agonist that reduces mesolimbic dopamine release and conditioned drug responses in laboratory animals—could inhibit mesolimbic activation elicited by subliminal cocaine cues in cocaine-dependent individuals. Twenty cocaine-dependent participants were randomized to receive baclofen (60 mg/d; 20 mg t.i.d.) or placebo. Event-related BOLD fMRI and a backward-masking paradigm were used to examine the effects of baclofen on subliminal cocaine (vs neutral) cues. Sexual and aversive cues were included to examine specificity. The authors observed that baclofen-treated participants displayed significantly less activation in response to subliminal cocaine (vs neutral) cues, but not sexual or aversive (vs neutral) cues, than placebo-treated participants in a large interconnected bilateral cluster spanning the ventral striatum, ventral pallidum, amygdala, midbrain, and orbitofrontal cortex (voxel threshold  $p < 0.005$ ; cluster corrected at  $p < 0.05$ ). These results suggest that baclofen may inhibit the earliest type of drug cue-

induced motivational processing-that which occurs outside of awareness-before it evolves into a less manageable state.

### **Vaccine For Cocaine Dependence: A Randomized Double-Blind Placebo-Controlled Efficacy**

**Trial** Kosten TR, Domingo CB, Shorter D, Orson F, Green C, Somoza E, Sekerka R, Levin FR, Mariani JJ, Stitzer M, Tompkins DA, Rotrosen J, Thakkar V, Smoak B, Kampman K. Drug Alcohol Depend. 2014 Jul; 140[Epub ahead of print] 42-7.

The authors evaluated the immunogenicity, efficacy, and safety of succinylnorcocaine conjugated to cholera toxin B protein as a vaccine for cocaine dependence. This 6-site, 24 week Phase III randomized double-blind placebo-controlled trial assessed efficacy during weeks 8 to 16. The authors measured urine cocaine metabolites thrice weekly as the main outcome. The 300 subjects (76% male, 72% African-American, mean age 46 years) had smoked cocaine on average for 13 days monthly at baseline. They hypothesized that retention might be better and positive urines lower for subjects with anti-cocaine IgG levels of  $\geq 42\mu\text{g/mL}$  (high IgG), which was attained by 67% of the 130 vaccine subjects receiving five vaccinations. Almost 3-times fewer high than low IgG subjects dropped out (7% vs 20%). Although for the full 16 weeks cocaine positive urine rates showed no significant difference between the three groups (placebo, high, low IgG), after week 8, more vaccinated than placebo subjects attained abstinence for at least two weeks of the trial (24% vs 18%), and the high IgG group had the most cocaine-free urines for the last 2 weeks of treatment (OR=3.02), but neither were significant. Injection site reactions of induration and tenderness differed between placebo and active vaccine, and the 29 serious adverse events did not lead to treatment related withdrawals, or deaths. The vaccine was safe, but it only partially replicated the efficacy found in the previous study based on retention and attaining abstinence.

### **Physiologic and Metabolic Safety Of Butyrylcholinesterase Gene Therapy In Mice**

Murthy V, Gao Y, Geng L, LeBrasseur NK, White TA, Parks RJ, Brimijoin S. Vaccine. 2014 Jul; 32(33): 4155-62.

In continuing efforts to develop gene transfer of human butyrylcholinesterase (BChE) as therapy for cocaine addiction, the authors conducted wide-ranging studies of physiological and metabolic safety. For that purpose, mice were given injections of adeno-associated virus (AAV) vector or helper-dependent adenoviral (hdAD) vector encoding human or mouse BChE mutated for optimal cocaine hydrolysis. Age-matched controls received saline or AAV-luciferase control vector. At times when transduced BChE was abundant, physiologic and metabolic parameters in conscious animals were evaluated by non-invasive Echo-MRI and an automated "Comprehensive Laboratory Animal Monitoring System" (CLAMS). Despite high vector doses (up to  $10^{13}$  particles per mouse) and high levels of transgene protein in the plasma (~1500-fold above baseline), the CLAMS apparatus revealed no adverse physiologic or metabolic effects. Likewise, body composition determined by Echo-MRI, and glucose tolerance remained normal. A CLAMS study of vector-treated mice given 40mg/kg cocaine showed none of the physiologic and metabolic fluctuations exhibited in controls. The authors conclude that neither the tested vectors nor great excesses of circulating BChE affect general physiology directly, while they protect mice from disturbance by cocaine. Hence, viral gene transfer of BChE appears benign and worth exploring as a therapy for cocaine abuse and possibly other disorders as well.

### **Kinetic Characterization Of Human Butyrylcholinesterase Mutants For the Hydrolysis Of Cocaethylene**

Hou S, Zhan M, Zheng X, Zhan CG, Zheng F. *Biochem J.* 2014 Jun; 460(3): 447-57. It is known that the majority of cocaine users also consume alcohol. Alcohol can react with cocaine to produce a significantly more cytotoxic compound, cocaethylene. Hence a truly valuable cocaine-metabolizing enzyme as treatment for cocaine abuse/overdose should be efficient for not only cocaine itself, but also cocaethylene. The catalytic parameters ( $k_{cat}$  and  $K_M$ ) of human BChE (butyrylcholinesterase) and two mutants (known as cocaine hydrolases E14-3 and E12-7) for cocaethylene are characterized in the present study, for the first time, in comparison with those for cocaine. On the basis of the obtained kinetic data, wild-type human BChE has a lower catalytic activity for cocaethylene ( $k_{cat}=3.3 \text{ min}^{-1}$ ,  $K_M=7.5 \mu\text{M}$  and  $k_{cat}/K_M=4.40 \times 10^5 \text{ M}^{-1}\cdot\text{min}^{-1}$ ) compared with its catalytic activity for (-)-cocaine. E14-3 and E12-7 have a considerably improved catalytic activity against cocaethylene compared with the wild-type BChE. E12-7 is identified as the most efficient enzyme for hydrolysing cocaethylene in addition to its high activity for (-)-cocaine. E12-7 has an 861-fold improved catalytic efficiency for cocaethylene ( $k_{cat}=3600 \text{ min}^{-1}$ ,  $K_M=9.5 \mu\text{M}$  and  $k_{cat}/K_M=3.79 \times 10^8 \text{ M}^{-1}\cdot\text{min}^{-1}$ ). It has been demonstrated that E12-7 as an exogenous enzyme can indeed rapidly metabolize cocaethylene in rats. Further kinetic modelling has suggested that E12-7 with an identical concentration as that of the endogenous BChE in human plasma can effectively eliminate (-)-cocaine, cocaethylene and norcocaine in simplified kinetic models of cocaine abuse and overdose associated with the concurrent use of cocaine and alcohol.

### **Hypocretin (Orexin) Facilitates Reward By Attenuating the Antireward Effects Of Its Cotransmitter Dynorphin In Ventral Tegmental Area**

Muschamp JW, Hollander JA, Thompson JL, Voren G, Hassinger LC, Onvani S, Kamenecka TM, Borgland SL, Kenny PJ, Carlezon WA. *Proc Natl Acad Sci U S A.* 2014 Apr; 111(16): E1648-55.

Hypocretin (orexin) and dynorphin are neuropeptides with opposing actions on motivated behavior. Orexin is implicated in states of arousal and reward, whereas dynorphin is implicated in depressive-like states. The authors show that, despite their opposing actions, these peptides are packaged in the same synaptic vesicles within the hypothalamus. Disruption of orexin function blunts the rewarding effects of lateral hypothalamic (LH) stimulation, eliminates cocaine-induced impulsivity, and reduces cocaine self-administration. Concomitant disruption of dynorphin function reverses these behavioral changes. The authors also show that orexin and dynorphin have opposing actions on excitability of ventral tegmental area (VTA) dopamine neurons, a prominent target of orexin-containing neurons, and that intra-VTA orexin antagonism causes decreases in cocaine self-administration and LH self-stimulation that are reversed by dynorphin antagonism. These findings identify a unique cellular process by which orexin can occlude the reward threshold-elevating effects of coreleased dynorphin and thereby act in a permissive fashion to facilitate reward.

### **Effects Of An Oxycodone Conjugate Vaccine On Oxycodone Self-Administration And Oxycodone-Induced Brain Gene Expression In Rats**

Pravetoni M, Pentel PR, Potter DN, Chartoff EH, Tally L, LeSage MG. *PLoS One.* 2014 ; 9(7): e101807.

Prescription opioid abuse is an increasing public health concern in the USA. A vaccine comprising a hapten (OXY) conjugated to the carrier protein keyhole limpet hemocyanin (OXY-KLH) has been shown to attenuate the antinociceptive effects of oxycodone. Here, the vaccine's ability to prevent acquisition of intravenous (i.v) oxycodone self-administration was studied in rats. Effects of vaccination on oxycodone-induced changes in the expression of several genes within the

mesolimbic system, which are regulated by chronic opiate use, were also examined. Vaccination with OXY-KLH reduced the proportion of rats acquiring i. v. self-administration of oxycodone under a fixed ratio (FR) 3 schedule of reinforcement compared to control rats immunized with the unconjugated KLH carrier protein. Vaccination significantly reduced the mean number of infusions at FR3, total number of infusions, and total oxycodone intake during the entire protocol. Compared to oxycodone self-administering control rats immunized with the carrier alone, rats vaccinated with the OXY-KLH immunogen showed increased levels of adenylate cyclase 5 (Adcy5) and decreased levels of early growth response protein 2 (Egr2) and the early immediate gene c-Fos in the striatum. These data suggest that vaccination with OXY-KLH can attenuate the reinforcing effects of oxycodone at a clinically-relevant exposure level. Analysis of mRNA expression identified some addiction-relevant markers that may be of interest in understanding oxycodone effects or the protection provided by vaccination.

### **Treatment With A Monoclonal Antibody Against Methamphetamine and Amphetamine Reduces Maternal And Fetal Rat Brain Concentrations In Late Pregnancy**

White SJ, Hendrickson HP, Atchley WT, Laurenzana EM, Gentry WB, Williams DK, Owens SM. Drug Metab Dispos. 2014 Aug; 42(8): 1285-91.

The authors hypothesized that treatment of pregnant rat dams with a dual reactive monoclonal antibody (mAb4G9) against (+)-methamphetamine [METH; equilibrium dissociation rate constant (KD) = 16 nM] and (+)-amphetamine (AMP; KD = 102 nM) could confer maternal and fetal protection from brain accumulation of both drugs of abuse. To test this hypothesis, pregnant Sprague-Dawley rats (on gestational day 21) received a 1 mg/kg i. v. METH dose, followed 30 minutes later by vehicle or mAb4G9 treatment. The mAb4G9 dose was 0.56 mole-equivalent in binding sites to the METH body burden. Pharmacokinetic analysis showed baseline METH and AMP elimination half-lives were congruent in dams and fetuses, but the METH volume of distribution in dams was nearly double the fetal values. The METH and AMP area under the serum concentration-versus-time curves from 40 minutes to 5 hours after mAb4G9 treatment increased >7000% and 2000%, respectively, in dams. Fetal METH serum did not change, but AMP decreased 23%. The increased METH and AMP concentrations in maternal serum resulted from significant increases in mAb4G9 binding. Protein binding changed from ~15% to > 90% for METH and AMP. Fetal serum protein binding appeared to gradually increase, but the absolute fraction bound was trivial compared with the dams. mAb4G9 treatment significantly reduced METH and AMP brain values by 66% and 45% in dams and 44% and 46% in fetuses ( $P < 0.05$ ), respectively. These results show anti-METH/AMP mAb4G9 therapy in dams can offer maternal and fetal brain protection from the potentially harmful effects of METH and AMP.

## **RESEARCH ON THE MEDICAL CONSEQUENCES OF DRUG ABUSE AND CO-OCCURRING INFECTIONS**

### **HIV and Drug Abuse**

#### ***ARP***

**Changes in HIV Incidence among People Who Inject Drugs in Taiwan following Introduction of a Harm Reduction Program: A Study of Two Cohorts** Huang YF, Yang J-Y, Nelson KE, Kuo H-S, Lew-Ting C-Y, Yang C-H, Chen C-H, Chang F-Y, Liu H-R. PLoS Med 11(4): e1001625. doi:10.1371/journal.pmed.1001625.

Harm reduction strategies for combating HIV epidemics among people who inject drugs (PWID) have been implemented in several countries. However, large-scale studies using sensitive measurements of HIV incidence and intervention exposures in defined cohorts are rare. The aim of this study was to determine the association between harm reduction programs and HIV incidence among PWID. The study included two populations. For 3,851 PWID who entered prison between 2004 and 2010 and tested HIV positive upon incarceration, the authors tested their sera using a BED HIV-1 capture enzyme immunoassay to estimate HIV incidence. Also, they enrolled in a prospective study a cohort of 4,357 individuals who were released from prison via an amnesty on July 16, 2007. The authors followed them with interviews at intervals of 6–12 months and by linking several databases. A total of 2,473 participants who were HIV negative in January 2006 had interviews between then and 2010 to evaluate the association between use of harm reduction programs and HIV incidence. The authors used survival methods with attendance at methadone clinics as a time-varying covariate to measure the association with HIV incidence. They used a Poisson regression model and calculated the HIV incidence rate to evaluate the association between needle/syringe program use and HIV incidence. Among the population of PWID who were imprisoned, the implementation of comprehensive harm reduction programs and a lower mean community HIV viral load were associated with a reduced HIV incidence among PWID. The HIV incidence in this population of PWID decreased from 18.2% in 2005 to 0.3% in 2010. In an individual-level analysis of the amnesty cohort, attendance at methadone clinics was associated with a significantly lower HIV incidence (adjusted hazard ratio: 0.20, 95% CI: 0.06–0.67), and frequent users of needle/syringe program services had lower HIV incidence (0% in high NSP users, 0.5% in non NSP users). In addition, no HIV seroconversions were detected among prison inmates. Although these data are affected by participation bias, they strongly suggest that comprehensive harm reduction services and free treatment were associated with reversal of a rapidly emerging epidemic of HIV among PWID.

**Expansion of HAART Coverage Is Associated with Sustained Decreases in HIV/AIDS Morbidity, Mortality and HIV Transmission: The “HIV Treatment as Prevention”**

**Experience in a Canadian Setting** Montaner JSG, Lima VD, Harrigan PR, Lourenço L, Yip B, Nosyk B, Wood E, Kerr T, Shannon K, Moore D, Hogg RS, Barrios R, Gilbert M, Krajden M, Gustafson R, Daly P, Kendall P. PLoS ONE 9(2): e87872. doi:10.1371/journal.pone.0087872 PLoS ONE 9(2): e87872. doi:10.1371/journal.pone.0087872.

There has been renewed call for the global expansion of highly active antiretroviral therapy (HAART) under the framework of HIV treatment as prevention (TasP). However, population-level sustainability of this strategy has not been characterized. The authors used population-level

longitudinal data from province-wide registries including plasma viral load, CD4 count, drug resistance, HAART use, HIV diagnoses, AIDS incidence, and HIV-related mortality. They fitted two Poisson regression models over the study period, to relate estimated HIV incidence and the number of individuals on HAART and the percentage of virologically suppressed individuals. HAART coverage, median pre-HAART CD4 count, and HAART adherence increased over time and were associated with increasing virological suppression and decreasing drug resistance. AIDS incidence decreased from 6.9 to 1.4 per 100,000 population (80% decrease,  $p = 0.0330$ ) and HIV-related mortality decreased from 6.5 to 1.3 per 100,000 population (80% decrease,  $p = 0.0115$ ). New HIV diagnoses declined from 702 to 238 cases (66% decrease;  $p = 0.0004$ ) with a consequent estimated decline in HIV incident cases from 632 to 368 cases per year (42% decrease;  $p = 0.0003$ ). Finally, the authors' models suggested that for each increase of 100 individuals on HAART, the estimated HIV incidence decreased 1.2% and for every 1% increase in the number of individuals suppressed on HAART, the estimated HIV incidence also decreased by 1%. These results show that HAART expansion between 1996 and 2012 in BC was associated with a sustained and profound population-level decrease in morbidity, mortality and HIV transmission. These findings support the long-term effectiveness and sustainability of HIV treatment as prevention within an adequately resourced environment with no financial barriers to diagnosis, medical care or antiretroviral drugs. The 2013 Consolidated World Health Organization Antiretroviral Therapy Guidelines offer a unique opportunity to further evaluate TasP in other settings, particularly within generalized epidemics, and resource-limited setting, as advocated by UNAIDS.

**[Effects Of Early Versus Delayed Initiation Of Antiretroviral Treatment On Clinical Outcomes Of HIV-1 Infection: Results From the Phase 3 HPTN 052 Randomised Controlled Trial](#)** Grinsztejn B, Hosseinipour MC, Ribaldo HJ, Swindells S, et al. the HPTN 052-ACTG Study Team; *The Lancet Infectious Diseases* - 1 April 2014; 14(4): 281-290. DOI: 10.1016/S1473-3099(13)70692-3.

Use of antiretroviral treatment for HIV-1 infection has decreased AIDS-related morbidity and mortality and prevents sexual transmission of HIV-1. However, the best time to initiate antiretroviral treatment to reduce progression of HIV-1 infection or non-AIDS clinical events is unknown. The authors reported previously that early antiretroviral treatment reduced HIV-1 transmission by 96%. They aimed to compare the effects of early and delayed initiation of antiretroviral treatment on clinical outcomes. The HPTN 052 trial is a randomised controlled trial done at 13 sites in nine countries. They enrolled HIV-1-serodiscordant couples to the study and randomly allocated them to either early or delayed antiretroviral treatment by use of permuted block randomisation, stratified by site. Random assignment was unblinded. The HIV-1-infected member of every couple initiated antiretroviral treatment either on entry into the study (early treatment group) or after a decline in CD4 count or with onset of an AIDS-related illness (delayed treatment group). Primary events were AIDS clinical events (WHO stage 4 HIV-1 disease, tuberculosis, and severe bacterial infections) and the following serious medical conditions unrelated to AIDS: serious cardiovascular or vascular disease, serious liver disease, end-stage renal disease, new-onset diabetes mellitus, and non-AIDS malignant disease. Analysis was by intention-to-treat. This trial is registered with [ClinicalTrials.gov](http://ClinicalTrials.gov), number [NCT00074581](https://clinicaltrials.gov/ct2/show/study/NCT00074581). 1763 people with HIV-1 infection and a serodiscordant partner were enrolled in the study; 886 were assigned early antiretroviral treatment and 877 to the delayed treatment group (two individuals were excluded from this group after randomisation). Median CD4 counts at randomisation were 442 (IQR 373—522) cells per  $\mu\text{L}$  in patients assigned to the early treatment group and 428 (357—522) cells per  $\mu\text{L}$  in those allocated

delayed antiretroviral treatment. In the delayed group, antiretroviral treatment was initiated at a median CD4 count of 230 (IQR 197—249) cells per  $\mu\text{L}$ . Primary clinical events were reported in 57 individuals assigned to early treatment initiation versus 77 people allocated to delayed antiretroviral treatment (hazard ratio 0.73, 95% CI 0.52—1.03;  $p=0.074$ ). New-onset AIDS events were recorded in 40 participants assigned to early antiretroviral treatment versus 61 allocated delayed initiation (0.64, 0.43—0.96;  $p=0.031$ ), tuberculosis developed in 17 versus 34 patients, respectively (0.49, 0.28—0.89,  $p=0.018$ ), and primary non-AIDS events were rare (12 in the early group vs nine with delayed treatment). In total, 498 primary and secondary outcomes occurred in the early treatment group (incidence 24. per 100 person-years, 95% CI 22.5—27.5) versus 585 in the delayed treatment group (29.2 per 100 person-years, 26.5—32.1;  $p=0.025$ ). 26 people died, 11 who were allocated to early antiretroviral treatment and 15 who were assigned to the delayed treatment group. Early initiation of antiretroviral treatment delayed the time to AIDS events and decreased the incidence of primary and secondary outcomes. The clinical benefits recorded, combined with the striking reduction in HIV-1 transmission risk previously reported, provides strong support for earlier initiation of antiretroviral treatment. Funding US National Institute of Allergy and Infectious Diseases.

## **SERVICES RESEARCH**

### ***DESPR***

**[Optimization of Human Immunodeficiency Virus Treatment During Incarceration: Viral Suppression at The Prison Gate](#)** Meyer JP, Cepeda J, Wu J, Trestman RL, Altice FL, Springer S. *JAMA Intern Med.* 2014; 174 (5): 721-9.

Human immunodeficiency virus (HIV) management in correctional settings is logistically feasible, but HIV-related outcomes before release have not been recently systematically examined. The objective of this study was to evaluate HIV treatment outcomes throughout incarceration, including jail and prison. This was a retrospective cohort study of longitudinally linked demographic, pharmacy, and laboratory data on 882 prisoners within the Connecticut Department of Correction (2005-2012) with confirmed HIV infection, who were continually incarcerated 90 days or more, had at least 2 HIV-1 RNA and CD4 lymphocyte measurements, and were prescribed antiretroviral therapy. Three electronic databases (correctional, laboratory, and pharmacy) were integrated to assess HIV viral suppression (HIV-1 RNA levels, 400 copies/mL) on intake and release. Secondary outcomes were mean change in log-transformed HIV-1 RNA levels and mean change in CD4 lymphocyte count during incarceration. Demographic characteristics, prescribed pharmacotherapies, receipt of directly observed therapy, and duration of incarceration were analyzed as possible explanatory variables for HIV viral suppression in logistic regression models. Among 882 HIV-infected prisoners with 1185 incarceration periods, mean HIV-1 RNA level decreased by 1.1  $\log_{10}$  and CD4 lymphocyte count increased by 98 cells/L over time, with a higher proportion achieving viral suppression by release compared with entry (70.0% vs 29.8%;  $P=.001$ ); 36.9% of antiretroviral therapy (ART) regimens were changed during incarceration. After adjusting for baseline HIV-1 RNA level, prerelease viral suppression correlated with female sex (adjusted odds ratio, 1.81; 95% CI, 1.26-2.59) and psychiatric disorder severity below the sample median (adjusted odds ratio, 1.50; 95% CI, 1.12-1.99), but not race/ethnicity, incarceration duration, ART regimen or dosing strategy, or directly observed therapy. Though just one-third of HIV-infected prisoners receiving ART

entered correctional facilities with viral suppression, HIV treatment was optimized during incarceration, resulting in the majority achieving viral suppression by release. Treatment for HIV within prison is facilitated by a highly structured environment and, when combined with simple well-tolerated ART regimens, can result in viral suppression during incarceration. In the absence of important and effective community-based resources, incarceration can be an opportunity of last resort to initiate continuous ART for individual health and, following the "treatment as prevention" paradigm, potentially reduce the likelihood of HIV transmission to others after release if continuity of HIV care is sustained.

### **[Association between Cannabis Use, Psychosis, and Schizotypal Personality Disorder: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions](#)**

Davis GP, Compton MT, Wang S, Levin FR, Blanco C. *Schizophr Res.* 2013; 151 (1-3): 197-202. Studies to date showing an association between cannabis use and schizophrenia-spectrum disorders are of relatively small sample sizes with limitations in generalizability. The present study addresses this gap by examining the relationship between cannabis use and psychotic-like symptoms in a large representative community sample. Data were derived from the 2004-2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, Wave 2), a large, nationally representative sample of 34,653 adults from the United States population. The authors evaluated the association between lifetime cannabis use, psychosis, and schizotypal personality features. The prevalence of psychosis and schizotypal personality disorder increased significantly with greater cannabis use in a dose-dependent manner. The associations between cannabis use and psychosis were 1.27 (95% CI 1.03-1.57) for lifetime cannabis use, 1.79 (95% CI 1.35-2.38) for lifetime cannabis abuse, and 3.69 (95% CI 2.49-5.47) for lifetime cannabis dependence. There was a similar dose-response relationship between the extent of cannabis use and schizotypal personality disorder (OR=2.02 for lifetime cannabis use, 95% CI 1.69-2.42; OR=2.83 for lifetime cannabis abuse, 95% CI 2.33-2.43; OR=7.32 for lifetime cannabis dependence, 95% CI 5.51-9.72). Likelihood of individual schizotypal features increased significantly with increased extent of cannabis use in a dose-dependent manner. This is the first population-based study to examine the association between lifetime cannabis use, psychosis, and schizotypal personality traits. These results add to evidence that cannabis use may be a risk factor for psychosis liability.

## **CLINICAL TRIALS NETWORK-RELATED RESEARCH**

### **[Identifying Patients With Problematic Drug Use In The Emergency Department: Results Of A Multisite Study](#)**

Macias Konstantopoulos WL, Dreifuss JA, McDermott KA, Parry BA, Howell ML, Mandler RN, Fitzmaurice GM, Bogenschutz MP, Weiss RD. *Ann Emerg Med.* 2014 Jul 3. [Epub ahead of print].

Drug-related emergency department (ED) visits have steadily increased, with substance users relying heavily on the ED for medical care. The present study aims to identify clinical correlates of problematic drug use that would facilitate identification of ED patients in need of substance use treatment. Using previously validated tests, 15,224 adult ED patients across 6 academic institutions were prescreened for drug use as part of a large randomized prospective trial. Data for 3,240 participants who reported drug use in the past 30 days were included. Self-reported variables related to demographics, substance use, and ED visit were examined to determine their correlative value for problematic drug use. Of the 3,240 patients, 2,084 (64.3%) met criteria for problematic drug use (Drug Abuse Screening Test score  $\geq 3$ ). Age greater than or equal to 30 years, tobacco smoking,

daily or binge alcohol drinking, daily drug use, primary noncannabis drug use, resource-intense ED triage level, and perceived drug-relatedness of ED visit were highly correlated with problematic drug use. Among primary cannabis users, correlates of problematic drug use were age younger than 30 years, tobacco smoking, binge drinking, daily drug use, and perceived relatedness of the ED visit to drug use. Clinical correlates of drug use problems may assist the identification of ED patients who would benefit from comprehensive screening, intervention, and referral to treatment. A clinical decision rule is proposed. The correlation between problematic drug use and resource-intense ED triage levels suggests that ED-based efforts to reduce the unmet need for substance use treatment may help decrease overall health care costs.

### **Reasons For Opioid Use Among Patients With Dependence On Prescription Opioids: The Role Of Chronic Pain**

Weiss RD, Potter JS, Griffin ML, McHugh RK, Haller D, Jacobs P, Gardin J 2nd, Fischer D, Rosen KD. *J Subst Abuse Treat.* 2014 Aug;47(2): 140-5. Epub 2014 Apr 4.

The number of individuals seeking treatment for prescription opioid dependence has increased dramatically, fostering a need for research on this population. The aim of this study was to examine reasons for prescription opioid use among 653 participants with and without chronic pain, enrolled in the Prescription Opioid Addiction Treatment Study, a randomized controlled trial of treatment for prescription opioid dependence. Participants identified initial and current reasons for opioid use. Participants with chronic pain were more likely to report pain as their primary initial reason for use; avoiding withdrawal was rated as the most important reason for current use in both groups. Participants with chronic pain rated using opioids to cope with physical pain as more important, and using opioids in response to social interactions and craving as less important, than those without chronic pain. Results highlight the importance of physical pain as a reason for opioid use among patients with chronic pain.

### **Multisite, Randomized, Double-Blind, Placebo-Controlled Pilot Clinical Trial To Evaluate the Efficacy Of Buspirone As A Relapse-Prevention Treatment For Cocaine Dependence**

Winhusen TM, Kropp F, Lindblad R, Douaihy A, Haynes L, Hodgkins C, Chartier K, Kampman KM, Sharma G, Lewis DF, VanVeldhuisen P, Theobald J, May J, Brigham GS. *J Clin Psychiatry.* 2014 May 27. [Epub ahead of print].

The objective of this study was to evaluate the potential efficacy of buspirone as a relapse-prevention treatment for cocaine dependence. A randomized, double-blind, placebo-controlled, 16-week pilot trial was conducted at 6 clinical sites between August 2012 and June 2013. Adult crack cocaine users meeting DSM-IV-TR criteria for current cocaine dependence who were scheduled to be in inpatient/residential substance use disorder (SUD) treatment for 12-19 days when randomized and planning to enroll in local outpatient treatment through the end of the active treatment phase were randomized to buspirone titrated to 60 mg/d (n=35) or placebo (n=27). All participants received psychosocial treatment as usually provided by the SUD treatment programs in which they were enrolled. Outcome measures included maximum days of continuous cocaine abstinence (primary), proportion of cocaine use days, and days to first cocaine use during the outpatient treatment phase (study weeks 4-15) as assessed by self-report and urine drug screens. There were no significant treatment effects on maximum continuous days of cocaine abstinence or days to first cocaine use. In the female participants (n=23), there was a significant treatment-by-time interaction effect ( $\chi^2_1=15.26$ ,  $P<.0001$ ), reflecting an increase in cocaine use by those receiving buspirone, relative to placebo, early in the outpatient treatment phase. A similar effect was not detected in the male participants (n=39;  $\chi^2_1=0.14$ ,  $P=.70$ ). The results suggest that buspirone is unlikely to have a

beneficial effect on preventing relapse to cocaine use and that bupirone for cocaine-dependent women may worsen their cocaine use outcomes. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT01641159.

**HIV Risk Reduction With Buprenorphine-Naloxone Or Methadone: Findings From A Randomized Trial**

Woody G, Bruce D, Korthuis PT, Chhatre S, Hillhouse M, Jacobs P, Sorensen J, Saxon AJ, Metzger D, Ling W. J Acquir Immune Defic Syndr. 2014 Apr 18. [Epub ahead of print].

The objective of this study was to compare HIV injecting and sex risk in patients being treated with methadone (MET) or buprenorphine-naloxone (BUP). This was a secondary analysis from a study of liver enzyme changes in patients randomized to MET or BUP who completed 24-weeks of treatment and had 4 or more blood draws. The initial 1:1 randomization was changed to 2:1 (BUP: MET) after 18 months due to higher dropout in BUP. The Risk Behavior Survey (RBS) measured past 30-day HIV risk at baseline and weeks 12 and 24. Among 529 patients randomized to MET, 391 (74%) were completers; among 740 randomized to BUP, 340 (46%) were completers; 700 completed the RBS. There were significant reductions in injecting risk ( $p < 0.0008$ ) with no differences between groups in mean number of times reported injecting heroin, speedball, other opiates, and number of injections; or percent who shared needles, did not clean shared needles with bleach, shared cookers, or engaged in front/back loading of syringes. The percent having multiple sex partners decreased equally in both groups ( $p < 0.03$ ). For males on BUP the sex risk composite increased; for males on MET, the sex risk decreased resulting in significant group differences over time ( $p < 0.03$ ). For females, there was a significant reduction in sex risk ( $p < 0.02$ ) with no group differences. Among MET and BUP patients that remained in treatment, HIV injecting risk was equally and markedly reduced, however MET retained more patients. Sex risk was equally and significantly reduced among females in both treatment conditions, but increased for males on BUP, and decreased for males on MET.

**Validity of Brief Screening Instrument For Adolescent Tobacco, Alcohol, and Drug Use**

Kelly SM, Gryczynski J, Mitchell SG, Kirk A, O'Grady KE, Schwartz RP. Pediatrics. 2014 Apr 21. [Epub ahead of print].

The National Institute on Alcohol Abuse and Alcoholism developed an alcohol screening instrument for youth based on epidemiologic data. This study examines the concurrent validity of this instrument, expanded to include tobacco and drugs, among pediatric patients, as well as the acceptability of its self-administration on an iPad. Five hundred and twenty-five patients (54.5% female; 92.8% African American) aged 12 to 17 completed the Brief Screener for Tobacco, Alcohol, and other Drugs (BSTAD) via interviewer-administration or self-administration using an iPad. Diagnostic and Statistical Manual, Fifth Edition substance use disorders (SUDs) were identified using a modified Composite International Diagnostic Interview-2 Substance Abuse Module. Receiver operating characteristic curves, sensitivities, and specificities were obtained to determine optimal cut points on the BSTAD in relation to SUDs. One hundred fifty-nine (30.3%) adolescents reported past-year use of  $\geq 1$  substances on the BSTAD: 113 (21.5%) used alcohol, 84 (16.0%) used marijuana, and 50 (9.5%) used tobacco. Optimal cut points for past-year frequency of use items on the BSTAD to identify SUDs were  $\geq 6$  days of tobacco use (sensitivity=0.95; specificity=0.97);  $\geq 2$  days of alcohol use (sensitivity=0.96; specificity=0.85); and  $\geq 2$  days of marijuana use (sensitivity=0.80; specificity=0.93). iPad self-administration was preferred over interviewer administration ( $z=5.8$ ;  $P < .001$ ). The BSTAD is a promising screening tool for

identifying problematic tobacco, alcohol, and marijuana use in pediatric settings. Even low frequency of substance use among adolescents may indicate need for intervention.

## **INTRAMURAL RESEARCH**

**2-isoxazol-3-phenyltropane derivatives of cocaine: Molecular and Atypical System Effects at the Dopamine Transporter** Hiranita T, Wilkinson DS, Hong WC, Zou M-F, Kopajtic TA, Soto PL, Lupica CR, Newman AH, Katz JL. *Journal of Pharmacology and Experimental Therapeutics*, 2014; 349: 297-309.

The present study examined RTI-371 (3 $\beta$ -(4-methylphenyl)-2 $\beta$ -[3-(4-chlorophenyl)-isoxazol-5-yl]tropane), a phenyltropane cocaine analog with effects distinct from cocaine, and assessed potential mechanisms for those effects by comparison with its constitutional isomer, RTI-336 (3 $\beta$ -(4-chlorophenyl)-2 $\beta$ -[3-(4-methylphenyl)-isoxazol-5-yl]tropane). In mice RTI-371 was less effective than cocaine and RTI-336 in stimulating locomotion, and incompletely substituted (~60% maximum at 5-min or 1-hr post-injection) in a cocaine (10 mg/kg, i.p.)/saline discrimination procedure; RTI-336 completely substituted. In contrast to RTI-336, RTI-371 was not self-administered, and its pretreatment (1.0-10 mg/kg, i.p.) dose-dependently decreased maximal cocaine self-administration more potently than food-maintained responding. RTI-336 pretreatment dose-dependently left-shifted the cocaine self-administration dose-effect curve. Both RTI-336 and RTI-371 displaced [3H]WIN35,428 binding to striatal dopamine transporters (DATs) with  $K_i$  values of 10.8 and 7.81 nM, respectively, and had lower affinities at serotonin or norepinephrine transporters, or muscarinic and sigma receptors. The relative low affinity at these sites suggests the DAT as the primary target of RTI-371 with minimal contributions from these other targets. In biochemical assays probing the outward-facing DAT conformation, both RTI-371 and RTI-336 had effects similar to cocaine, suggesting little contribution of DAT conformation to the unique pharmacology of RTI-371. The locomotor-stimulant effects of RTI-371 (3.0-30 mg/kg, i.p.) were comparable in CB1R WT and KO mice, indicating that previously reported CB1 allosteric effects do not decrease cocaine-like effects of RTI-371. DAT occupancy in vivo was most rapid with cocaine and least with RTI-371. The slow apparent association rate may allow compensatory actions that in turn dampen cocaine-like stimulation, and give RTI-371 its unique pharmacological profile.

**Critical Role Of Peripheral Vasoconstriction In Fatal Brain Hyperthermia Induced By MDMA (Ecstasy) Under Conditions That Mimic Human Drug Use** Kiyatkin EA, Kim A,

Wakabayashi KT, Baumann MH, Shaham Y *The Journal of Neuroscience* 2014; 34:7754 –7762.

MDMA (Ecstasy) is an illicit drug used by young adults at hot, crowded “rave” parties, yet the data on potential health hazards of its abuse remain controversial. Here, the authors examined the effect of MDMA on temperature homeostasis in male rats under standard laboratory conditions and under conditions that simulate drug use in humans. They chronically implanted thermocouple microsensors in the nucleus accumbens (a brain reward area), temporal muscle, and facial skin to measure temperature continuously from freely moving rats. While focusing on brain hyperthermia, temperature monitoring from the two peripheral locations allowed the authors to evaluate the physiological mechanisms (i.e., intra-cerebral heat production and heat loss via skin surfaces) that underlie MDMA-induced brain temperature responses. Their data confirm previous reports on high individual variability and relatively weak brain hyperthermic effects of MDMA under standard control conditions (quiet rest, 22-23°C), but demonstrate dramatic enhancements of drug-induced

brain hyperthermia during social interaction (exposure to male conspecific) and in warm environments (29°C). Importantly, the authors identified peripheral vasoconstriction as a critical mechanism underlying the activity- and state-dependent potentiation of MDMA-induced brain hyperthermia. Through this mechanism, which prevents proper heat dissipation to the external environment, MDMA at a moderate non-toxic dose (9 mg/kg or ~1/5 of LD50 in rats) can cause fatal hyperthermia under environmental conditions commonly encountered by humans. These results demonstrate that doses of MDMA that are non-toxic under cool, quiet conditions can become highly dangerous under conditions that mimic recreational use of MDMA at rave parties or other hot, crowded venues.

### **Differential Effects Of Presynaptic Versus Postsynaptic Adenosine A2A Receptor Blockade On Δ9-Tetrahydrocannabinol (THC) Self-Administration In Squirrel Monkeys**

Justinová Z, Redhi GH, Goldberg SR, Ferré S. *Journal of Neuroscience*,. 2014, 34(19): 6480-4.

Different doses of an adenosine A2A receptor antagonist MSX-3 [3,7-dihydro-8-[(1E)-2-(3-ethoxyphenyl)ethenyl]-7-methyl-3-[3-(phosphoxy)propyl-1-(2-propynyl)-1H-purine-2,6-dione] were found previously to either decrease or increase self-administration of cannabinoids delta-9-tetrahydrocannabinol (THC) or anandamide in squirrel monkeys. It was hypothesized that the decrease observed with a relatively low dose of MSX-3 was related to blockade of striatal presynaptic A2A receptors that modulate glutamatergic neurotransmission, whereas the increase observed with a higher dose was related to blockade of postsynaptic A2A receptors localized in striatopallidal neurons. This hypothesis was confirmed in the present study by testing the effects of the preferential presynaptic and postsynaptic A2A receptor antagonists SCH-442416 [2-(2-furanyl)-7-[3-(4-methoxyphenyl)propyl]-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine] and KW-6002 [(E)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1H-purine-2,6-dione], respectively, in squirrel monkeys trained to intravenously self-administer THC. SCH-442416 produced a significant shift to the right of the THC self-administration dose-response curves, consistent with antagonism of the reinforcing effects of THC. Conversely, KW-6002 produced a significant shift to the left, consistent with potentiation of the reinforcing effects of THC. These results show that selectively blocking presynaptic A2A receptors could provide a new pharmacological approach to the treatment of marijuana dependence and underscore corticostriatal glutamatergic neurotransmission as a possible main mechanism involved in the rewarding effects of THC.

**Orbitofrontal Neurons Infer the Value and Identity Of Predicted Outcomes** Stalnaker, TA, Cooch, NK, McDannald, MA, Liu, TL, Wied, H, and Schoenbaum, G. *Nature Communications*. 2014, 5: 3926. doi: 10.1038/ncomms4926.

The best way to respond flexibly to changes in the environment is to anticipate them. Such anticipation often benefits us if we can infer that a change has occurred, before we have actually experienced the effects of that change. Here the authors test for neural correlates of this process by recording single-unit activity in the orbitofrontal cortex in rats performing a choice task in which the available rewards changed across blocks of trials. Consistent with the proposal that orbitofrontal cortex signals inferred information, firing changes at the start of each new block as if predicting the not-yet-experienced reward. This change occurs whether the new reward is different in number of drops, requiring signalling of a new value, or in flavour, requiring signalling of a new sensory feature. These results show that orbitofrontal neurons provide a behaviourally relevant signal that

reflects inferences about both value-relevant and value-neutral information about impending outcomes.

**Intravenous Ghrelin Administration Increases Alcohol Craving In Alcohol-Dependent Heavy Drinkers: A Preliminary Investigation**

Leggio L, Zywiak WH, Fricchione SR, Edwards SM, de la Monte SM, Swift RM, Kenna GA. Biological Psychiatry 2014. Available Online March 25, 2014.

In this proof-of-concept human laboratory study, it was shown that intravenous (IV) administration of exogenous ghrelin increased alcohol craving in alcohol-dependent heavy-drinking individuals.

This represents the first study testing the effects of IV ghrelin administration to an addictive population. These findings are consistent with previous preclinical work and provide preliminary human evidence that ghrelin may play a role in the neurobiology of alcohol craving, thus demonstrating a novel pharmacologic target for treatment.

## NIH/HHS POLICY UPDATES

For a complete list see <http://grants.nih.gov/grants/policy/policy.htm>

### 2014

- August 4 [Revised Policy: Descriptions on the Use of Individual Development Plans \(IDPs\) for Graduate Students and Postdoctoral Researchers Required in Annual Progress Reports beginning October 1, 2014](#)
- July 30 [Notice of Annual Reporting Requirements and Revised Financial Closeout Requirements for NIH Administrative Supplements Awarded to Recover Losses Due to Hurricane Sandy under the Disaster Relief Appropriations Act](#)
- July 11 [Revised Timeline for NIH Domestic Awards Transition to Payment Management System Subaccounts](#)
- July 3 [NIH Announces Change in Policy Requirements for Activation Notices for Fellows Sponsored by Foreign and Federal Institutions](#)
- May 29 [Notice of Change in Criteria for Renewal of Domestic Animal Welfare Assurances](#)
- May 16 [Transition to Payment Management System Subaccounts for Domestic Awards](#)
- May 16 [NIH Will Require the Research Performance Progress Report \(RPPR\) for All Type 5 Non-SNAP Progress Reports on October 17, 2014](#)
- May 16 [Piloting Modified NIH Biographical Sketch \(Biosketch\)](#)
- May 2 [Notice of Clarification of Career \(K\) Award Eligibility](#)
- April 30 [Transition Plans for Reporting Sex/Gender, Race, and Ethnicity Information in Non-Competing Type 5 Progress Reports](#)
- April 30 [NIH Launching New System and Procedures for Reporting Sex/Gender, Race, and Ethnicity Information to the NIH](#)
- April 24 [NIH Updating Grant Closeout Policies and Procedures to Align with New HHS Requirements](#)
- April 22 [Clarifications to the NIH and AHRQ Policy for Application Submission](#)
- April 18 [Notice of NIH Improving the Financial Conflict of Interest \(FCOI\) Module for Submission of Financial Conflict of Interest Reports to the NIH Beginning on April 25, 2014](#)
- April 17 [NIH and AHRQ Announce Updated Policy for Application Submission](#)
- April 15 [NIH Will Open the Research Performance Progress Report \(RPPR\) for All Type 5 Non-SNAP Progress Reports on April 25, 2014](#)

**CONGRESSIONAL AFFAIRS**  
**(Prepared August 11, 2014)**

**Congressional Hearings/Meetings**

**May 9, 2014:** At the request of the Congressional Hepatitis Caucus, NIDA Deputy Director Dr. Wilson Compton participated in a briefing entitled Hepatitis on the Hill. The Assistant Secretary for Health and HRSA also participated. The briefing was organized by the Harm Reduction Coalition and the National Association of State and Territorial AIDS Directors.

**May 14, 2014:** The Senate Caucus on International Narcotics control held a hearing on the Causal Role Prescription Drug Abuse has had on the Increased Use of Heroin in the United States. Dr. Nora Volkow, Director, NIDA, testified, along with Michael Botticelli, Acting Director, Office of National Drug Control Policy; Dr. H. Westley Clark, Director, Substance Abuse and Mental Health Services Administration; and Dr. Andrew Kolodny, Chief Medical Officer, Phoenix House.

**May 28, 2014:** NIDA Associate Director for Scientific Affairs Dr. Susan Weiss briefed Senator Elizabeth Warren's (D-MA) staff on marijuana research at NIDA.

**June 3, 2014:** NIDA Deputy Director Dr. Wilson Compton briefed Senator Jack Reed's (D-RI) staff on opiate abuse and addiction research at NIDA.

**June 10, 2014:** NIDA Director Dr. Nora Volkow met with and briefed Senator Lisa Murkowski (R-AK) on marijuana health and research issues.

**June 18, 2014:** NIDA Director Dr. Nora Volkow participated in a Senate Forum focused on buprenorphine use in the treatment of opiate addiction. The Forum was sponsored by Senator Carl Levin (D-MI) and Senator Orrin Hatch (R-UT).

**June 19, 2014: Friends of NIDA Capitol Hill Briefing** – NIDA Deputy Director Wilson Compton participated in a briefing titled “**Marijuana: Health Effects, Changing Patterns of Use and Societal Impact.**” This was a heavily attended congressional event which also featured Dr. Robert Booth and former Congressman Patrick Kennedy. Please see <http://www.apa.org/science/about/psa/2014/07/marijuana-impacts.aspx> for a full description from our colleagues at the American Psychological Association.

**June 20, 2014:** NIDA Director Dr. Nora Volkow briefed U.S. Representative John Fleming (R-LA) on the health effects of and NIDA research into marijuana abuse and addiction.

**June 20, 2014:** The House Oversight and Government Reform Subcommittee on Government Operations [Chairman, John Mica, (R-FL)] held a hearing on marijuana. Dr. Nora Volkow, Director, NIDA, testified. This was the third in a series of hearings held by this Subcommittee on this topic. Also testifying at this hearing were Dr. Douglas Throckmorton of FDA, and Dr. Carl Hart of Columbia University.

**June 27, 2014:** NIDA Director Dr. Nora Volkow briefed the Clerks of the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Pensions on NIDA research priorities and challenges.

**July 9, 2014:** NIDA Deputy Director Dr. Wilson Compton briefed Senator Mitch McConnell's (R-TN) staff for McConnell staff on opiate abuse and addiction research at NIDA.

**July 15, 2014:** NIDA Director Dr. Nora Volkow participated in a Capitol Hill briefing focused on Womens Health. The briefing was sponsored by the Womens Health Caucus, and organized by Womens Policy, Inc., with support from the Robert Wood Johnson Foundation.

**July 22, 2014:** NIDA Division of Epidemiology, Services and Prevention Acting Director Dr. Redonna Chandler chaired a panel at the second Senate Addiction Forum. The Forum focused on women and drug abuse/addiction issues, and also featured some NIDA grantees.

**August 6, 2014:** NIDA Director Dr. Nora Volkow participated in a community forum in Boston, MA. The event, organized and sponsored by U.S. Senator Edward Markey (D-MA), focused on opiate addiction and overdose issues. Other federal agencies participating were ONDCP, SAMHSA, and DEA.

**August 13-14, 2014:** NIDA Director Dr. Nora Volkow participated in a community forum and "coalfields tour" in southeastern West Virginia. The events, organized and sponsored by U.S. Representative Nick Rahall (D-WV), focused on opiate addiction and overdose issues. Other federal agencies participating were ONDCP, SAMHSA, CDC, DOJ/BJA.

### **Some Bills of Interest**

**HR 486** – On February 4, 2013, Representative William Keating (D-MA) introduced the Stop Tampering of Prescription Pills act of 2013, to amend the Food, Drug and Cosmetic Act to incentivize the development of abuse-deterrent drugs. The bill was referred to the Committee on Energy and Commerce.

**HR 498** – On February 5, 2013, Representative Lucille Roybal-Allard (D-CA) introduced a bill to reauthorize the Sober Truth on Preventing Underage Drinking (STOP) Act. The bill was referred to the House Committee on Energy and Commerce.

**HR 499** – On February 5, 2013, Representative Jared Polis (D-CO) introduced the Ending Federal Marijuana Prohibition Act of 2013, to generally decriminalize and change the way the Controlled Substances Act is applied to marijuana. The bill was referred to the Committee on the Judiciary, the Committee on Ways and Means, the Committee on Energy and Commerce, the Committee on Natural Resources, and the Committee on Agriculture.

**HR 672** – On February 13, 2013, Representative Nick Rahall (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and

deaths. The bill was referred to the Committee on Energy and Commerce and the Committee on the Judiciary. See also S 348.

**HR 1263** – On March 19, 2013, Representative Doris Matsui (D-CA) introduced the Excellence in Mental Health Act, to increase access to community behavioral health services for all Americans and to improve Medicaid reimbursement for community behavioral health services. The bill was referred to the Committee on Energy and Commerce. See also S 264, S 265.

**HR 1285** – On March 20, 2013, Representative Vern Buchanan (R-FL) introduced Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary, and Judiciary. See also S 621. [NOTE: The FDA has recommended to HHS the reclassification of hydrocodone combination products as Schedule II controlled substances.]

**HR 1366** – On March 21, 2013, Representative Stephen Lynch (D-MA) introduced the Stop Oxycontin Abuse Act of 2013, to direct the Commissioner of Food and Drugs to modify the approval of any drug containing controlled-release oxycodone hydrochloride to limit such approval to use for the relief of severe-only instead of moderate-to-severe pain, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

**HR 1523** – On April 12, 2013, Representative Dana Rohrbacher (R-CA) introduced the Respect State Marijuana Laws Act of 2013, to amend the Controlled Substances Act to provide for a new rule regarding the application of the Act to marijuana, and for other purposes. The bill was referred to the Committee on the Judiciary and the Committee on Energy and Commerce.

**HR 3717** – On December 12, 2013, Representative Tim Murphy (R-PA) introduced the Helping Families in Mental Health Crisis Act of 2013, to make available needed psychiatric, psychological, and supportive services for individuals diagnosed with mental illness and families in mental health crisis, and for other purposes. The bill was referred to the House Committees on: Energy and Commerce; Judiciary; Energy and the Workforce; Ways and Means; and Science, Space and Technology.

**HR 4046** – On February 11, 2014, Representative Steve Cohen (D-TN) introduced the Unmuzzle the Drug Czar Act of 2014, to strike provisions that prohibit the Director of the ONDCP from studying the legalization of marijuana, that require the Director to oppose any attempt to legalize marijuana, and for other purposes. The bill was referred to the Committees on Oversight and Government Reform and Energy and Commerce.

**HR 4169** – On March 6, 2014, Representative Donna Edwards (D-MD) introduced the Stop Overdose Stat Act, to prevent deaths occurring from drug overdoses. The bill was referred to the Committee on Energy and Commerce. See S 2755.

**HR 4241** – On March 13, 2014, Representative Stephen Lynch (D-MA) introduced the Act to Ban Zohydro, to withdraw approval for the drug Zohydro ER and prohibit the FDA from approving such drug unless it is reformulated to prevent abuse. The bill was referred to the Committee on Energy and Commerce. See S. 2134

**HR 5226** – On July 28, 2014, Representative Scott Perry (R-PA) introduced the Charlotte’s Web Medical Hemp Act of 2014, to amend the Controlled Substances Act to exclude therapeutic hemp and cannabidiol from the definition of marijuana, and for other purposes. The bill was referred to the Committees on Energy and Commerce, and Judiciary.

**HR 5136** – On July 17, 2014, Representative Marcia Fudge (D-OH) introduced the Breaking Addiction Act of 2014, to direct the Secretary of HHS to establish a demonstration project under the Medicaid program under title XIX of the Social Security Act under which payment may be made to states for expenditures for medical assistance with respect to substance abuse disorder services, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

**HR 5294** – On July 30, 2014, Representative Roybal-Allard (D-CA) along with 65 other Members of Congress introduced the Health Equity and Accountability Act of 2014. The bill contains ten titles, many of which include provisions for NIH. The titles include: Data Collection and Reporting; Culturally and Linguistically Appropriate Health Care; Health Workforce Diversity; Improvement of Health Care Services; Improving Health Outcomes for Women, Children, and Families; Mental Health; Addressing High Impact Minority Diseases (including cancer, viral hepatitis and liver cancer control and prevention, acquired bone marrow failure disease, cardiovascular disease, and chronic disease, HIV/AIDS, diabetes, lung disease, osteoarthritis and musculoskeletal diseases, and sleep and circadian rhythm disorders); Health Information Technology; Accountability and Evaluation; and Addressing Social Determinants and Improving Environmental Justice. The bill was referred to the Committee on Energy and Commerce, and in addition to the Committees on Ways and Means, Agriculture, Education and Workforce, the Budget, Veteran’s Affairs, Armed Services, the Judiciary, and Natural Resources.

**HR 5339** – On July 31, 2014, Representative Bill Foster (D-IL) introduced the Expanding Opportunities for Recovery Act of 2014, to authorize the Administrator of SAMHSA, acting through the director of CSAT, to award grants to states to expand access to clinically appropriate services for opioid abuse, dependence, or addiction. The bill was referred to the Committee on Energy and Commerce.

**S 237** – On February 7, 2013, Senator Lisa Murkowski (R-AK) introduced the Advancing FASD Research, Prevention and Services Act, to amend the Public Health Service Act to reauthorize and extend the FAS prevention and services program, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

**S 264** – On February 7, 2013, Senator Debbie Stabenow (D-MI) introduced the Excellence in Mental Health Act, to expand access to community mental health centers and improve the quality of mental health care for all Americans. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See also S 265, HR 1263

**S 265** – On February 7, 2013 Senator Jack Reed (D-RI) introduced Community-Based Mental Health Infrastructure Improvements Act, to amend the Public Health Service Act to provide grants for community-based mental health infrastructure improvement. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also S 264, HR 1263

**S 348** – On February 14, 2013, Senator John Rockefeller (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also HR 672.

**S 621** – On March 20, 2013, Senator Joe Manchin (D-WV) introduced the Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary. See also HR 1285. [NOTE: The FDA has recommended to HHS the reclassification of hydrocodone combination products as Schedule II controlled substances.]

**S 644** – On March 21, 2013, Senator Robert Casey (D-PA) introduced the Preventing Abuse of Cough Treatments Act of 2013, to amend the Food, Drug, and Cosmetic Act to prevent the abuse of dextromethorphan, and for other purposes. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

**S 1277** – On July 10, 2013, Senator Barbara Boxer (D-CA) introduced the Combating Prescription Drug Abuse Act, to establish a commission for the purpose of coordinating efforts to reduce prescription drug abuse, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

**S 2134** – On March 13, 2014, Senator Joe Manchin ((D-WV) introduced the Act to Ban Zohydro, to withdraw approval for the drug Zohydro ER and prohibit the FDA from approving such drug unless it is reformulated to prevent abuse. See H.R. 4241

**S 2755** – On July 31, 2014, Senator Jack Reed (D-RI) introduced the Overdose Prevention Act, to support community-based efforts to prevent fatal drug overdoses from opioid pain medications, heroin, and other drugs. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 4169.

## PROGRAM ACTIVITIES/FOAS

### New NIDA RFAs

On July 22, 2014, NIDA issued an RFA entitled **Interventions for Youth who Misuse/Abuse Prescription Stimulant Medications in High School and/or College-Attending Youth (U01)** [RFA-DA-15-010](#). This RFA solicits U01 applications conducting either hypothesis-driven or hypothesis-generating controlled research to build an evidence base to address the problem of prescription stimulant medication (PSM) misuse in youth. Specifically this RFA solicits research applications that develop and test the efficacy of interventions to either prevent or reduce the misuse and diversion of PSMs among high school students and/or college students. Open date: October 13, 2014. Application due date(s): November 13, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): November 13, 2014, by 5:00 PM local time of applicant organization.

On July 16, 2014, NIDA issued an RFA entitled **Extracellular Vesicles in HIV/AIDS and Substance Abuse (R01)** [RFA-DA-15-011](#) **(R21)** [RFA-DA-15-012](#). The purpose of this RFA is to encourage research projects that investigate extracellular vesicles in HIV infection/progression or as potential HIV/AIDS biomarkers or therapeutics. Proposed projects must also explore the potential impact of exposure to substances of abuse. Open date: November 15, 2014. Application due date(s): December 15, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): December 15, 2014, by 5:00 PM local time of applicant organization.

On July 3, 2014, NIDA issued an RFA entitled **The National Drug Abuse Treatment Clinical Trials Network (UG1)** [RFA-DA-15-008](#). This RFA invites applications from clinical investigators to participate in the National Drug Abuse Treatment Clinical Trials Network (CTN). NIDA intends to expand its research to develop and test interventions for the management of the wide spectrum of substance use disorders (SUD) with input from and collaboration with clinical research investigators, healthcare providers, patients and relevant stakeholders. It is expected that successful applicants will describe working alliances with existing and newly created practice-based primary care or other general medical research networks. Open date: November 3, 2014. Application due date(s): December 3, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

### New NIDA Program Announcements

On May 19, 2014, NIDA, in conjunction with NIMH, NCI and NIAAA, issued a PAR entitled **Exploratory Studies of Smoking Cessation Interventions for People with Schizophrenia (R21/R33)** [PAR-14-230](#), **(R33)** [PAR-14-231](#). The purpose of this PAR is to provide support for grant applications to generate and conduct preliminary tests of targeted smoking cessation treatments for individuals with schizophrenia. Smokers with schizophrenia who have co-occurring alcohol and/or substance abuse disorders are also a population of interest. This PAR encourages Phased Innovation (R21/R33) applications that focus on early-stage, treatment generation and pilot clinical trials that are consistent with an experimental therapeutic approach. This approach requires the identification of a theory-derived target based on putative mechanisms of nicotine addiction in

individuals with schizophrenia, and clear hypotheses about how an intervention directed at changing the target can lead to clinical benefits. Open date: July 15, 2014. Application due date(s): August 15, 2014, December 16, 2014, April 15, 2015, August 17, 2015, December 15, 2015, April 15, 2016, August 16, 2016, December 15, 2016, April 17, 2017, by 5:00 PM local time of applicant organization. AIDS application due date(s): August 15, 2014, December 16, 2014, April 15, 2015, August 17, 2015, December 15, 2015; April 15, 2016, August 16, 2016, December 15, 2016, April 17, 2017, by 5:00 PM local time of applicant organization.

On May 15, 2014, NIDA, in conjunction with NCCAM and NCI, issued a PAR entitled **Clinical Evaluation of Adjuncts to Opioid Therapies for the Treatment of Chronic Pain (R01)** [PAR-14-225](#). This announcement aims to fund applications designed to assess the clinical value of adjuncts prescribed to chronic pain patients together with opioid analgesics. Adjuncts of interest are either approved by the FDA or have previously been studied as an Investigational New Drug. Studies with adjuncts of interest should be focused on enhancing analgesia, rather than on reducing an adverse effect. A secondary purpose is to increase awareness among opioid prescribers of the potential value of adjunctive therapies by focused data dissemination. Open date: September 5, 2014. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On May 15, 2014, NIDA issued a PA entitled **Long-Term Retention in Care for U.S. Substance Using Populations (R01)** [PA-14-224](#), **(R21)** [PA-14-223](#), **(R34)** [PA-14-222](#). Until there is a cure, people living with HIV (PLWH) will have to be retained in care throughout their lives. Therefore, the purpose of this Funding Opportunity Announcement (FOA) is to encourage research on long-term retention in care leading to sustained viral suppression among substance abusers. Open date(s): August 7, 2014. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On April 23, 2014, NIDA issued a PAR entitled **NIDA Core "Center of Excellence" Grant Program (P30)** [PAR-14-186](#). NIDA Core Center of Excellence Grants (P30) are intended to bring together investigators currently funded by NIH or other Federal or non-Federal sources, to enhance the effectiveness of existing research and also to extend the focus of research to drug abuse and addiction. It is expected that a Center will transform knowledge in the sciences it is studying. Incremental work should not be the focus of Center activities; rather, new and creative directions are encouraged. A P30 should integrate and promote research in existing funded projects, to achieve new and creative directions. It is expected that individual core activities reflect a relationship to the integrating theme of the Center and the Center is expected to support the education, training, and mentoring of new investigators, and share findings, data and their resources. Open date(s): August 25, 2014. Application due date(s): September 25, 2014; September 25, 2015; September 26, 2016, by 5:00 PM local time of applicant organization. AIDS application due date(s): January 7, 2015; January 7, 2016; January 7, 2017, by 5:00 PM local time of applicant organization.

## **New FOAs Issued by the NIH Blueprint for Neuroscience Research**

**Neuroscience Information Framework (U24) [RFA-DA-15-009](#).**

**Blueprint Neurotherapeutics Network (BPN): Small Molecule Drug Discovery and Development for Disorders of the Nervous System (U44) [PAR-14-292](#)**

**Blueprint Neurotherapeutics Network (BPN): Small Molecule Drug Discovery and Development for Disorders of the Nervous System (UH2/UH3) [PAR-14-293](#)**

**Limited Competition for a Connectome Coordination Facility (R24) [RFA-MH-15-750](#)**

## **New FOAs Issued by the NIH Roadmap**

On July 24, 2014, the NIH Common Fund issued a Roadmap RFA entitled **NIH Transformative Research Awards (R01) [RFA-RM-14-003](#)**. The NIH Transformative Research Awards complement NIH's traditional, investigator-initiated grant programs by supporting individual scientists or groups of scientists proposing groundbreaking, exceptionally innovative, original and/or unconventional research with the potential to create new scientific paradigms, establish entirely new and improved clinical approaches, or develop transformative technologies. Little or no preliminary data are expected. Projects must clearly demonstrate the potential to produce a major impact in a broad area of biomedical or behavioral research. Open date: September 10, 2014. Application due date(s): October 10, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): October 10, 2014, by 5:00 PM local time of applicant organization.

## **New RFAs Issued by Other NIH/HHS Components in which NIDA is a participant**

**U.S.-China Program for Research Toward a Cure for HIV/AIDS (R01) [RFA-AI-14-057](#)**

**Revisions to Add Biomedical Big Data Training to Active Institutional Training Grants (T32) [RFA-HG-14-005](#)**

**Predoctoral Training in Biomedical Big Data Science (T32) [RFA-HG-14-004](#)**

## **New PAs Issued by Other NIH/HHS Components in which NIDA is a participant**

**Administrative Supplements for Tobacco Regulatory Research on the Role and Impact of Flavors in Cigarettes, Cigars, E-Cigarettes and Smokeless Tobacco (Admin Supp) [PA-14-320](#)**

**Platform Delivery Technologies for Nucleic Acid Therapeutics (R43/R44) [PA-14-307](#)**

**Platform Delivery Technologies for Nucleic Acid Therapeutics (R41/R42) [PA-14-308](#)**

**High Throughput Screening (HTS) to Discover Chemical Probes (R21) [PAR-14-283](#)**

**High Throughput Screening (HTS) to Discover Chemical Probes (R01) [PAR-14-284](#)**

**Connectomes Related to Human Disease (U01) [PAR-14-281](#)**

**Discovery of in vivo Chemical Probes (R01) [PAR-14-279](#)**

**Ethical, Legal, and Social Implications (ELSI) of Genomic Research Small Research Grant Program (R03) [PA-14-277](#)**

**Ethical, Legal, and Social Implications (ELSI) of Genomic Research Regular Research Program (R01) [PA-14-276](#)**

**Ethical, Legal, and Social Implications (ELSI) of Genomic Research Exploratory/Developmental Research Program (R21) [PA-14-278](#)**

**Interventions for Health Promotion and Disease Prevention in Native American Populations (R01) [PAR-14-260](#)**

**Multidisciplinary Studies of HIV and Viral Hepatitis Co-Infection (R01) [PAR-14-255](#)**

**Administrative Supplements for the U.S.-Japan Brain Research Cooperative Program (BRCP) - U.S. Entity (Administrative Supplement) [PA-14-249](#)**

**Basic Research on HIV Persistence (R21) [PAR-14-248](#)**

**Basic Research on HIV Persistence (R01) [PAR-14-247](#)**

**National Cooperative Drug Discovery/Development Groups (NCDDG) for the Treatment of Mental Disorders, Drug or Alcohol Addiction (U19) [PAR-14-234](#)**

**Limited Competition for NIH-Industry Program: Discovering New Therapeutic Uses for Existing Molecules (UH3) [PAR-14-211](#)**

**Limited Competition for NIH-Industry Program: Discovering Pediatric New Therapeutic Uses for Existing Molecules (UH2/UH3) [PAR-14-210](#)**

**Limited Competition for NIH-Industry Program: Discovering New Therapeutic Uses for Existing Molecules (UH2/UH3) [PAR-14-212](#)**

**National Cooperative Drug Discovery/Development Groups (NCDDG) for the Treatment of Mental Disorders, Drug or Alcohol Addiction (U01) [PAR-14-184](#)**

## COMMUNICATIONS

### PUBLICATIONS/VIDEOS

#### NIDA Publications and Online Resources

##### NIDA Notes (now online only)

A new podcast with Dr. Kevin Gray initiates a project to engage NIDA Notes readers in research in action. In the podcast, Dr. Gray presents a clinical trial (acetylcysteine for marijuana addiction) that is just starting. Coverage of two studies related to marijuana abuse have proven to be big readership draws as some states legalize the drug and others debate doing so. NIDA Notes currently receives around 35,000 article page views per month.

##### Videos

- **NIDA NOTES: NIDA@Work Presents, Dr. Elizabeth F. Howell**  
<http://youtu.be/3SOaxPZ-EG0>
- **NIDA TV Spotlight: Tobacco Partnership with FDA**  
<http://youtu.be/h82TqGml-JQ>
- **NIDA NOTES: NIDA@Work Presents, Dr. Joni Rutter**  
[http://youtu.be/W\\_kq2fWrQps](http://youtu.be/W_kq2fWrQps)
- **What's New at NIDA: Office of Science Policy & Communication Director's Notes for April**  
<http://youtu.be/IL62x6HLGiw>
- **NIDA's 2014 Avant-Garde Awards Announced**  
<http://youtu.be/pvV95T67uQQ>
- **NIDA TV Spotlight: Dr. ElSohly and the University of Mississippi Marijuana Farm**  
<http://youtu.be/IEJf2-TdU68>
- **National Institutes of Health-Take Your Child To Work Day @ NSC**  
[http://youtu.be/ayLr0\\_mIYuw](http://youtu.be/ayLr0_mIYuw)
- **What's New at NIDA: Office of Science Policy & Communication Director's Notes for June**  
<http://youtu.be/X7rIhbqXP8A>
- **Investigating Drug Abuse: Brain Neurons**  
<http://youtu.be/Nl0nwKcNJ0Y>
- **Investigating Drug Abuse: Brain Imaging**  
<http://youtu.be/DaifOWSKjdA>
- **Investigating Drug Abuse: Building Molecular Tools**  
<http://youtu.be/H4rx7Nkw4Wk>
- **NIDA Notes: Researchers Speak Presents Dr. Antonello Bonci**  
<http://youtu.be/j1yf0eFs3aM>

### **CTN-Related Publications**

Five editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and Node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 32 CTN studies are now available on the NIDA Data Share website <http://datashare.nida.nih.gov/>. Over 2,700 data sets have been downloaded by researchers from 55 countries. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The NIDA Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

### **COMMUNITY AND PRESS EVENTS**

#### **NIDA's Deputy Director Speaks at US-Mexico Addiction Summit**

On April 28, 2014, NIDA Deputy Director Dr. Wilson Compton presented at the U.S.-Mexico Addiction Summit in Albuquerque, NM about addiction. In anticipation of his participation, he was interviewed by the *Albuquerque Journal* about the effects of marijuana on the body and brain.

#### **NIDA Director Presents at APA Conference about Addiction**

On May 3, 2014, NIDA Director Dr. Nora Volkow presented *Frontiers of Science: Advances in Addiction Research* to attendees at the 167th American Psychiatry Association Annual Meeting in New York City, NY. The NIDA press team arranged for an interview with APA TV as well as provided social media outreach.

#### **NIDA Director Speaks at World Science Festival**

On May 31, 2014, Dr. Volkow presented on "*The Brain and Addiction*" at the World Science Festival in New York City, NY, where several leading scientists discussed the latest developments in the fields of addiction neuroscience to over 600 attendees. The NIDA press team provided logistical and social media support for the event.

#### **NIDA Director Receives Nathan B. Eddy Award**

On June 15, 2014, NIDA Director Dr. Nora Volkow received the Nathan B. Eddy Award from the College on Problems of Drug Dependence (CPDD) in San Juan, Puerto Rico. The Nathan B. Eddy Award is named after a pioneer in the field of drug dependence and acknowledges outstanding research efforts that have advanced our knowledge of drug dependence. Dr. Volkow delivered a keynote address on the state of addiction research at the annual meeting of the CPDD, which featured 800 presentations by scientists from the United States and other nations, many of them supported by grants from NIDA. The NIDA press team issued a media advisory and provided social media support for the event.

#### **Dr. Wilson Compton Presents at 2014 ESOF Conference in Copenhagen**

Deputy Director Dr. Wilson Compton presented on three panels about brain addiction, e-cigarettes and global policy on drug abuse at the ESOF 2014 Copenhagen Euroscience Open Forum held in

Denmark June 21-26, 2014. The NIDA press team coordinated local press interviews on these topics.

### **Dr. Nora Volkow Receives Students Against Destructive Decisions (SADD) Award**

On June 24, 2014, Dr. Volkow received the 2014 National Outstanding Contribution Award at the SADD national conference in Washington, D.C. The award is presented to “that individual or group who has made a contribution that stands out in size, creativity, sacrifice or commitment to SADD or to the themes of SADD, including the health and safety of teens.” NIDA promoted the award through social media, including Twitter and Facebook.

### **Addiction Science Award Winners Present at NIDA**

On June 30, 2014, the 2014 winners of NIDA’s Addiction Science Awards, part of the Intel International Science and Engineering Fair (ISEF) -- the world’s largest science competition for high school students -- presented their projects to NIDA Director Nora Volkow and other NIDA scientists and were given a tour of the NIH campus. The Addiction Science Awards are coordinated by NIDA as well as Friends of NIDA, a private group dedicated to furthering NIDA’s mission. The ISEF awards ceremony occurred on May 15, 2014, at the Los Angeles Convention Center in CA and NIDA Press Officer Dr. Sheri Grabus served as judge for the Addiction Science Awards. The press team sent information about each winner to their hometown newspapers and schools, to internal NIDA and NIH publications, and provided social media outreach.

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## **PRESS RELEASES**

- |                      |  |
|----------------------|--|
| <b>May 6, 2014</b>   | <a href="#"><u>Dr. Joni Rutter to lead NIDA’s genetics and basic science research division</u></a>                 |
| <b>May 16, 2014</b>  | <a href="#"><u>Study of third hand nicotine from e-cigarette exposure wins top NIH Addiction Science Award</u></a> |
| <b>May 19, 2014</b>  | <a href="#"><u>2014 Avant-Garde Awards focus on strengthening the immune system</u></a>                            |
| <b>May 20, 2014</b>  | <a href="#"><u>NIDA offers tools for talking to teens about marijuana</u></a>                                      |
| <b>May 21, 2014</b>  | <a href="#"><u>NIH Pain Consortium’s first pain care curriculum improves clinical skills</u></a>                   |
| <b>June 3, 2014</b>  | <a href="#"><u>MDMA can be fatal in warm environments</u></a>  |
| <b>June 4, 2014</b>  | <a href="#"><u>NIDA review summarizes research on marijuana’s negative health effects</u></a>                      |
| <b>July 17, 2014</b> | <a href="#"><u>NIH system to monitor emerging drug trends</u></a>  |

## **SCIENCE SPOTLIGHTS AND ANNOUNCEMENTS**

- May 9, 2014**      [Early interventions can decrease drug use in young women](#)
- May 27, 2014**      [More Colorado drivers in fatal car crashes testing positive for marijuana](#)
- June 10, 2014**      [CPDD conference features NIDA Director Dr. Nora Volkow as well as Media Forum](#)
- June 16, 2014**      [Study compares effectiveness of oral drug tests for recent marijuana use](#)
- July 1, 2014**      [Social media can influence teens with pro-drug messages](#)
- July 3, 2014**      [New brain imaging dataset now available to enhance reliability and reproducibility](#)
- July 15, 2014**      [Passive e-cigarette exposure may urge young adults to smoke](#)
- July 30, 2014**      [Regular marijuana users may have impaired brain reward centers](#)
- August 20, 2014**      [Journal issue explores early interventions to prevent risky sexual behaviors related to HIV/AIDS.](#)

## MEETINGS/CONFERENCES

### Select Meetings and Conferences in which NIDA played a significant role

On June 26-27, 2014, the Office of Diversity and Health Disparities, hosted a two-day Research Development Seminar Series Part II Workshop **Mock Grant Review** at NIDA Headquarters in Rockville, Maryland. Chaired by Flair Lindsey, Program Analyst, this workshop convened 14 new early stage investigators, who participated in an initial Research Development Seminar Series Part I Workshop, to submit their “draft” research grant applications for a mock grant review. Led by Scientific Review Officer (SRO) Dr. Jose Ruiz, Office of Extramural Affairs (OEA), NIDA, and consisting of a review panel of NIDA-funded investigators and select NIDA program officials, the mock grant review enabled early stage investigators to experience a first-hand look at an actual Study Section (Scientific Review Group, SRG) review. Participants gained a thorough understanding of reviewers’ evaluations, critiques and outside opinions, as well as scoring. For the sake of this workshop, all applications were discussed. Following the mock grant review, participants received overall feedback and updates on the grants submission process, as well as have individual consultations with assigned reviewers. Through this workshop, ODHD strived to thoroughly evaluate and identify areas of strengthening early stage investigators’ “draft” research grant applications, so that they can be successful and competitive.

NIDA’s African American Researchers and Scholars Workgroup, with support from the Office of Diversity and Health Disparities, convened the **6<sup>th</sup> annual Addiction Research Training Institute (ARTI) at Morehouse School of Medicine** in Atlanta, Georgia, July 14-17, 2014. The four-day workshop provided 13 early stage investigators with mentoring and invaluable grantsmanship tools and technical assistance on grant writing, grant development, NIH application/grant submission, funding mechanisms and opportunities, peer review, scientific writing and research training. Flair Lindsey, Program Analyst, provided 13 early stage substance abuse and addiction research investigators with information on NIDA research priorities and funding opportunities. Flair individually consulted with select early stage investigators to provide guidance on the most appropriate funding mechanisms for their proposed research.

NIDA awarded 20 **Director’s Travel Awards** for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 14-19, 2014, in San Juan, Puerto Rico. Awardees are National Research Service Award (NRSA) trainees and fellows, and Diversity Supplement recipients to present at the CPDD meeting and attend the NIDA Grant-Writing and Career Workshop.

Drs. Mimi Ghim, Ericka Boone, and Michele Rankin, and Ms. Usha Charya, OSPC, coordinated the **NIDA Grant-Writing and Career Workshop** and the **NIDA/CPDD Training Networking Event** at CPDD, June 17 and 16 respectively, in San Juan, Puerto Rico. The Grant-Writing and Career Workshop provided information on NIDA research priorities, program interests and funding opportunities, review procedures, and training on grantsmanship and other career-building skills. Drs. Kevin Walton and Gerald McLaughlin presented some of the core content in this workshop, as well as guest speakers Drs. Linda Cottler (University of Florida) and Frances Levin (Columbia University). The Training Networking Event provided a forum for training directors, trainees, and

NIDA staff to learn about the different training programs that NIDA supports and for trainees to find future training and employment opportunities.

### **PLANNED MEETINGS (pending approval)**

#### **Society for Neuroscience Frontiers in Addiction Research Mini-convention – Washington D.C., November 14, 2014**

NIDA will present its annual Frontiers in Addiction Research Mini-convention as a satellite event of the Society for Neuroscience Annual meeting on November 14, 2014 in Natcher auditorium on the NIH campus. The mini-convention provides a forum for presentations on contemporary topics in the areas of neuroscience and addiction research. The NIDA Mini-convention includes: four scientific symposia, keynote presentations by the 2013 and 2014 winners of the SfN Jacob P. Waletzky Award which recognizes excellence in research in the area of substance abuse and the brain and nervous system, and a poster session showcasing the work of early career investigators. The symposia this year are:

- Emerging and Novel Aspects of Neuronal Transmission
- Extracellular RNAs in Neuroscience: Biology, Biomarkers, and Therapeutics
- Advances in High Resolutions and Large Scale Imaging of Brain Networks and Circuits
- The Effects of Drug-, Stress-, and Pain-induced Neuroinflammation on Glymphatics and Sleep

#### **So You Want to Be a Scientist...and Get Paid Along the Way: A NIH Grant Workshop for Early Career Investigators – Washington D.C., Sunday November 16, 2014**

NIDA will once again present an Early Career Workshop at the Society for Neuroscience annual meeting. The focus of this year's workshop is on the individual Ruth L. Kirschstein National Research Service Award (NRSA) grant applications for predoctoral and dual degree candidates, and postdoctoral fellows. This workshop offers the opportunity for graduate students and postdoctoral fellows to have their questions answered concerning their role in working on research projects and in preparing NRSA fellowship applications.

#### **NIH Funding Opportunity: Longitudinal Study of Neurodevelopmental Consequences of Substance Use – Washington D.C., Monday, November 17, 2014**

The Collaborative Research on Addiction at NIH (CRAN), comprising NIDA, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the Division of Cancer Control and Population Sciences at the National Cancer Institute (NCI), in partnership with the Eunice Kennedy Shriver National Institute of Clinical Health and Human Development (NICHD) are hosting a workshop to solicit input for a large-scale prospective cohort study to assess developmental effects of substance use from early adolescence into young adulthood in human subjects. The study goals are to understand the impact of various patterns and trajectories of substance exposure on brain structure and function; future substance use disorders or other psychopathology; and functional outcomes, including academic achievement, social development and other behaviors of public health importance.

**Novel RNA Modifications in the Nervous System: Form and Function – Washington D.C., Date TBD.**

NIDA will hold a satellite symposium at the Annual Society for Neuroscience meeting in November 2014. Modified RNA molecules have recently been shown to regulate nervous system functions. This mini-symposium will provide an overview of the types and known functions of novel modified RNAs in the nervous system, include (1) methylated RNAs in intellectual disability and dopamine neuron function, (2) circular RNAs in microRNA regulation and specification of neuron fate; and (3) the consequences of adenosine-to-inosine RNA editing in neurological diseases and substance abuse.

**Bath Salts, Spice, and Related Designer Drugs: The Science Behind the Headlines – Washington D.C., Date TBD**

NIDA will hold a satellite symposium at the Annual Society for Neuroscience meeting in November 2014. Recently, there has been an alarming increase in the nonmedical use of novel psychoactive substances known as “designer drugs.” Synthetic cathinones and synthetic cannabinoids are two of the most widely abused classes of designer drugs. This mini-symposium will present the most up-to-date information about the molecular sites of action, pharmacokinetics and metabolism, and in vivo neurobiology of synthetic cathinones and cannabinoids.

## GRANTEE HONORS AND AWARDS

**Dr. Michael Bardo** received the 2014 CPDD Mentorship Award in June 2014 during the 2014 College on Drug Problems of Dependence 76th Annual Meeting which took place in San Juan, Puerto Rico. This award is given annually to a member of CPDD who has been an exemplary mentor to developing researchers in the field of drug abuse dependence.

**Drs. C. Hendricks Brown**, Northwestern University; **Dr. William B. Hansen**, Tanglewood Research; and **Dr. Helene R. White**, Rutgers University NIDA grantees were selected for the 2<sup>nd</sup> cohort of Fellows of the Society for Prevention Research (SPR), during the 22<sup>nd</sup> annual meeting, on May 29, 2014. The SPR Fellows Program, in its second year, is an honor SPR bestows upon a small and select group of members who have a particularly distinguished record of contributions in the field of prevention science.

**Brian K. Bumbarger, MEd**, received the Translational Science Award during the 22<sup>nd</sup> annual meeting of the Society for Prevention Research, on May 29, 2014. This award recognizes contributions to the field of prevention science in the area of Type 1 or Type 2 translational research.

**Dr. Donna Coffman** received the ECPN John B. Reid Early Career Award during the 22<sup>nd</sup> annual meeting of the Society for Prevention Research, on May 29, 2014. The award is presented to a person early in their career in prevention who has shown a commitment to prevention science through outstanding contributions to research, policy or practice.

**Dr. Benjamin Cravatt** of The Scripps Research Institute in La Jolla, CA, was the winner of the American Society for Biochemistry and Molecular Biology/Merck Award.

**Dr. Elizabeth D'Amico**, RAND, received the 2014 Medal Award June 2014, RAND's highest honor for recognizing individuals for inspiring contributions for developing innovative methods, tools, approaches to policy, or process as well as furthering RAND's mission and impact and advancing the business strategy. Dr. D'Amico received the award for extending the reach and impact of research findings on stemming teen alcohol and drug use in an innovative manner. Dr. D'Amico oversaw the launch of a website (<http://groupmiforteens.org>) that provides support for Group MI for teens, an intervention developed by Dr. D'Amico and that has been shown through her research to reduce teen drug and alcohol use. Dr D'Amico's success in making an effective intervention freely available to the public was recognized as exceptional.

**Dr. Brian Hicks**, University of Michigan, received the J. L. Fuller & J. P. Scott memorial award for outstanding scientific accomplishments by a member early in their career at the 2014 annual meeting of the Behavior Genetics Association.

**Dr. Stephanie Lanza** received the Friend of ECPN (Early Career Preventionist Network) award during the 22<sup>nd</sup> annual meeting of the Society for Prevention Research, on May 29, 2014. The

Friend of ECPN award is presented to a mid-career or senior preventionist who has supported and encouraged early career prevention scientists or issues.

**Dr. Steffanie Strathdee**'s profile will appear in a forthcoming issue of the Lancet in which she will also serve as guest Editor of a new Lancet Series on HIV prevention in sex workers. Dr. Strathdee is widely considered a leader in the field of drug abuse and infectious disease research and prevention, both domestically and internationally, and effectively disseminates the evidence from her research to policy makers, local law enforcement and other community non-government groups. Among her numerous NIDA awards she currently holds a MERIT (R37 DA019829) examining the impacts of Mexico's 2010 change in drug possession laws, decriminalizing "personal" possession of heroin, cocaine, methamphetamine and marijuana.

#### **NIDA CTN Florida Node Alliance**

**Dr. Carlos del Rio** received the 2014 Thomas Jefferson Award, Emory University's highest award for distinguished service to the University. Dr. del Rio is the Hubert Professor and Chair of the Hubert Department of Global Health and Professor of Epidemiology at Rollins School of Public Health, as well as a professor of medicine at Emory School of Medicine and chief of the infectious disease service at Emory University Hospital. He is also the director for clinical sciences and international research of the Emory Center for AIDS Research (CFAR) and directs the Emory AIDS International Training and Research Program. Dr. del Rio has spent his career as a clinician and researcher, working to prevent, treat, and improve patient outcomes for infectious diseases locally and globally. He has focused his work on HIV/AIDS prevention and early diagnosis, access to care and compliance with anti-retrovirals in hard-to-reach populations, including substance abusers.

#### **NIDA CTN Pacific Northwest Node**

**Dr. Dennis Donovan** was appointed to the National Academy of Sciences' Institute of Medicine (IOM) Committee to Evaluate the Department of Veterans Affairs Mental Health Services. The 17-member committee will comprehensively assess the quality, capacity, and access to mental health care services, including treatment of substance use disorders, for veterans who served in the Armed Forces during Operation Enduring Freedom, Operation Iraqi Freedom, or Operation New Dawn. This IOM committee will assess the spectrum of mental health services available across the entire Department of Veterans Affairs. It will determine the extent to which veterans are afforded treatment choices, as well as the extent to which Iraq and Afghanistan war veterans are being offered a full range of necessary mental health services in the VA. The scope of the Committee's assessment will also include barriers faced by patients in utilizing the services offered. In addition to providing expertise in substance use disorder treatment to the committee, Dr. Donovan also brings his experience working within the VA system for nearly 20 years prior to assuming his role at the UW Alcohol & Drug Abuse Institute.

## STAFF HONORS AND AWARDS

### 2014 NIH DIRECTOR'S AWARDS

**Dr. Steven Grant**, DCNBR, received a NIH Director's Team Award for his participation in the BRAIN Initiative.

**Dr. Michael Baumann**, IRP, received an NIH Director's Award for "significant and timely contributions to the NIH mission by serving as an ambassador for educating the public about the dangers of designer drugs".

The **Collaborative Research on Addictions at NIH (CRAN) Coordination Committee** received an NIH Director's Award for "outstanding work implementing the first round of funding announcements in the new CRAN (Collaborative Research on Addictions at NIH) program". NIDA Staff receiving this award were: **Kevin P. Conway**, **Matthew S. Finger**, **Denise A. Pintello** (now with NIMH), **David Shurtleff** (now with NCCAM) and **Susan R. Weiss**.

The **NIDA/NIH SPIRES Automated Publication Carts Team** received an NIH Director's Award "in recognition of NIDA/NIH's new SPIRES real-time and continuous publication carts to enhance portfolio review activities. NIDA Staff receiving this award were: **Augusto Diana**, **Matthew S. Finger**, **Marsha F. Lopez**, **Genevieve C. Vullo**, and **Tisha R. Wiley**.

### 2014 NIDA DIRECTOR'S AWARDS

#### **CENTER FOR THE CLINICAL TRIALS NETWORK**

**David Liu** -- In recognition of scientific expertise, unselfish sharing of his wisdom with colleagues, and willingness to assume ever increasing challenges contributing to the accomplishment of NIDA's mission.

#### **The CCTN Clinical Trials Implementation Steering Group**

**Carol Cushing**, **Ronald Dobbins** and **Carmen Rosa**

In recognition of extraordinary efforts in continuous acquiring new knowledge and skills in meeting the ever-evolving clinical research advancement in furtherance of NIDA's mission

#### **DIVISION OF BASIC NEUROSCIENCE AND BEHAVIORAL RESEARCH**

**Susan Volman** -- In recognition of leading NIDA's CEBRA, EUREKA and CRCNS programs and coordinating the poster award program for junior investigators at the NIDA Frontiers in Neuroscience SfN meeting

**DBNBR Portfolio Coding & Analysis Team**

**Paul Hillery, Minda Lynch, Nancy Pilotte, Jonathan Pollock, Dena Procaccini, Vishnudutt Purohit, Rao Rapaka, Jose Ruiz, John Satterlee, Roger Sorensen, Hari Singh, and Da-Yu Wu**  
In recognition of dedication, contributions, and support to meet the mission of NIDA

**NIH BRAIN Initiative Teams and Coordinators**

**James Bjork, Gayathri Dowling, Melissa Ghim, Steven Grant, Jonathan Pollock, Joni Rutter, Catherine Sasek, Roger Sorensen, Susan Volman, Susan Weiss, and Da-Yu Wu**  
In recognition of exceptional dedication to promote an interdisciplinary effort of extraordinary scope to advance Brain Research through Advancing Innovative Neurotechnologies

**DIVISION OF CLINICAL NEUROSCIENCE & BEHAVIORAL RESEARCH**

**Will Aklin --** In recognition of leadership on neurobehavioral targets for behavioral treatments for drug abuse

**Cheryl Boyce --** In recognition of public dissemination of neuroscience and child maltreatment research

**Samia Noursi --** In recognition of exceptional leadership contributions to the success of the trans-HHS symposium on Intimate Partner Violence Screening and Counseling, December 9, 2013

**NIDA Pain Leadership Group**

**Richard Denisco and David Thomas**

In recognition of dedication and longstanding contributions to the field of pain research and treatment. This sustained work has contributed significantly to the mission of NIDA

**DIVISION OF EPIDEMIOLOGY, SERVICES AND PREVENTION RESEARCH**

**Peter Hartsock --** In recognition of support of NIDA research addressing the HCV epidemic among injection drug users

**American Indian/Alaska Native Research Development Group**

**Will Aklin, Albert Avila, Aria Crump, Augusto Diana, Kathleen Etz and Carmen Rosa**

In recognition of efforts to develop and facilitate research programs conducted by AI/AN investigator that address issues of the AI/AN population.

**DIVISION OF PHARMACOTHERAPIES AND MEDICAL CONSEQUENCES OF DRUG ABUSE**

**Aidan Hampson --** In recognition of leadership to support NIDA's mission of improving clinical trials by developing novel medication adherence markers

## **INTRAMURAL RESEARCH PROGRAM**

**Mariena Mattson** -- In recognition of your dedication, contributions, and support to meet the mission of NIDA

### **NIDA IRP Office of Education and Career Development**

**Stephen Heishman, Mary Pfeiffer and Rolanda Morris**

In recognition of exceptional leadership and vision to further the training and development of career skills of trainees at NIDA IRP

## **NIDA OFFICE OF THE DIRECTOR**

**Pamela Goodlow** -- In recognition of dedication, contributions, and commitment to NIDA and the Diversity Supplement Program

### **NIDA Consortium on Diversity Workgroup**

**Will Aclin, Debra Battle-Dudley, Dionne Jones, Guifang Lao, Yu Lin, Vishnudutt Purohit, Belinda Sims, Kevin Walton and Ericka Wells**

In recognition of dedication, contributions, and commitment to NIDA Diversity Supplement Program

## **OFFICE OF EXTRAMURAL AFFAIRS**

### **OEA Contract Review Handbook Team**

**Jayson Hill, Minna Liang and Jose Ruiz**

In recognition for creating the OEA Contract Review Handbook, a guide aimed at increasing efficiencies and improvements in service to NIDA and external research community

## **OFFICE OF MANAGEMENT**

### **Financial Management Branch**

**Donna Jones, Stacy Gardner, Sharon Goon, Yvonne Moskal and Nakia Walters**

In recognition of your ability to develop innovative solutions in order to meet fiscal challenges and for significant contributions in efficiently managing NIDA's budget under extraordinary circumstances

## **OFFICE OF SCIENCE POLICY AND COMMUNICATIONS**

### **"Principles of Adolescent Substance Use Disorder Treatment" Publication Team**

**Ericka Boone, Cheryl Boyce, Redonna Chandler, Jessica Cotto, Elisabeth Davis, Gayathri Dowling, Bennett Fletcher, Mark Fleming, Carol Krause, Ivan Montoya, Stephanie Older, Geetha Subramaniam, Isabelle Thibau and Eric Wargo**

In recognition of efforts to develop and disseminate resources to help parents, health care providers, and treatment specialist address substance use disorders among adolescents.

### **2014 NIDA DIRECTOR'S AWARD FOR EEO, DIVERSITY AND QUALITY OF WORKLIFE**

#### **Minority Scholars Team**

##### **Nadine Rogers and Jose Ruiz**

In recognition of efforts to provide training and guidance in NIH grants administration in the areas of drug abuse and addiction to young minority scientists.

### **NIDA DIRECTOR'S INNOVATOR AWARD**

#### **Portfolio Analysis Team**

##### **Kristopher Bough and Mark Caulder**

In recognition of collegiality, diligence, focus, and creativity for developing a new portfolio analysis tool to help the advancement of science within NIDA

#### **NIDA TV Team**

##### **Josie Anderson and Janet Linton**

In recognition of creativity and innovativeness in developing a portal for cataloging and viewing NIDA-related videos to enhance their dissemination

### **30 YEARS OF GOVERNMENT SERVICE AWARDS**

**Joan Deckow, Peter Hartsock, Andrea McGee, Rosanne Ogoh, Hari Singh and Susan Weiss**

### **40 YEARS OF GOVERNMENT SERVICE AWARD**

**Debra Haynes, Donna Jones and Mark Lombardi**

### **Other Staff Honors and Awards**

**Dr. Elizabeth Robertson**, DESPR, was named a fellow of the Society for Prevention Research on May 29, 2014. The SPR Fellows Program, in its second year, is an honor SPR bestows upon a small and select group of members who have a particularly distinguished record of contributions in the field of prevention science.

**Flair Lindsey**, ODHD, received "The Exemplary Leadership Award" from the African American Researchers and Scholars Work Group for leadership in Office of Diversity and Health Disparities programs, including the Research Development Seminar Series.

**Dr. Amy Newman**, IRP, received the 2014 Marian W. Fischman Lectureship Award from the College on Problems of Drug Dependence (CPDD). The award was presented to her at the 76th Annual Scientific meeting of the CPDD where she presented a lecture entitled “What’s a Nice Girl Like You Doing in a Field Like This?”.

**Dr. Irina Krasnova**, IRP, received a mentoring award on May 14, 2014 from the Office of Education and Training. Dr. Krasnova was one of three recipients honored for mentoring students from diverse and under-represented populations.

**Dr. Mary Pfeiffer**, IRP, received a Special Act Award for her work on the IRP’s Animal Care and Use Committee.

**Dr. Michael Baumann**, IRP, received a Staff Scientist Mentoring Award from the NIDA IRP.

**Dr. Suchankova Karlsson**, IRP, received a 2014 RSA Junior Investigator Travel Award.

**Dr. Petra Suchankova Karlsson**’s work on GLP-1 conducted in Dr. Leggio’s section was selected as a finalist for the Young Investigator Award at the SCNP Meeting (Copenhagen, Denmark), and was selected as a finalist at the 2014 joint RSA/ISBRA meeting (Bellevue, WA) for both the Enoch Gordis Postdoctoral Award and the ISBRA President Award.

**Dr. Dong Wang**, IRP, received a \$1,000 travel award as a winner of NIH Fellows Award for Research Excellence 2014 competition.

**Dr. Satoshi Ikemoto**, IRP, received a NIDA-IRP Investigator Mentoring Award.

**Dr. Lorenzo Leggio**, IRP, was recently appointed as Editor-in-Chief for North America for ‘Alcohol and Alcoholism’ (Oxford University Press), the official Journal of the European Society for Biomedical Research on Alcoholism (ESBRA) and the Medical Council on Alcohol (MCA).

**Dr. Vivek Kumar**, IRP, won a 2014 NIH FARE Travel Award.

**Dr. Leslie Whitaker**, IRP, received a 2014 NIH FARE award.

**Dr. Javier Rubio**, IRP, received a 2014 NIH FARE award.

**Dr. Jana Drgonova**, IRP, was approved for appointment as a Staff Scientist.

**Dr. William Kowalczyk**, IRP, received the Intramural AIDS Research Fellowship and the 2015 FARE award.

**Dr. Melody Furnari**, IRP, received a 2015 NIH FARE Award.

## STAFF CHANGES

### New Employees

**Dr. Maureen Boyle** joined NIDA in June 2014, as the Chief of the Science Policy Branch (SPB) in the Office of Science Policy and Communications (OSPC). Prior to joining NIDA, Dr. Boyle was a Lead Public Health Advisor for Health Information Technology (HIT) at the Substance Abuse and Mental Health Services Administration (SAMHSA) where she coordinated efforts to promote the use of technology to improve the delivery of substance abuse treatment. Prior to joining SAMHSA, Dr. Boyle was an American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellow serving at the National Institutes of Health, Office of Behavioral and Social Sciences Research (OBSSR). In this role she led multiple initiatives to improve data collection and clinical quality measurement within behavioral health. Dr. Boyle received her Ph.D. in neuroscience from Washington University in St. Louis where she studied the genetic and molecular basis of depression and anxiety-related behaviors. She completed a postdoctoral fellowship at the Allen Institute for Brain Science where she investigated neuropathological, molecular, and genetic abnormalities in Autistic children and animal models of autism.

**Amy Bucheimer** recently joined NIDA's Grants Management Branch. Amy comes to NIDA from NCI, where she worked as a grants specialist for close to seven years. She has a B.S. in Psychology from Pennsylvania State University and a M.Ed. in Special Education from Millersville University, PA.

**Sara Crocoll** joined the Public Information and Liaison Branch (PILB), Office of Science Policy and Communications (OSPC), in May 2014, filling NIDA's newest position as Social Media Strategist. She manages NIDA's social media initiatives to enable dissemination of NIDA's scientific findings in language that is accessible to the general public. She oversees all NIDA social media platforms in order to promote a strategic, proactive social media presence that is well integrated with NIDA's traditional media outreach, Web content and design, and other dissemination mechanisms. Prior to NIDA, Sara was a Presidential Management Fellow with the National Institute of Allergy and Infectious Diseases and completed rotations with various federal communications offices over two years. She served in the United States Air Force (USAF) for four years as a Logistics Readiness Officer, and she is currently a Captain in the USAF Reserves, serving as a Public Health Officer. Sara holds a Masters in Public Health in Leadership from the University of North Carolina-Chapel Hill.

**Dr. Philip Krieter** joined DPMCDA's Chemistry and Pharmaceuticals Branch as a Health Scientist Administrator on July 27, 2014. Dr. Keieter has 30 years of experience working in the area of drug disposition in the pharmaceutical industry at various companies before he joined NIDA in 2014. He has done both discovery and development preclinical ADME studies and also designed and conducted clinical pharmacology studies. He received his doctorate at the Department of Pharmacology and Toxicology at the University of Iowa with postdoctoral positions at the Mayo Clinic and the University of Texas at Austin. At NIDA, he oversees bioanalytical aspects of studies and contributes pharmacokinetic expertise to Phase 1 studies.

**Dr. Roger Little** has been selected as Deputy Director of NIDA's Division of Neuroscience and Behavioral Research (DBNBR). Roger has over 16 years of post-graduate research in Neuroscience, including 10 years devoted to work at NIH. Most recently, Roger was a Senior Advisor at the National Institute of Mental Health (2006-2014). He also served as a liaison and coordinator for the NIH Common Fund, the NIH Blueprint for Neuroscience, and for Public Private Partnerships, coordinated involvement of NIMH staff in these activities, and is a program co-lead for NIMH for the Common Fund Genes, Tissue, and Expression initiative (<https://commonfund.nih.gov/GTEEx/index>). He led a trans-NIH workgroup to develop a new model for brain banking at NIH which is called the Neurobiobank (<https://neurobiobank.nih.gov/>) and is now funding via contract 6 brain banks and an IT system to federate them and facilitate access for researchers and provide information to the public. He also served as the NIMH Appeals Officer and helped develop institute policies. His areas of focus since coming to the NIMH in 2004 have been psychiatric and molecular genetics. Prior to NIH, he was a post-doc at the CDC-NIOSH where he conducted basic molecular neurobiology research focused on the neural signaling pathways related to astroglial activation in response to brain injury. Dr. Little has been recognized with over 25 awards since he began at the NIMH and serves on the Science Advisory Committee of the National Disease Research Interchange. Dr. Little received his B.S. in Biology and English from the University of Vermont and his M.S. in Neurotoxicology and Ph.D. in Molecular Neurobiology from New York University. His doctoral work involved cloning and characterizing a novel G-coupled protein receptor (the calcium-independent receptor of alpha-Latrotoxin or Latrophilin) which was identified because it is a specific receptor for one of the toxins in black widow spider venom. His Masters work involved the signaling mechanisms involved in astroglial activation following brain injury.

**Sussana Morales**, the latest addition to NIDA's Management Analysis Branch, has been at the NIH since 2001. Most recently she was a Management Analyst at the National Institute of Nursing Research where she specialized in continuity of operations planning, emergency response, and risk management. At NIDA, Ms. Morales will be leading our Risk Management Efforts as well as managing the composition and retention of OM's policies and procedures.

**Dr. Thomas Radman** joined DBNBR as a Health Scientist Administrator on June 15, 2014. Dr. Radman earned his doctorate from the City College of New York conducting research on the electrical stimulation of neural tissue in the lab of Dr. Marom Bikson. Following graduate school he conducted post-doctoral research pertaining to cognitive neuroscience, attention, multi-electrode implantable recording, current source density and signal processing at the New York University Medical Center, with co-mentoring by Dr. Charlie Schroeder and Dr. Helen Scharfman. Dr. Radman served for 3 years as lead reviewer and expert scientific reviewer in the subject areas of electrical stimulation and diagnostics, in the Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices in the Center for Devices and Radiological Health, FDA. At the FDA, Dr. Radman reviewed wide-ranging indications for ophthalmic and neurological devices for therapy and diagnosis and assembled center-wide internal curriculum to disseminate the current thinking on the safety and effectiveness for the electrical stimulation of neural tissue. Most recently, Dr. Radman has spent 2 years in Algorithm Development at medical device start-up BrainScope where he has created cutting edge machine learning tools to provide a diagnosis of traumatic brain injury utilizing EEG recordings. Tom is now leading our efforts in Big Data and helping grow our presence in computational neuroscience.

**Dr. Tanya Ramey** recently joined DPMCDA as a Medical Officer. Dr. Ramey is a psychiatrist with 18 years of clinical experience, and a physician-scientist with a 15-year-career in the pharmaceutical industry in clinical drug development, translational medicine, and medical affairs at Eli Lilly and Pfizer. She was an executive director and psychiatry lead in Pfizer's neuroscience research unit in Cambridge, MA, before joining NIDA in 2014. Dr. Ramey received her U.S. training in psychiatry at Vanderbilt University. She was previously an assistant professor of psychiatry at the Moscow State University of Medicine and Dentistry (MSUMD). Her Ph.D. is in psychiatric genetics. Her areas of expertise are in addictions, depression, anxiety, psychoses and cognition. She has an extensive experience in all phases of drug development. At NIDA she provides medical and safety monitoring for clinical trials, design and development of clinical trials protocols, and is involved in other pertinent aspects of drug development.

**Jennifer Schermerhorn** joined NIDA's Grants Management Branch in May 2014 as a Grants Management Specialist. Jen joins us from NIAID, where she was a grants management specialist for a little over 6 years. She is from Salisbury, Maryland and has a B.S. in Psychology from Salisbury University.

**Dr. Shelley Su** recently joined DNBDR's Behavioral and Cognitive Science Research Branch. Dr. Su received her Bachelor's degree from the University of North Carolina/Chapel Hill, where she studied memory reconsolidation, cue-induced drug seeking and relapse in animal models of drug abuse, working with Dr. Rita Fuchs. She then completed her graduate training at the University of California, Santa Barbara with a long-standing NIDA grantee Dr. Aaron Ettenberg, where she conducted research on the neurobiology of positive and aversive effects induced by drugs of abuse, the influence of extended access or escalation, the role of conditioned cue-associations, and sex differences. Her post-doctoral training was with Dr. Stan Floresco at the University of British Columbia, where she developed models for decision making and ways to understand cognitive flexibility during the addictive process. Dr. Su has vast experience in animal behavioral paradigms used to investigate diverse features of abuse and addiction, neurobiological techniques and approaches, and a sophisticated understanding of contemporary issues and problems falling within NIDA's priority research areas. She will be a great asset to DNBDR's program areas and the future of integrating behavioral approaches for studying substance use disorders.

**Yvonne Smith Walker** joined the OEA as a program specialist and will be the NIDA Guide Liaison responsible for coordinating the Funding Opportunity Announcement process. Before coming to NIDA/OEA, Yvonne Walker was a Program Specialist at the National Cancer Institute at Frederick. She was responsible for developing and implementing comprehensive plans and strategies for internal and external integration of day to day and long range projects, actions, and managing the education outreach program and other administrative functions within the Office of Scientific Operations. Prior to NCI, Yvonne worked for the Emergency Management Institute and National Fire Academy which is a part of DHS/FEMA located in Emmitsburg. She provided programmatic and administrative support for training specialists and branch chiefs developed and maintained briefing and training materials, also maintained numerous computerized databases. Yvonne is a veteran of the United States Air Force, serving from 2001 to 2009 as an Information Manager. She was responsible for the overall administration, management and life cycle of information and control of information resources as well as supervising a team of airmen and

providing workgroup management support. Ms. Walker has a bachelors' degree in Management Studies from University of Maryland University College.

### **Departures**

**Lisa Coleman** left the NIDA COAC as the COAC's Deputy Director on August 9, 2014 to return to the National Cancer Institute (NCI) where she will assume an Operational Contracting Officer position at the NCI's FFRDC Facility in Frederick MD. Amy Siller has assumed some of the Deputy functions while NIDA is recruiting to fill this vacancy.

**Dr. Augie Diana** left NIDA on June 24, 2014. Dr. Diana was a Health Scientist Administrator in the Prevention Research Branch from 2006 through 2014. Dr. Diana oversaw the SBIR program in DESPR, was an active member of the NIDA Worklife Advisory Committee, took the lead on a number of physical activity initiatives, and also was a member of NIDA TOADS. Dr. Diana's new position is Health Scientist Administrator in the Office of Extramural Science Programs in the Division of Extramural Science Programs at the NIH National Institute of Nursing Research. Dr. Diana's role will include overseeing the SBIR program at NINR.

### **Retirements**

**Loretta Beuchert** retired after 32 years at NIH. She started in 1982 at the Neurology Institute back in a time when the Collaborative Perinatal Project was coming to a close, working under Dr. Martha Denckla, Chief of the section of autism and related disorders. Loretta spent many years in at NINDS but has also worked in the Office of Director, National Heart, Lung, and Blood Institute, and in the Training Office in Building 1. The NIH Training Activities Committee (TAC) was established at that time and she wrote the newsletter for this trans-NIH committee. Loretta came to NIDA in January 2000 and has worked in the Office of Extramural Affairs ever since. At first managing I/START reviews and writing Council minutes among a myriad of other responsibilities before becoming the NIDA Guide Liaison. She considered this position her most challenging but at the same time the most interesting of all the various positions she's held at NIH, mainly because it gave her the opportunity to work with so many different people not only at NIDA but across the institutes.

**Deborah S. Wertz** of the Grants Management Branch, Office of Management retired from Federal service on June 28, 2014. Debbie's Federal career began 41 years ago when she was recruited directly from high school to work at Division of Research Grants/DRG (now Center for Scientific Review/CSR). She has also worked at the FDA, NCI, Center for Nursing Research (now NINR), and Agency for Health Care Policy and Research (AHCPR). Debbie was hired to work at NIDA 24 years ago by Jack Manischewitz (NIDA was under Alcohol, Drug Abuse and Mental Health Administration/ADAMHA at that time). She has administered many complex grant programs at NIDA including NIDA's Clinical Trials Network. We will miss Debbie and are very grateful for her outstanding service and commitment to GMB.



