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Poster Session I - Monday

1. Differences in rCBF Response between Abstinent Cocaine-addicted Subjects and Healthy Controls to the 5HT3 Antagonist, Ondansetron

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Sponsor: David Self

5HT3 receptors are abundant in central dopamine terminal areas, such as the nucleus accumbens and striatum. These 5HT3 receptors, normally quiescent under basal conditions, appear to mediate the excitatory effect of compounds acting upstream from dopamine neurons. Preclinical studies suggest that 5HT3 receptors mediate the stimulatory effects of cocaine, cocaine withdrawal, and cocaine-induced sensitization, and that chronic cocaine administration alters 5HT3 receptors on the nucleus accumbens (NAc). Furthermore, the 5HT3 antagonist ondansetron may decrease drinking in early-onset alcohol-dependent subjects. Our previous studies have revealed that the regional cerebral blood flow (rCBF) response to procaine, a limbic-stimulant with relatively high affinity to the 5HT3 receptors, was different in cocaine-addicted subjects compared to controls. The present study was therefore designed to specifically assess differences in the 5HT3 receptor systems in men and women with cocaine-dependence. Methods: Cocaine-addicted subjects (25 to 45 y/o) (n=6) were studied at two to six weeks abstinence. Exclusion criteria included any lifetime history of a co-occurring Axis I non-substance use disorder (except nicotine or caffeine) or history of any substance use disorder (except nicotine or caffeine) in the previous six months. Addicted subjects were compared to age-matched healthy controls (n=6). Subjects were administered ondansetron 15 mg/kg by intravenous infusion over fifteen minutes, followed fifteen minutes later by the radioligand Tc-99m HMPAO. Ondansetron and saline sessions were counter-balanced and at least 48 hours apart. Single photon emission computed tomography (SPECT) was used to compare the rCBF response to procaine and saline. SPM99 analytic techniques were used to assess differences within groups. Significant differences are reported at $p < 0.01$. Results: In controls, increased rCBF was observed in the right orbitofrontal cortex (OFC) and NAc region following ondansetron in comparison to saline. Decreased rCBF was found in the medial OFC, anterior cingulate, and brainstem in controls following ondansetron. In cocaine-dependent subjects, the anterior cingulate and right anterior temporal cortex demonstrated increased rCBF following ondansetron relative to saline, whereas there were no regions of interest that showed a decrease in rCBF. Conclusions: Differences between groups in the response to the 5HT3 antagonist ondansetron were noted primarily in the NAc region, OFC, and anterior cingulate. These findings suggest that chronic cocaine use alters 5HT3 receptor systems, possibly related to the chronic effects of cocaine upon dopaminergic receptors that are modulated by 5HT3 receptors. Alterations in ondansetron-induced rCBF are most prominent in brain regions associated with reward, craving, emotional conflict, impulsivity, and/or decision-making. 5HT3 receptor systems may therefore be implicated in relapse, offering preliminary evidence that these receptors may provide useful targets for medications in the treatment of cocaine addiction. This work was funded by NIDA 2R01DA011434.

2. Activity Of Orexin/Hypocretin Neurons Corresponds With Reward Value of Food or Morphine-Paired Stimuli

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Previously we found that the number of Fos+ neurons in the lateral hypothalamus (LH) increase with the amount of preference shown for food- or morphine-associated cues during conditioned place preference (CPP) testing. Orexin/hypocretin (OH) neurons in the LH send excitatory projections to dopamine (DA) neurons in the VTA, indicating a possible mechanism whereby LH stimulation could influence motivated behavior. We used double labeling immunohistochemistry to establish the number of OH cells that become Fos+ during preference testing. When compared to non-conditioned animals, exposure to environments previously paired with either morphine, cocaine or food produced a significant increase in Fos+ OH cells in the LH. Furthermore, there was a significant correlation between the amount of preference and the number of Fos+ OH cells in the LH. This indicates that activation of OH cells in the LH maybe involved in the preference (or craving) for reward-related cues. In additional studies, we found that microinjections of orexin A (500 nM) into the VTA, or of rat pancreatic polypeptide (rPP, a potent stimulator of OH cells; 150 nM) into the LH reinstated an extinguished CPP for morphine similar to an injection of morphine. These data indicate that OH cells in the LH are active during reward seeking and may play an important role in activating the VTA DA system during reward seeking behavior. Support contributed by PHS grant DA06214.

3. Effects of D_1 Ligands on Cocaine's Reinforcing Strength in Monkeys

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The success of the partial agonist/antagonist buprenorphine in the treatment of opioid addiction has spurred interest in the preclinical evaluation of pharmacologically analogous medications for psychostimulant addiction. The present experiments were conducted to characterize one such candidate medication, the dopamine D_1 partial agonist/antagonist SKF 83959 by comparing its effects on cocaine's relative reinforcing strength to the effects of other D_1 ligands. The effects of SKF83959 and comparison drugs on cocaine's relative reinforcing strength were evaluated in rhesus monkeys that self-administered psychostimulants under concurrent 30-response fixed-ratio schedules of reinforcement (FR30: food; FR30: i.v. injection). Initial studies showed that the relative reinforcing strength of i.v. cocaine, measured by the distribution of behavior on the food-lever and injection-lever, was dose-dependent under these conditions. Thus, subjects allocated behavior exclusively to the food-lever when vehicle or low unit doses of cocaine (<0.01 mg/kg/injection) were available for i.v. delivery. Approximately 50% of behavior was allocated to the injection-lever when a threshold unit dose of cocaine (0.01 mg/kg/injection) was available for i.v. self-administration, and subjects responded exclusively for i.v. injections of yet higher unit doses of cocaine (0.03 and 0.1 mg/kg/injection). Subsequent experiments were conducted to compare the modification of cocaine's relative reinforcing strength by D_1 ligands including the D_1 receptor blocker SCH 23390 (0.03 and 0.1 mg/kg), the D_1 high efficacy agonist SKF 82958 (0.1-1.0 mg/kg), and the D_1 partial agonist SKF 83959 (0.1-1.0 mg/kg). SCH 23390 produced dose-dependent decreases in the relative reinforcing strength of cocaine; pretreatment with 0.1 mg/kg

SCH 23390 shifted the function relating unit dose of cocaine to the distribution of behavior 3-fold rightward. A low or intermediate pretreatment dose of SKF 82958 or SKF 83959 (0.1 or 0.32 mg/kg) moderately attenuated the relative reinforcing strength of cocaine, evident in a slight rightward (<3-fold) shift in the cocaine dose-effect function. The highest pretreatment dose of both drugs (1.0 mg/kg) had more pronounced effects that depended on the unit dose of i.v. cocaine; each D_1 agonist greatly increased the relative reinforcing strength of the threshold unit dose of cocaine (0.01 mg/kg), yet markedly reduced allocation of behavior to the injection-lever during the availability of 0.032 mg/kg cocaine. These data suggest that D_1 agonists differing in efficacy comparably modulate the relative reinforcing strength of i.v. cocaine and that the direction of their effects may be opposite—accentuation vs. attenuation—when unit doses of cocaine differing in reinforcing strength are available for self-administration.

4. Schedule-Induced Reinstatement of Nicotine Self-Administration Self-Administration in Rats: Effects of Nicotine and Bupropion

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Sponsor: Past Travel Awardee, Memorial, 2003

Exposure to stressful stimuli induces reinstatement of drug-seeking and taking behaviors in human drug addicts as well as in laboratory animals even after extended periods of abstinence. Previous research also suggested that compared with the ratio schedules of reinforcement, interval schedules have aversive properties and are less preferred by the subjects. Also, it was argued that excessive behaviors such as polydipsia generated by intermittent schedules of reinforcement may have a stress-reducing role. Accordingly, exposure to the concurrent intermittent food reinforcement schedule retarded the extinction and reinstated the extinguished responding that was previously reinforced by water or electrical stimulation of the brain reward system. In the present study, rats were first trained to nose-poke for intravenous nicotine deliveries (0.03 mg/kg/infusion) during 30 consecutive training sessions (schedule requirements gradually increased to fixed ratio 5) before being subjected to extinction conditions for additional ten sessions. Then, the subjects were exposed to fixed time (FT) 1-min schedule of food reinforcement that resulted in a gradual recovery of the previously extinguished responding over the course of the next several days (subjects did not have to emit any responses in order to obtain food). When the schedule-induced behavior stabilized, animals were given drug tests with response-noncontigent pre-session administration of nicotine (0.1-0.4 mg/kg) or bupropion (5, 10, 20, or 40 mg/kg). Drug dose ranges were selected based on their ability to suppress intravenous nicotine self-administration, to affect responding under fixed interval 1-min schedule of food reinforcement and/or to attenuate FT 1-min schedule-induced polydipsia (assessed in separate sets of experiments). Using independent groups of rats, each drug dose was given once daily 15 min prior to the test session for a period of 21 days. Nicotine had no significant effects on the operant responding at any of the doses tested but tended to increase locomotion at the highest dose level with no evidence of sensitization developing to these motor stimulating effects. At 40 mg/kg, bupropion increased locomotor activity but only after two weeks of daily administration. Low dose of bupropion (5 mg/kg) facilitated nose-poke behavior during the first two days of administration and was without any appreciable effects during the remainder of this study. Higher doses of bupropion (10-40 mg/kg) reduced schedule-induced nicotine-seeking behavior with a maximum suppression of about 40% achieved on Day 6 and maintained until the end of the study. Thus, this study compared two existing treatments for nicotine addiction and revealed that bupropion, but not nicotine, may attenuate nicotine-seeking triggered by the exposure to schedule-induction contingencies. Supported by the Russian State Research Program #621/147/050 and the U.S. NIDA grant #R03TW00714.

5. CB1 Receptor Modulation of Opiate Reinforcement: Involvement of the Mesopallidal GABA Projection

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Sponsor: George Koob

Several lines of evidence suggest an involvement of cannabinoid CB1 receptors in the regulation of opiate reinforcement, though the neurochemical mechanisms involved in this process have not been elucidated. Because opiate-induced reductions in ventral pallidal GABA efflux are proposed to contribute to opiate reward, and CB1 receptors are densely located in the ventral pallidum (VP), the present study tested the hypothesis that CB1 receptors participate in the mediation of opiate reward through a modulation of opiate-induced inhibition of the mesopallidal GABA projection. Using in vivo microdialysis we found that ventral pallidal GABA efflux is significantly reduced by both intravenous heroin self-administration (20 μg/infusion, i.v.) and non-contingently administered morphine (3 mg/kg, i.p.). The morphine-induced reduction in pallidal GABA efflux was dose-dependently reversed by pretreatment with the selective CB1 receptor antagonist SR 141716A (1 and 3 mg/kg, i.p.). Consistent with our previous observation that the SR 141716A-induced reduction in heroin reward occurs through a dopamine-independent mechanism, we observed no effect of SR 141716A pretreatment on morphine-induced increases in nucleus accumbens dopamine. Moreover, there was no significant effect of SR 141716A on either cocaine-induced (10 mg/kg, i.p.) increases in accumbens dopamine efflux, or cocaine-induced reductions in pallidal GABA efflux, providing further indication that the effects of CB1 receptor blockade on opiate-induced reductions in pallidal GABA efflux do not result from a CB1 receptor-induced alteration in accumbens dopamine levels. Heroin self-administration (20 μg/infusion, i.v.; FR-1) was significantly reduced by bilateral infusions of SR 141716A (1 and 3 μg/side) into the nucleus accumbens shell, while intra-ventral pallidal SR 141716A infusions were without effect. These findings suggest a CB1 receptor involvement in opiate-induced reductions in ventral pallidal GABA efflux that is independent of opiate-induced increases in nucleus accumbens dopamine, and indicate that nucleus accumbens CB1 receptors play a role in the regulation of heroin self-administration.

6. Effects of Metabotropic Glutamate R5 Receptor Antagonists on Cocaine Self-Administration and Cocaine Discrimination in Rats

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In a recent report, mutant mice lacking the metabotropic glutamate R5 receptor subtype (mGluR5) did not self-administer cocaine and did not respond to the motor stimulant effects of cocaine (Chiamulera et al., Nature Neuroscience 4:873, 2001). Also in that report, the mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) decreased cocaine self-administration in wild type mice at doses that did not decrease food maintained responding. In another report, MPEP reduced cocaine conditioned place preference in C57BL6/J mice (McGeehan and Olive, Synapse 47:240, 2003). Although these previous findings are intriguing, to date, modification of the behavioral effects of cocaine through mGluR5 has been evaluated in only a few published studies and primarily in mutant mice or intact animals treated with MPEP. The goal of the present study is to test the hy-

pothesis that in intact rats, treatment with several standard and novel mGluR5 antagonists alters the reinforcing and discriminative stimulus effects of cocaine. Previously described mGluR5 antagonists including MPEP, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP), methoxy-MPEP and methoxy-MTEP, as well as the novel diaryl acetylene analogs YP272, YP282 and YP283 were synthesized in the Department of Psychiatry, Yale University / VA Medical Center. All of the compounds exhibited nanomolar IC50 values derived from an in vitro functional assay of phosphoinositol hydrolysis in cells expressing mGluR5 receptors and using glutamate as an agonist. The novel compounds were inactive in assays used for screening activity at mGluR1, mGluR2, mGluR4, mGluR6 and mGluR8 receptors. Several of the mGluR5 compounds have been evaluated in vivo in male Sprague-Dawley rats that were trained to self-administer cocaine (0.032-1.0 mg/kg, iv) in a standard self-administration assay or to discriminate cocaine (5.6 mg/kg, ip) from saline in a standard drug discrimination assay. Pretreatment with MPEP (18.0-32.0 mg/kg) reduced cocaine self-administration, but MPEP exhibited relatively low potency by the iv route of administration and was ineffective given by the ip route of administration in the same dose range. Administration of methoxy-MPEP (5.6-18.0 mg/kg, ip) dose-dependently decreased cocaine self-administration, and importantly, these same treatments did not alter food maintained responding in rats under similar experimental conditions. In the drug discrimination assay, the mGluR5 antagonists methoxy-MPEP and methoxy-MTEP (1.0-18.0 mg/kg, ip) did not substitute for the cocaine discriminative stimulus nor did they significantly alter the position or shape of cocaine dose-effect functions (0.18-18.0 mg/kg, ip). Ongoing studies are aimed at evaluating whether the novel mGluR5 antagonists YP272, YP282 and YP283 attenuate the reinforcing and/or discriminative stimulus effects of cocaine in rats. Standard dopaminergic agonists and antagonists are also being evaluated for comparison to the mGluR5 antagonists. Supported by NIDA DA07252, DA12142, DA16180, NARSAD and the Zaffaroni Foundation. Carried out in accordance with NIH guidelines (Guide for the Care and Use of Laboratory Animals).

7. Stress-induced Potentiation of Cocaine Conditioned Place Preference Requires Kappa Opioid Receptor Activation Through a GRK3-Dependent Mechanism

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Sponsor: Mark Hamblin

Repeated forced-swim stress (FSS) produced analgesia, immobility and potentiation of cocaine conditioned place preference (CPP) in wildtype C57Bl/6 mice, but not in littermates lacking the kappa opioid receptor gene. To address the underlying mechanisms responsible for stress-induced potentiation, the kappa agonist U50,488 was administered to mice at various intervals preceding cocaine conditioning. The U50,488 dose selected produced equivalent analgesia to that evoked by FSS. Mice given U50,488 60 min prior to cocaine showed a robust, nor-BNI-sensitive potentiation of cocaine CPP, whereas administration 15 min before cocaine significantly suppressed cocaine CPP. The results indicate that prior KOR activation is both necessary and sufficient for the FSS-induced potentiation of cocaine CPP. Pre-treatment with U50,488 also induced acute analgesic tolerance that may have contributed to the enhanced cocaine CPP. Supporting this hypothesis, mice lacking G protein receptor kinase 3 did not show acute analgesic tolerance or FSS-induced potentiation of cocaine CPP. However, inactivation of the kappa system by KOR gene knockout or acute receptor antagonism did not mimic stress-induced potentiation, suggesting KOR inactivation alone was not responsible. Alternatively, GRK3-mediated acute desensitization might have changed the mode of kappa receptor signaling. Prior studies suggested that internalization of G protein coupled receptors enhances coupling to the MAPK pathways. Consistent with this concept, kappa receptor activation by FSS or agonist treatment significantly enhanced p38-MAPK phosphorylation in striata of wild-type, but not GRK3 knockout mice. The results suggest a molecular mechanism that may underlie stress-induced potentiation of the reinforcing actions of cocaine.

8. How Does the Brain Modulate Cue-Induced Craving for Natural (Sex) and Drug (Cocaine) Rewards?

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Both sexual and drug cues can trigger profound desire/craving states that are difficult to manage. Though individuals with addictions may be at a particular disadvantage for modulating these states, it is our evolutionary legacy that even "normal", non-addicted individuals may struggle with the pull of natural rewards such as sex. Neuroimaging studies have implicated limbic activation in cue-induced craving ("GO!") for both natural and drug rewards; the brain regions responsible for successful craving inhibition are not yet characterized. We hypothesized that the brain's prefrontal circuitry, known to exert downstream modulation on limbic structures , would be activated when subjects attempted to inhibit ("STOP!") their craving by considering the negative consequences of a history-relevant activity (cocaine use or sex). We used ASL perfusion fMRI and our previously-validated video stimuli to study brain activity during attempted inhibition ("STOP!") of desire for cocaine (n=19 thusfar) or for sex (n=15 thusfar; young adult male non-users). Overall, neither the cocaine patients nor the young adult males were very effective inhibitors of their history-relevant craving states. "Attempted" vs. "successful" inhibition of cocaine craving was associated, respectively, with increased activity in the VLPFC (ventrolateral prefrontal cortex, a region responsive to aversive consequences) and ventromedial PFC (a region known to be compromised in cocaine patients, yet critical for advantageous decision-making). Young adult males showed robust limbic (amygdalar) activation ("GO!") to the sexual video cues, but were relatively ineffective in activating VPFC regions during attempted "STOP!". This lack of VMPFC activation in young male controls may reflect either an over-ride of frontal inhibition (during conditions of strong desire/subcortical limbic activation) and/or minimal attempts to inhibit their sexual arousal, as there was no consequence attached to their performance. To address this issue, future studies will examine the impact of behavioral incentives and medications (e.g., GABAegics such as baclofen) on participants' ability to modulate cue-induced craving for natural (sex) and drug (cocaine) reward. The "GO!"-"STOP!" neuroimgaging paradigm is being used both to reveal the brain substrates for inhibition of desire and to screen potential treatments for problematic desire states: the substance and non-substance addictions.

9. Formation of New Brain Cells During Prolonged Ethanol Abstinence

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Neuroprogenetor (NPC) cell proliferation increases aberrantly in regionally and temporally specific patterns following binge alcohol (EtOH) exposure. To investigate the effect of EtOH abstinence on neurogenesis and long term survival of proliferating NPC, adult rats were administered EtOH or control diet (3X a day

for 4 days) and then observed for withdrawal behavior between 10 and 24 h after the last dose of EtOH. At 48 h after the last dose of ethanol when no behavioral withdrawal was apparent, bromodeoxyuridine (BrdU) was administered (300mg/kg, i.p.) and rats sacrificed 28 days later. In the EtOH group, BrdU-positive (BrdU+) cells were noted across the entire hippocampus whereas few cells were noted in controls. The hilus (>700% $p<0.01$), dentate gyrus (>350%, $p<0.05$) molecular layer (>400%, $p<0.01$), CA1 (>500%; $p<0.05$) and CA2/3 (>650%; $p<0.05$) all showed significant increases in BrdU immunoreactivity (BrdU-IR). Triple fluorescent labeling for neuronal (NeuN) and glial (GFAP) proteins with BrdU revealed that cells in the dentate gyrus of EtOH rats do not differentiate into neurons at the same rate as in controls. In controls, 75% of BrdU+ cells co-label with NeuN versus 22% in the EtOH group. In the EtOH group most BrdU+ cells (>50%) do not label for either NeuN or GFAP. However, when neurogenesis is calculated, it is similar between EtOH rats and controls. Thus, EtOH abstinence is associated with cell genesis of an as yet unidentified population of new brain cells. These data suggest that EtOH abstinence causes abnormal cell proliferation those results in long-term changes in hippocampal neuroanatomy. (Supported by NIAAA)

10. DBH Genotype in Disulfiram Treatment for Cocaine Dependence

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Background: Disulfiram inhibits dopamine β-hydroxylase (DBH), which converts dopamine to norepinephrine in brain reward and other pathways. We identified a single nucleotide polymorphism (SNP), -1021C>T, at the DBH locus accounting for almost 50% of the variance in plasma DBH; the T allele associates with low DBH activity. We hypothesized that -1021C>T genotype may affect response to disulfiram for treating cocaine dependence. **Aims:** To evaluate pharmacogenetic interactions between -1021C>T and disulfiram. **Methods:** Subjects dependent on cocaine and opioids (N=128) completed 2-week buprenorphine induction, were then maintained on buprenorphine 24 mg SL daily, provided weekly group drug counseling, and randomized to double-blind disulfiram 250 mg daily or placebo for 12 weeks. **Primary outcomes:** proportion cocaine-positive urine tests (COC+) and treatment efficacy score (TES-number of cocaine-negative tests), based on 3x/wk urine toxicology testing. Subjects with CC genotype (high DBH; N=78) were compared with carriers of the T allele (low DBH: N=50). Because % COC+ during induction was correlated with % COC+ during treatment ($r=.73$, $p<.001$), and differed between disulfiram vs. placebo groups within genotype cluster (high DBH: 48% vs. 60%; low DBH: 57% vs, 47%), subjects were stratified into high (>50% COC+, N=64) and low cocaine severity during induction (<50% COC+, N=64) for data analyses. **Results:** In high- severity subjects, disulfiram vs. placebo was associated with greater reductions in % COC+ (mean±SD): 69±26 vs. 82±23, $p=0.21$) and higher TES (7.9 ±7.3 vs. 3.7±5.0, $p=0.13$) in T carriers but not CC subjects (%COC+: 88±22 vs. 83±25; TES: 2.3±3.7 vs. 4.2±7.5). For low severity subjects, cocaine use remained low and was not reduced by disulfiram or placebo in either genotype group. **Conclusions:** The findings suggest differential efficacy of disulfiram 250 mg daily in high-severity, T-carrier subjects; higher disulfiram dose may be needed for high DBH subjects; low baseline severity of cocaine use in some subjects creates difficulties for detecting medication effects. Supported by: R01 DA12422, K02 DA015766 and K24 DA00445, and the VAMC

11. Alcohol-seeking and Self-administration: Effects of Manipulations of Serotonin Function in the Nucleus Accumbens

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Sponsor: Past Travel Awardee, Memorial, 2003

Behaviorally relevant stimuli, including alcohol, are processed through the neural circuit involving the ventral tegmental area (VTA), the nucleus accumbens (NAcc) and the prefrontal cortex (PFC). It is hypothesized that serotonin (5HT) affects ethanol-directed behaviors by interacting with the VTA/PFC/NAcc system via projections from the dorsal raphe to the VTA and the NAcc. Studies are ongoing to assess both increases and decreases in 5HT activity throughout this circuit, and two previous experiments examined the administration of a 5HT1B agonist in the NAcc to determine the effects of decreased activity specifically in this region. Overall, the 5HT1B agonist preferentially decreased ethanol-reinforced responding with minimal effects on sucrose-reinforced responding, and seeking behaviors were more sensitive than drinking behaviors. For the present study, two parallel experiments assessed the effects of a 5HT1A agonist (8-OH-DPAT; 1-5.0ug), microinjected directly into the NAcc using the same sipper tube appetitive/consummatory model of ethanol access. The 5HT1A agonist binds postsynaptically in this region, mimicking the effects of 5HT specifically in the NAcc. Male Long Evans rats (n = 6-9/group) were trained to complete a single response requirement that resulted in access to 10% ethanol (Ethanol Groups) or 2% sucrose (Sucrose Groups) for a 20-min drinking period. In the seeking experiment, Ss were consuming an average of 0.74g/kg ethanol and making approximately 50-100 responses during intermittent non-reinforced sham (no drug) sessions (Sucrose Groups had similar baseline response levels). Microinjections of the 5HT1A agonist had no effect on ethanol- or sucrose-seeking. In the intake experiment, drug treatment decreased ethanol intake only at the highest dose, again with no effect on sucrose intake. Interestingly, ethanol (but not sucrose) intake was also decreased in the seeking experiment on the session following the non-reinforced/drug treatment session. Overall, the findings from this project show that ethanol-reinforced responding is more sensitive than sucrose-reinforced responding to manipulations of 5HT activity in the NAcc. Moreover, increases and decreases in 5HT activity at this point in the VTA/PFC/NAcc circuit had differential effects on seeking versus intake, suggesting that this area may play a complex role in the stimulus processing of external and internal alcohol-associated cues.

12. A Double-blind, Placebo-controlled Trial of Modafinil in Cocaine Dependence

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Sponsor: Charles O'Brien

Modafinil is a novel, wake-promoting agent that has been reported to blunt cocaine-induced euphoria in two controlled studies. This glutamate-enhancing agent may also normalize cocaine-induced glutamate depletion (reported by several studies in animals), increase frontal lobe metabolic activity (which is deficient in cocaine addicted patients), and reverse cocaine withdrawal symptoms. Results of our preliminary open-label study suggest that modafinil may facilitate cocaine abstinence and improve treatment retention in cocaine dependence. The current study is the first controlled trial to evaluate modafinil treatment of cocaine dependence. **Methods:** This double-blind, placebo-controlled study included 62 cocaine-dependent outpatient subjects. None of the subjects were addicted to other substances or had unstable medical or psychiatric disor-

ders. After signing informed consent, patients were randomized to receive modafinil 400 mg/day (n = 30) or matching placebo (n = 32) given as a single morning dose for 8 weeks. All patients received twice-weekly, manual guided cognitive behavioral therapy (CBT). Cocaine use was assessed by thrice weekly urine testing for benzoylecgonine (BE), a cocaine metabolite. Abstinence was conservatively defined as the number of BE negative urines supplied, divided by the total number of urines requested (ie, three per week). **Results:** There were no statistically significant differences in baseline demographic and clinical characteristics of the modafinil vs. placebo treated subjects. With regard to efficacy, modafinil-treated subjects had higher mean abstinence rates (42.3%) than placebo-treated subjects (24.0%), and longitudinal generalized estimating equation (GEE) models showed a significant main effect for cocaine abstinence in the modafinil-treated group compared with the placebo-treated group (odds ratio = 2.41, p = 0.03). Modafinil-treated patients were also more likely to achieve a protracted period (> 3 weeks) of cocaine abstinence (p = 0.05). Modafinil was well tolerated, there were no serious adverse events, and none of the 30 modafinil-treated subjects discontinued modafinil because of adverse effects. **Conclusions:** This randomized, placebo-controlled, double-blind study found that patients treated with modafinil attained significantly greater levels of cocaine abstinence than patients treated with placebo. If our findings are confirmed by larger controlled studies, modafinil may become a first-line treatment for cocaine dependence.

13. Cannabinoids Stimulate ATPase Activity of P-glycoprotein

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The ABC transporter P-glycoprotein (P-gp) has been increasingly recognized to play an important role in the absorption and disposition of a variety of drugs. Accumulating evidence indicates that P-gp is abundantly distributed in brain capillary endothelial cells and may greatly limit access of its substrates into the CNS. Marijuana is the most commonly used illicit drug in the United States. Delta-9-tetrahydrocannabinol (THC) is the main source of the pharmacological effects caused by the consumption of marijuana. Several other important cannabinoids which may be functionally significant include 11-nor-delta-9-THC-carboxylic acid (THC-COOH), cannabinol, and cannabidiol. Cannabinoids exert many effects through activation of G-protein-coupled cannabinoid receptors in the brain. To test the potential role of P-gp in the transport of cannabinoids across the blood-brain-barrier (BBB), the effects of the major aforementioned cannabinoids on ATPase activity were examined using P-gp expressing membranes in which stimulated inorganic phosphate was used as a marker of the binding affinity to P-gp. Verapamil was tested as a positive control substrate of P-gp. At concentrations ranging from 1 to 100 microM, verapamil caused apparent stimulatory effects on ATPase activity. All cannabinoids tested stimulated P-gp ATPase activity to some extent in a time- and concentration-dependent manner. The rank order for stimulation of ATPase activity (V_{max}/K_m) was verapamil (3.8) > THC-COOH (1.3) > cannabinol (0.7) > THC (0.1) > cannabidiol (0.05). Although cannabidiol exhibited the weakest stimulatory effect on P-gp ATPase, it inhibited P-gp ATPase activity in a concentration dependent manner with an IC_{50} value of approximately 40 microM. These data suggest that THC-COOH and cannabinol are substrates of P-gp while THC and cannabidiol are unlikely to be transported. However, cannabidiol inhibited P-gp ATPase activity in clinically relevant concentrations. Thus, interactions between cannabinoids at the level of P-glycoprotein in the BBB may affect the pharmacodynamics of marijuana by influencing the overall passage of these compounds into the CNS.

14. CDT Predicts Heavy Drinking Days in Adolescent Alcoholics: Preliminary Data

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Carbohydrate deficient transferrin (CDT) is a biological marker that has been shown to be sensitive and specific in detecting heavy alcohol consumption in adults. To date, there is no published evidence of its utility in adolescent alcoholic populations. The purpose of this study was to explore the usefulness of CDT as a biological marker for drinking among adolescents. Blood from 25 treatment seeking adolescent alcohol dependent subjects and 8 adolescent controls was collected and assayed for % baseline CDT levels. Alcohol dependent adolescents did not differ from controls on mean % baseline CDT levels (2.33 vs. 2.32), although alcohol dependent subjects endorsed significantly more drinks per drinking day, percent heavy drinking days, and peak number of drinks than controls. The relationship between drinking variables and % baseline CDT levels was examined for alcohol dependent subjects. Percent CDT was highly correlated with percent heavy drinking days (r=. 54; p<. 02) but not with drinks per drinking day or peak number of drinks. Data suggest that while CDT levels at baseline don't differentiate alcohol dependent adolescents from controls, CDT level is highly correlated with percent heavy drinking days among alcohol dependent adolescents. It is possible that adolescents have not been drinking heavy amounts for enough years to effect the liver metabolic pathway that will elevate CDT above normal levels but enough to begin to show changes related to drinking. CDT levels may be useful in clinical practice and research for detecting change in heavy alcohol consumption over time. Further exploration of CDT with a larger sample size in this population is warranted.

15. Decreased Monkey Brain Dopamine Utilization During Nicotine Withdrawal - Reversal By Nicotine

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The hypothesis for the present research is that repeated daily administration of nicotine produces changes in brain D_2 binding with [^{11}C] raclopride and DA utilization with ([β-^{11}C] L-DOPA. Six young *Macaca* mulatta monkeys were given 0.9% NaCl or nicotine in doses of 32 μg/kg (low) or 100 μg/kg (high) i.m. bid for 9 days. On the 10th day, PET measurements were repeated before and after nicotine administration. The PET studies were done in habituated, trained, and fully conscious animals. Compared to the control condition, the binding potential (k_3/k_4) of [^{11}C]raclopride in dorsal or ventral striatum did not change with either dose following acute, repeated nicotine, or in the nicotine abstinent state. These negative data in unanesthetized monkeys are similar to what we previously reported for single acute doses of nicotine. The effects of nicotine on monkey brain DA are apparently too small to be detected by [^{11}C]raclopride. Compared to control, acute nicotine in either dose did not affect the DA utilization rate constant (k_3) in dorsal or ventral striatum. However, in monkeys given nicotine repeatedly, after overnight nicotine abstinence, DA utilization was significantly reduced. Subsequently, nicotine increased DA utilization to slightly above control levels. The ventral striatum showed greater changes than the dorsal striatum. The reduced rate of DA synthesis as assayed with [β-^{11}C] L-DOPA during nicotine abstinence and its reversal by nicotine provides an important PET measure of brain nicotine dependence and withdrawal.

16. fMRI Study of the Interaction of Stress and Cocaine Cues on Craving

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Sponsor: Clinton Kilts

Cocaine-use related cues can elicit drug craving and drug-seeking behavior that provoke the maintenance of cocaine addiction and of relapse in treatment-seeking individuals. Stress can also provoke maintenance and relapse in cocaine addiction, possibly by activation of craving-related neural circuitry. Ten male subjects with cocaine dependence in early abstinence were studied in a functional magnetic resonance imaging (fMRI) paradigm. Subjects listened to and mentally re-enacted personalized scripts about cocaine use and about an emotion- and drug-neutral experience. Each of the two scripts were presented once during a stressor (anticipation of electrical wrist shock) and again without the stressor in a counterbalanced design. Cocaine craving ratings were obtained before and after each script. Blood oxygen level-dependent (BOLD) fMR images (3T) were analyzed with statistical parametric mapping software (SPM 99), using a threshold for significance set at $p<0.005$, uncorrected. Self-ratings indicated higher levels of cocaine craving during cocaine vs. neutral scripts ($p=0.03$). Both cocaine scripts activated the left insula compared to both neutral scripts. The cocaine script during the stressor was associated with greater anterior cingulate activation compared to the cocaine script without the stressor. The contrast of the cocaine vs. neutral script indicated significantly greater posterior cingulate activation in the presence of the stressor, but this contrast was not significant during the non-stress half of the session. An interaction analysis between script content and stress condition revealed an interaction effect in the posterior cingulate cortex, with greater activation during the cocaine script in the presence of the stressor. In conclusion, stress during cocaine use imagery enhanced the activation of brain areas associated with cocaine craving. These data support the hypothesis that stress may enhance maintenance and relapse in cocaine addiction by enhancing the salience of cocaine cues. Supported by the Office of National Drug Control Policy.

17. Genetic Linkage To Alcohol Craving In Mission Indians

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Alcohol dependence is a leading cause of morbidity and mortality in Native Americans, yet biological factors contributing to the disorder in this ethnic group remain illusive. Underlying alcohol dependence are appetitive drive states or instincts that: lead to drug "craving", contribute to compulsive drug usage, and influence relapse following abstinence. Studies determining whether craving has a genetic component and if so what genes may confer risk for craving have not previously been reported. The purpose of this set of analyses was to identify genetic loci associated with "craving" for the use of alcohol in a sample of reservation dwelling Native Americans with a high prevalence of alcohol use and dependence. Mission Indian participants gave a blood sample and completed an interview using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) which was used to develop the phenotype of alcohol craving defined as "strong desire for alcohol". One hundred pedigrees containing 885 individuals were used in the analyses. The data includes: 77 parent-child, 212 sibling, 26 half sibling, 8 grandparent-grandchild, 151 avuncular, and 245 cousin relative pairs. High density microsatellite genotyping was done as previously described. The total additive genetic heritability (H2r) was estimated using SOLAR. Variance component estimate methods were used to calculate LOD scores using SOLAR v2.0.4 and Merlin with similar results. A total of 280 out of a larger sample of 466 participants (60%) met the criteria for a lifetime DSM-III-R diagnosis of alcohol dependence. The estimated heritability (h2r) for the "strong desire for alcohol" phenotype in this population was 0.65 ± 0.06. Analyses of multipoint variance component LOD scores revealed evidence for linkage on chromosome 3 with a maximal LOD score of 2.2 and on chromosome 5 with a maximal LOD score of 4.5 These data represent the first family-based genome-wide chromosome segregation analyses using "craving" for alcohol as a phenotype, and suggest linkage to a region on chromosome 5, a site not previously identified in genomic scans for alcoholism related phenotypes. One assumption is that the long history of dependence on foraging and subsistence agriculture of Mission Indians may have led to selective enrichment of traits that improve genetic fitness, so called "thrifty" or "fat sparing" genes. We speculate that this same selective pressure may have enriched for genetic variants that increase the risk for consumption of calorie rich beverages such as alcohol. The regions identified in this analysis may play key roles in the development of alcoholism as well as other consumptive behaviors in this population. the localization of the genes involved may be productive in identifying the mechanisms associated with consumptive behaviors and make also reveal targets for the development of drugs aimed at treating such disorders.

18. GABRA2 Haplotype Frequencies Differ Significantly Between High Anxiety Alcoholics, Low Anxiety Alcoholics and Non-Alcoholics in Two Ethnically Diverse Populations

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Sponsor: David Goldman

GABAA receptors play a key role in the regulation of neuronal excitability. Ethanol and benzodiazepines show cross-tolerance and cross-dependence and many of their behavioral effects are mediated by GABAA receptor activation. GABAAa2 receptors (GABRA2) in the chromosome 4 complex, which are predominantly present in the hippocampus, are thought to play a major role in anxiety pathways sensitive to benzodiazepine therapy. The aim of our study was to capture genetic variation in GABRA2 by haplotype-based and single locus analyses and determine the relationship with alcoholism and anxiety. Two ethnically distinct populations were recruited: 332 men and women from a Plains American Indian tribe (187 alcoholics, 145 non-alcoholics), and 475 Caucasian men from Finland (239 alcoholics, 236 non-alcoholics). DSM-III-R lifetime psychiatric diagnoses were derived from the SADS-L (Plains Indians) and the SCID (Finns). The Tridimensional Personality Questionnaire Harm Avoidance (HA) scores, a dimensional measure of anxiety, were determined. Genotyping of nine SNPs across the GABRA2 gene (142 Kb) was undertaken by fluorescent exonuclease assays. Two haplotype blocks were identified; block 2 (7 SNPs) extended downstream from intron 4. There were four common (>5%) block 2 haplotypes in each population. In the Plains Indians, the most abundant block 2 haplotype was associated with DSM-III-R anxiety disorders in women ($p<0.05$), and in both groups of men it was associated with increased HA in alcoholics but not in non-alcoholics ($p<0.05$). There was no relationship between haplotype frequency and DSM-III-R alcoholism. Nevertheless, single locus analyses showed that 5 of the 7 SNPs were significantly associated with alcoholism. Closer inspection revealed that this was due to the increased frequency of both homozygotes in alcoholics, suggesting the existence of alcoholic subtypes with differing allelic association. Subsequent analyses showed that in both Plains Indians and Finns, high HA alcoholics (above mean HA of population) had the highest frequency of the most abundant haplotype, non-alcoholics were intermediate, and low HA

alcoholics (below mean HA of population) had the lowest frequency of this haplotype. In an inverse relationship, low HA alcoholics had higher frequencies of the less abundant haplotypes, non-alcoholics were intermediate and high HA alcoholics had lower frequencies ($p<0.05$). Analysis by sex in the Plains Indians showed that this finding was confined to men. In contrast, haplotype frequencies in non-alcoholics with high and low HA did not differ in either sample. The combination of haplotype-based and single locus analyses has shown that male alcoholics with high and low dimensional anxiety may be distinctive subtypes that have opposite GABRA2 genetic associations. A functional GABRA2 polymorphism has not yet been identified. However, other studies have shown that both alleles of a common functional polymorphism (e.g. 5-HTTLPR and COMT Val158Met) can contribute to subtypes of a heterogeneous disease such as alcoholism.

19. The Effects of Exogenous Progesterone Administration on the Response to Smoked Cocaine in Men

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In non-treatment seeking male cocaine smokers, a cocaine dose-response curve was conducted on two occasions separated by 2-3 weeks: once when men were administered oral micronized progesterone and once when they were administered placebo. The order of progesterone and placebo administration was counterbalanced across men and the order of cocaine doses was randomized. During each phase, cocaine administration sessions occurred at 9:00 AM and again at 1:00 PM on 2 consecutive days, for a total of 4 sessions. During each session, participants smoked 6 doses of cocaine (either 0, 6, 12 or 25 mg cocaine base) at 14 min intervals. Oral micronized progesterone (150 mg) or placebo capsules were administered 2.5 hours before each cocaine session. The dose of progesterone was selected to mimic normal progesterone levels in women during the luteal phase. To date 9 men have completed the protocol. During the placebo phase, mean estradiol levels were 34.4 pg/ml and progesterone levels were 0.74 ng/ml. During the progesterone phase mean estradiol levels were 32.8 pg/ml and progesterone levels were 6.7 ng/ml. Cocaine produced dose-related increases in heart rate and blood pressure and progesterone administration, particularly after 25 mg smoked cocaine, decreased the cardiovascular response to cocaine. In contrast, Good Drug Effect, Drug Quality Ratings clusters and ratings of I Want Cocaine, and Like the Dose were increased when progesterone was administered compared to placebo, particularly after 25 mg cocaine. However, there were no differences in peak cocaine plasma levels between the two phases. These preliminary results indicate that exogenously administered progesterone blunts the cardiovascular effects of cocaine, but enhances the subjective effects of cocaine in men. These data are in contrast to previous data we have collected in women, showing that progesterone significantly reduces the positive subjective effects of cocaine. Supported by NIDA grant DA-08105 and NIH grant MOI-RR-00645

20. High Impulsivity Non-Smokers Have a Robust Brain Metabolic Response to Nicotine

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Sponsor: Steven Potkin

The brain mechanisms underlying the cause of nicotine dependence are unknown. Impulsivity traits are associated with increased susceptibility to nicotine dependence. We used FDG PET to measure brain metabolic response to nicotine administered by patch to 43 non-smokers, while the subjects performed a continuous performance task (CPT) or a control task. The Barratt Impulsivity Scale was used to divide subjects into those with low and those with high impulsivity traits. Low impulsivity trait subjects demonstrated no significant change in brain metabolic response to nicotine. In contrast, high impulsivity non-smokers demonstrated dramatic metabolic changes to low dose nicotine (3.5 mg. patch) while performing the CPT tasks, but not a control task involving retaliatory responding (Bushman 1995). In high impulsive subjects, nicotine patch activated cortical and subcortical structures bilaterally throughout the brain. The greatest differences were observed in the dorsal cerebral areas, including the dorsal visual stream, dorsal somatosensory, motor, premotor, prefrontal cortices, the dorsal interior cingulate, retrosplenial, parahippocampal cortices, and insula. Subcortically, increases were present in the medial and posterior thalamus, amygdala, and adjacent basalis nuclei, ventral mesencephalon, ventral/midline, and cerebellum. The observed differences were not a consequence of plasma nicotine or cotinine levels. These metabolic changes were not observed when subjects performed the control task. This PET study demonstrates a conspicuous lack of the brain metabolic response to nicotine in low impulsivity non-smokers in contrast to a dramatic impulsivity task-dependent brain response to nicotine in high impulsivity subjects. This biological difference in brain metabolic response to nicotine between high and low impulsivity trait subjects may explain differences in susceptibility to nicotine dependence. Supported by NIH grant DA13332.

21. Changes In 14-3-3 Protein Expression Mediates NMDA-Induced Neurotoxicity and the Neuroprotective Effect Of Δ9-Tetrahydrocannabinol

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In a previous study, we found that THC and capsaicin can protect AF5 cells from NMDA-induced cell toxicity, an effect apparently related to the antioxidant properties of these compounds. We have investigated the protective mechanism of THC and capsaicin. Gene expression patterns in AF5 cells exposed to NMDA, with or without THC, was analyzed by using a mouse developmental cDNA microarray. The 14-3-3 transcript (YWHAH) was down-regulated by 2.14-fold after exposure to 7.5 mM NMDA, while 14-3-3 expression was increased by 3.08-fold in the cells treated with THC prior to NMDA as compared NMDA alone. Capsaicin plus NMDA produced a smaller change, while WIN 55212-2 plus NMDA treatment produced no significant changes. The 14-3-3 transcript was not changed in cells treated with THC, WIN 55212-2 or capsaicin alone. Changes in 14-3-3 expression were quantified by QPCR. THC, but not capsaicin or WIN 55212-2 increased 14-3-3 zeta expression in NMDA-induced apoptosis. The 14-3-3 protein was detectable in AF5 cells by Western Blotting (30KDa), and was increased significantly following exposure to THC plus NMDA, as compared to NMDA alone. A primary function of 14-3-3 proteins is to inhibit apoptosis and this effect is mediated partially by the differential regulation of MAPK pathways. Mediation of NMDA and THC effects by the p38 MAPK pathway was therefore investigated. NMDA treatment increased phosphorylated p38 MAPK, while activation of phosphorylated p38 MAPK was blocked by pretreatment with THC. In addition, SB203580, a specific P38 MAPK inhibitor, inhibited cell death induced by NMDA in AF5 cells in a dose-dependent manner. These data indicate that 14-3-3 proteins and the p38 MAPK pathway are involved in the cell death induced by NMDA. The neuroprotective effect of THC is mediated, at least in part, by up-regulation of 14-3-3 protein expression and suppressing NMDA receptor-mediated activation of signaling pathways. The 14-3-3 proteins may therefore play an important role in the initiation of NMDA-induced apoptosis.

22. Regional Brain Metabolism and Negative Affect in Opiate Abusers Receiving or Removed from Long-Term Methadone Maintenance

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Sponsor: Edythe London

Objective: Methadone maintenance is the primary treatment for opiate addiction, but controversy surrounds the merits of its use in long-term treatment. This study tested whether subjects in protracted opiate abstinence, who had abused heroin have functional abnormalities in the neural circuitry that mediates negative affect, and whether such problems are less evident in individuals who are receiving methadone maintenance therapy. **Methods:** Three groups were compared on measures of negative affect and relative regional cerebral glucose metabolism (18F fluorodeoxyglucose positron emission tomography) while performing an auditory discrimination task. Fifteen former heroin users in protracted abstinence (over 6 months), twelve former heroin users receiving methadone maintenance (stable dose over 6 months), and thirteen control subjects from a residential treatment facility and the community participated. Self-reports of depressive symptoms and anxiety, and regional relative cerebral glucose metabolism were measured in brain regions implicated in negative affective states. **Results:** Methadone-withdrawn subjects had lower relative metabolic activity than control subjects in bilateral perigenual and the left middle cingulate gyrus. In contrast, methadone-maintained subjects exhibited lower relative activity (vs. control) in the left insula, the thalamus, and the left inferior parietal lobule; they exceeded control activity in the perigenual anterior cingulate gyrus and the right inferior parietal lobule. Measures of depression covaried positively with relative activity in the left perigenual and mid-cingulate gyrus in methadone-withdrawn subjects; analogous associations in control subjects covaried negatively. Methadone-maintained subjects exhibited negative covariance between state measures of depression and relative activity in the right inferior parietal lobule and the right perigenual anterior cingulate, and between trait measures of depression and relative activity in the left inferior parietal lobule. **Conclusions:** Methadone maintenance ameliorates functional abnormalities in the neural circuitry sub-serving negative affective states, but depresses brain function in some regions of high opiate receptor density.

23. Male African American Teenage Suicide Not Associated with Substance Abuse

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The goal of this investigation was to identify patterns and potential predictors for suicide in victims aged 20 and younger. The principal hypothesis was that completed suicide in this age group would be associated with a high degree of substance abuse, in particular ethanol (EtOH) and cocaine use. The death investigation and autopsy records for all suicides declared by the Fulton County Medical Examiner, from 01/01/1994 through 12/31/2002 were included. An experienced emergency psychiatrist (SG or DP) and a forensic pathologist (MH) examined and extracted these records. Information extracted from the records included age, sex, race, method of suicide, medical findings at autopsy, toxicology results, interval from self-inflicted wound to death, level of decomposition if present, and location of incident for each suicide victim. Teenagers were defined as those victims aged 20 and below and adults as those aged 21 and above and these terms are used interchangeably. Ethanol and cocaine toxicology was considered informative if it was affirmatively documented in the autopsy record and the autopsy occurred within 48 hours of death. A parallel analysis of national suicide statistics was undertaken, but cocaine and ethanol toxicology results are not reported in the national data. There were 62 suicide victims aged 20 and younger in Fulton County during the study interval; 34 (54.8%) black, 26 (41.9%) white, and 2 (3.2%) other-race minorities. The group specific suicide rate (suicides/100,000) for victims aged 10 to 20 were 10.5 for black males, 1 black females, 2.6 white females and 9.6 white males. Of the black victims, 84% were negative for cocaine or ethanol at autopsy, while 50% of the white victims were positive for one or both substance (χ^2=7.661, df=2, p=0.02). Only 2 (6.45%) of the black teenage suicide victims had used EtOH prior to death compared to 8 (33.3%) whites (χ^2=7.762; df=2; p<0.02). Teenaged (32.1%) and adult (38.4%) suicide victims had similar rates of detection of EtOH and cocaine at autopsy. In the Fulton County data set, logistic regression modeling indicates race as a significant predictive factor for teenaged suicide, with black teenagers having three times the risk of whites (odds ratio (OR) 3.08; 95% confidence interval (CI) 1.75-5.5; χ^2=19.879, df=4, p<0.0005). There were 4235 suicides in the United States in 1999 and 2000 inclusive that were aged 20 and below. Self-inflicted gunshot accounted for more than half (55.7%) of all teen suicides nationally. Logistic regression modeling revealed that non-white teenagers had twice the suicide risk of whites (OR 1.92, 95% CI 1.765-2.097) and males had increased risk compared to females (OR 1.25, 95% CI 1.15-1.36). This model was recalculated with race coded as white, black and other (whole model χ^2=230.729; df=4; p<0.0001) and black teenagers (OR 1.5, 95% CI 1.27-1,76) and non-white, non-black teenagers (OR 1.6, 95% CI 1.32-1.95) had increased risk compared to whites. Use of intoxicating substances does not appear to be the source of the increased risk for suicide in African American teenagers. Only a small proportion of black teenagers had used cocaine or ethanol prior to death compared to half of all white suicide victims.

24. Brain Imaging and Genetics of Dopamine Transporter in Bipolar Disorder

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Sponsor: John Nurnberger

Introduction: It has been hypothesized that intermittent periods of mania and depression seen in bipolar disorder (BD) may be due to increased and decreased availability of dopamine (DA), respectively. Reuptake activity of the dopamine transporter (DAT) protein is primarily responsible for termination of DA neurotransmission. Therefore, measurement of DAT may provide clues to the pathophysiology of BD. A population based study has reported DAT gene (SLC6A3) 3' VNTR polymorphisms on chromosome 5 to be associated with BD (1). Brain imaging studies have indicated that 10/10 and 9/10 genotypes are associated with differences in DAT availability as measured with SPECT (2,3). In our ongoing study, we investigated whether DAT availability is different in BD patients from matched healthy control subjects using positron emission tomography (PET) with the DAT specific radiotracer [11C] -CFT (2 -[11C]carbomethoxy-3 -(4-fluorophenyl)-tropane). We also investigated whether this difference is related to specific SLC6A3 VNTR alleles. **Methods:** Unmedicated BD patients, either in the euthymic or depressed phase, and matched healthy control subjects were included in the study. After signing informed consent, subjects were screened for any significant medical problems. Each subject received a structural MRI and a [11C] -CFT PET scan. **Image Analysis:** Images were

reconstructed with a conventional filtered backprojection algorithm with corrections for deadtime, scatter, and attenuation. Regions of interest (ROIs) were placed directly on average PET images on Caudate (eight slices), Putamen (six slices), and cerebellum (six slices) in both hemispheres. Time activity curves (TACs) were generated in MEDx (Sensor Systems, Sterling, VA), and then analyzed via a multilinear regression implementation of the Logan plot (4,5) using a reference region (cerebellum) as the input function. Binding potentials were estimated from each TAC as (BP = distribution volume ratio -1) and compared between groups. **Results:** A total of 9 BD patients (Age: 25 +/- 4; 4 M, 5F) and 5 healthy subjects (Age: 24 +/- 3; 2M, 3F) have completed the study. Preliminary analysis using ANOVA revealed a trend for significant difference between BD patients (2.1 +/- 0.3) and healthy subjects (2.45 + 0.4) for right putamen [11C] -CFT BP ($p = 0.07$). No significant differences were found between depressed ($n = 4$) and non-depressed BD patients ($n = 5$). Genotype analysis revealed that among BD patients 2 (22%) had a 9 genotype (one was 9/9 and one was 9/10) and 7 (78%) were 10/10. In healthy controls, 3 subjects had a 9 genotype (60%) and 2 were10/10 (40%). For all subjects combined, the right putamen [11C] -CFT BP was lower for those with the 10/10 genotype (2.1 +/- 0.3) compared to those with a 9 genotype (2.5 +/- 0.2;$p = 0.05$). BD patients with 10/10 genotype had the lowest values for right putamen DAT binding (2.03 +/- 0.2). **Discussion:** The striatum is an integral part of the brain's mood regulating circuit and changes in DAT transporter availability in this region maybe responsible for abnormalities in DA transmission seen in BD. More subjects need to be studied to confirm these findings. Conclusion: The combination of direct in vivo imaging of DAT availability and genotyping of subjects may reveal the relationship between SLC6A3 polymorphism and BD. References: 1. Kelsoe JR et al. Am J Med Genet 1996;67:533-40; 2. Heinz A et al. Neuropsychopharmacology 2000;22:133-9; 3.Jacobsen et al. American Journal of Psychiatry, 2000;157:1700-3; 4. Logan, J et al. J. Cerebral Blood Flow and Metabolism 1996;16:834-840; 5. Ichise M et al. J. Cerebral Blood Flow and Metabolism 22:1271-1281.

25. Mapping Cortical Gray Matter Abnormalities in Children with 22q11 Deletions

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The 22q11.2 deletion syndrome (22q11DS), also known as Velocardiofacial/DiGeorge Syndrome, is characterized by cardiac and craniofacial anomalies, marked deficits in visuospatial cognition, and elevated rates of psychosis. Although conventional volumetric methods have identified reductions in posterior brain areas in children with 22q11DS, gray matter abnormalities have not yet been mapped over the entire cortical surface in this syndrome. In this study, 15 children with confirmed 22q11.2 deletions (age: 12.2 +/- 2.98) and 7 demographically matched controls (age: 12.43 +/- 2.64) completed a 3-D MP-RAGE magnetic resonance imaging (MRI) scan at 1.5 Tesla. We used computational cortical pattern-matching methods to measure local proportions of gray matter at thousands of homologous cortical surface locations. Results indicate approximately 4.5 % global reduction in gray matter in children with 22q11.2 deletions, as compared to similarly aged controls, with the largest clusters of reduced gray matter density in the right-hemisphere frontal operculum, superior parietal, and extrastriate regions, areas critical for visuospatial processing. There was a corresponding reduction in thickness of the cortical mantle in right striatal cortex. Bilateral decreases were noted in primary somatosensory regions, but were of greater magnitude in the right hemisphere. In contrast, the left superior temporal gyrus was the sole region where a localized increase in gray matter was observed in patients with 22q11DS. These asymmetries of gray matter distribution suggest that aberrant lateralization may, in part, underlie the abnormal neurodevelopment associated with 22q11 deletions. There are at least 30 genes encoded in the deleted segment, several of which are highly expressed in brain tissue and known to affect early neuronal migration and brain lateralization (i.e., COMT, Goosecoid-like (gscl)]. These findings suggest a possible underlying pathophysiology of the cognitive deficits seen in this syndrome, and provide insight into complex gene-brain-behavior relationships.

26. Neurobiological Correlates of Social Conformity and Independence During Mental Rotation

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When individual judgment conflicts with a group, the individual will often conform his judgment to the group. Conformity may arise at an executive level of decision making, or it may arise because the social setting alters the individual's perception of the world. We used functional magnetic resonance imaging (fMRI) and a task of mental rotation in the context of peer pressure to investigate the neural basis of individualistic and conforming behavior in the face of wrong information. With a modification of a paradigm developed by Solomon Asch in the 1950's, we used fMRI to examine the alterations in brain activity associated with social conformity and independence. 33 normal adult volunteers mentally rotated three-dimensional objects and had to judge whether the objects were the "same" or "different". This task has been well characterized both behaviorally and with functional brain imaging, and activity increases in the intraparietal sulcus have been associated with the process of mental rotation. To induce conformity while performing the mental rotation task, on two-thirds of the trials, subjects were presented with the responses of four peers (2 male, 2 female), who, unknown to the subject, were actors giving wrong answers half of the time. On the remaining one-third of the trials, subjects made their judgments after mentally rotating the shapes but with the group's response blinded to them, thus providing a baseline measure of each subject's accuracy. To generate a credible social context, both subjects and actors performed a practice round outside the scanner on a network of five computers set up to give the illusion of interactivity. To differentiate the effect of social conformity from the conflict engendered by misinformation, each subject performed one round of trials with the group and another round in which the actors were replaced by computers. Independence was associated with increased amygdalar and caudate activity, findings consistent with the assumptions of social norm theory about the behavioral saliency of standing alone. Conformity was associated with functional changes in an occipital - parietal network, especially when the wrong information originated from other people, and these changes were not present when originating from an inanimate source. These findings provide the first biological evidence for the involvement of perceptual processes during social conformity.

27. Persistent Dysfunction of Cortical GABA and NAA Levels in Affective Disorders

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Advances in proton magnetic resonance spectroscopy (MRS) allow quantification of cortical gamma-aminobutyric acid (GABA)

levels in humans. GABA levels have been shown to be reduced in acutely depressed unipolar subjects with normalisation of levels following treatment. We have recently shown that the increase in GABA levels following treatment is more likely to be a pharmacological effect rather than a consequence of clinical remission. In order to ascertain state or trait abnormalities in GABA function we have now studied cortical GABA and n-acetyl aspartate (NAA) concentrations in a cohort of medication-free, euthymic subjects with unipolar and bipolar disorder using MRS. Methods: We studied 13 patients with a diagnosis of bipolar disorder type I who were off medication, euthymic and symptom free for at least 3 months. We also studied 12 patients who had experienced at least two episodes of major depression in the past and who were also off medication, euthymic and symptom free for at least 3 months in addition to a group of 14 matched controls. Occipital cortex GABA and NAA levels were quantified in all subjects with MRS on a 3.0T scanner. Results: Occipital cortex GABA/creatine ratios were significantly lower in euthymic, drug free bipolar subjects ($F=7.94$; $p=0.009$) and euthymic drug free unipolar subjects ($F=5.89$; $p=0.023$) than in age- and sex-matched healthy controls without a history of psychiatric disease. Occipital cortex NAA/creatine ratios also were significantly lower in euthymic, drug free bipolar subjects ($F=8.31$; $p=0.008$) and euthymic drug free unipolar subjects ($F=5.95$; $p=0.022$). Preliminary analysis of a subset of volunteers showed no significant differences in partial volumes of grey matter, white matter or cerebrospinal fluid in the voxel. Conclusions: We have found evidence for decreases in brain occipital GABA and NAA concentrations in euthymic, medication free, fully recovered subjects with a diagnosis of affective disorder. These may either be a reflection of dysregulated GABA-glutamatergic function, a consequence of neuronal loss as documented by post-mortem studies or secondary to alterations in other candidate neurotransmitter systems. Further studies are required to determine whether these changes are trait markers of vulnerability to affective illness or a consequence of the illness.

28. Autoradiographic Localization of AMPA Receptors Potentiator [3H]-LY451395 Binding and the Effects of LY451395 on Cerebral Glucose Utilization in Rat Brain

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The biaryl sulphonamide, LY451395, is a novel allosteric potentiator of the AMPA receptor subfamily of glutamate receptor ion channels. AMPA receptor potentiators have the potential for use in the treatment of a number of psychiatric and neurological disorders including depression, cognitive deficits associated with Alzheimer's disease, schizophrenia and Parkinson's disease. Quantitative autoradiographic techniques were used to characterize the binding of [^{3}H]-LY451395 to rat brain while ^{14}C-2-Deoxyglucose (^{14}C-2-DG) autoradiography was used to assess the effects of systemically administered LY451395 on cerebral glucose utilization. Low levels of binding of [^{3}H]-LY451395 were observed in the absence of added glutamate (500$_\mu$M). In the presence of added glutamate, binding of [^{3}H]-LY451395 was significantly higher in multiple brain regions. Under these conditions, [^{3}H]-LY451395 bound to sections of rat forebrain with 85-90% specific binding. Addition of the competitive AMPA receptor antagonist NBQX (50$_\mu$M) markedly reduced [^{3}H]-LY451395 binding. A high level of binding was observed in the CA1, CA2 and CA3 regions of the hippocampus, layers I-III of the cortex, and the molecular layer of the cerebellum. Moderate levels of binding were observed in the inner layers of the cortex, the caudate putamen, acumbens and dorsal raphe. Low levels of binding were found in the globus pallidus and the geniculate nucleus. The distribution of binding sites using the AMPA potentiator is comparable to that obtained in previous studies using [^{3}H]-AMPA. The effects of LY451395 were also examined on cerebral glucose utilization in the rat using ^{14}C-2-Deoxyglucose (^{14}C-2-DG) autoradiography. Male rats received a subcutaneous administration of LY451395 (0.15, 0.5 and 1.5mg/kg) or vehicle (5% DMSO, 24% $_\beta$CD) 15 minutes prior to administration of 50$_\mu$Ci ^{14}C-2-DG. Arterial blood samples were collected at fixed time points over the subsequent 45 mins. Cerebral glucose utilization was quantified in 40 anatomical regions using a computer based densitometer. LY451395 produced statistically significant increases in glucose utilization at the high dose of LY451395 (1.5mg/kg) which effected increases in 11 anatomical brain regions including hippocampus, frontal and parietal cortex, dorsal raphe nucleus and nucleus accumbens. These findings suggest that AMPA receptor potentiator, LY451395 enhances specific AMPA receptor mediated processes in the cortex and limbic system.

29. Genetic Variants in the Alpha4 Subunit of Nachr and in COMT Predict Smoking-Induced Dopamine Release in Mesolimbic Reward Pathways

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Background: Despite a wealth of evidence that nicotine administration and smoking lead to dopamine (DA) release in the ventral striatum (VST)/nucleus accumbens (NAc), there is considerable variability in the extent of DA release in different individuals. Smoking-induced DA release in the VST/NAc is due (at least in part) to nicotine stimulation of nicotinic acetylcholine receptors (nAChRs) in DA-containing ventral tegmental area (VTA) neurons projecting to the VST/NAc. A possible explanation for the range of DA release seen with nicotine/smoking is genetic variability along this mesolimbic reward pathway. **Method:** 63 human smokers (> 15 cigs/d) underwent both genetic testing for known polymorphisms of components of the mesolimbic reward pathway and positron emission tomography (PET) scanning using the 11C-raclopride bolus-plus-continuous-infusion method to determine changes in brain DA concentration associated with smoking. PET scanning was performed after 3 hours of abstinence, and 43 subjects smoked a regular cigarette during scanning, while 20 subjects underwent the same scanning procedure but did not smoke. PCR and restriction enzyme analysis were used to determine genotypes for known polymorphisms of the alpha4 and beta2 subunits of the nAChR, the dopamine transporter, D2 dopamine receptor, and the enzyme catechol-O-methyltransferase (COMT). **Results:** The group of smokers who smoked during scanning had greater reductions in binding potential (BP) (an indirect measure of DA release) in VST/NAc regions than smokers who did not smoke. Within the group that smoked, smokers with the G/G genotype of the CHRNa4 polymorphism at the 26th nucleotide position of the intron2 region had greater reductions in BP in both the left (Students t-test, $p = .02$) and right (Students t-test, $p = .03$) VST/NAc when compared with smokers with the A substitution at this site. Smokers with the val/val genotype of the Val158Met COMT polymorphism had greater reductions in BP in the right VST (Students t-test, $p = .05$) and dorsal caudate (Students t-test, $p = .03$) than those with the met substitution. There were no other associations between genotype and smoking-induced BP change. **Conclusion:** Individual genetic variability in nicotinic and dopaminergic components of the mesolimbic reward system appears to account for some of the inter-individual differences in smoking-induced DA release. The CHRNa4 polymorphism result may represent differences in nAChR pre-mRNA stability or splicing which could affect the ability of nicotine to stimulate nAChRs on VTA neurons. The COMT polymor-

phism result may be due to low COMT activity in subjects with the met allele, leading to increased tonic levels of DA and less susceptibility to phasic smoking-induced DA release (compared to the val/val genotype).

30. Simple Auditory Processing in Schizotypal Personality Disorder

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Sponsor: Martha Shenton

Background: Schizotypal personality disorder (SPD) is genetically related to schizophrenia and shares many biologic features, including brain morphometric abnormalities. We have previously shown SPD subjects to have 21% reduced volume in left Heschl's gyrus gray matter, a region important for processing pure tones. The goal of this study was to determine whether SPD subjects activate this region similarly to control subjects while listening to tones in order to evaluate simple auditory processing in SPD. **Methods:** Thirteen male SPD and thirteen comparison subjects were recruited from the community, all neuroleptic naive. Subjects heard tones through headphones and were instructed to keep their eyes closed and to disregard the tones that they would hear. The paradigm consisted of 2 runs, each with 3 blocks of standard tones (500 Hz) and 3 blocks of deviant tones (75% 500 Hz, 25% 2000Hz standard), all 100ms with 10 rise and fall times. Between blocks was low level scanner background noise muffled by headphones. Activation from the deviant block was subtracted from the standard tone block. **Results:** Pilot data was available one SPD and one comparison subject. The control subject compared with the SPD subject demonstrated greater activation in the region of left Heschl's gyrus during the subtraction of the standard tones from the deviant tones.**Discussion:** These preliminary data suggested that SPD subjects may not process simple tones as well as control subjects. Further analysis of the remaining subjects is needed to confirm this hypothesis. If confirmed, these data would point to a deficit early in the auditory processing stream in SPD.

31. 6-[18F]Fluoro-A-85380, A New PET Ligand for the Nicotinic Acetylcholine Receptor: Studies in the Human Brain and In Vivo Demonstration of Specific Binding in White Matter

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Objectives: Nicotinic acetylcholine receptors (nAChR) are involved in various pharmacological effects of nicotine and are altered in various disease states, such as schizophrenia, Parkinson's and Alzheimer's diseases. The goal of this research is to develop suitable PET radioligands to study nAChR in humans. **Methods:** We prepared F-18 labeled nicotinic agonists, 2-[18F]fluoro-A-85380 (2-[18F]FA) and 6-[18F]fluoro-A-85380 (6-[18F]FA), and carried out comparative PET studies in baboons. These two ligands bind to the $\alpha4\beta2$ receptor (nAChR subtype associated with reinforcing effects of nicotine) with high affinity but without the pronounced toxicity of epibatidine. Tracer studies were carried out with 6-[18F]FA in six non-smokers (2F and 4M, 29-60 yr) (injection dose <4 mCi and <2 μg).**Results:** Our baboon studies showed that 6-[18F]FA displays better kinetics and higher specific binding than 2-[18F]FA (the distribution volume (DV) ratio for TH/CB was higher for 6-[18F]FA (2.5-3.5) than for 2-[18F]FA (1.9-2.1) at 180 min). We then conducted toxicology studies and obtained IND approval to use 6-[18F]FA for determining nAChR availability in humans. Studies were done in six normal controls (2F and 4M, 29-60 yr). There were no adverse effects associated with the administration of 6-[18F]FA (injection dose < 4 mCi and < 0.3-0.6 mg). The distribution of radioactivity was consistent with that of nAChR in human (TH>MB>CB>FC). Cortical brain regions peaked early (<60 min) and cleared rapidly; white matter accumulated F-18 and cleared very slowly so that at later times (> 4 hours) thalamus, brain stem, cerebellum, and white matter were clearly delineated. The fact that tracer uptake was relatively high in white matter was most intriguing. This uptake appears to be anatomically specific since it is observed in cortical white matter but not in the corpus callosum (CC). The average of DV ratio for TH/CC was >4.0. Our in vivo PET imaging studies in baboon further demonstrated that binding of 6-[18F]FA in baboon white matter can be blocked and displaced with unlabeled 6-FA and nicotine. Furthermore, the blocking of 6-[18F]FA binding in baboon white matter by nicotine was dose-dependent. This is the first in vivo demonstration of the specific nAChR binding in white matter, and it corroborates a recent in vitro autoradiographic study in human brain sections using 5-[125I]-A-85380 showing relatively high concentrations of nAChR in white matter. **Conclusion:** PET images with 6-[18F]FA in human demonstrate high brain uptake and the distribution of radioactivity was consistent with that of nAChR (predominantly $\alpha4\beta2$ receptor subtype) in humans. These results demonstrate: (1) 6-[18F]FA is a suitable radioligand for quantitative PET studies of nAChR in the human brain and that a total 4 h study with 2 h actual scanning time is adequate for kinetic analysis; (2) white matter binding of 6-[18F]FA is specific for nAChR. These studies also showed that 6-[18F]FA is potentially a useful in vivo tool to better understand the role of nAChR in various diseases, and their relationship with the abnormality in white matter. Supported by USDOE/BER (DE-AC02-98CH10886), NIBIB, ONDCP and NIDA.

32. Decreased Striatal D1 Binding as Measured Using PET and [11C]SCH 23,390 in Patients with Major Depression with Anger Attacks

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Objective: This study assessed striatal D1 binding in patients with major depression with anger attacks (MDD+A) and healthy volunteers. **Method:** Positron emission tomography with [11C]SCH 23,390 was used to compare ten patients with MDD+A to ten healthy volunteers. **Results:** [11C]SCH 23,390 binding in bilateral striatum was significantly lower in the MDD+A group when compared to healthy volunteers. **Conclusions:** These results implicate striatal D1 receptor dysfunction in MDD+A and further suggest an association between dopaminergic transmission and anger or aggression.

33. Effects of Social and Monetary Stimuli on the Reward Circuitry Activation in Healthy Volunteers

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Sponsor: Alan Green

Illuminating reward circuitry function in humans has important implications for understanding normal reinforcement processes

and the pathophysiology of neuropsychiatric illnesses. Although extensively investigated in laboratory animals, there is relatively less information about the direct impact of reward stimuli on local metabolic brain function from human studies. Since there are different types of reward, it is likely that individual brain regions may have differential responses predicted on the type of reward. With the aim of determining the differential impact of reward on human brain function, we examined the effects of two distinct categories of reward that were previously demonstrated to reliably activate reward centers in humans, (one social and the other monetary), on local hemodynamic responses using BOLD functional magnetic resonance imaging in 12 healthy volunteers (age=23.3, SD=1.8; 6 females and 6 males). The social reward was viewing attractive vs. average male and female faces. The monetary reward involved financial incentives incorporated in a gambling-like task, which allowed assessment of signal changes that either anticipate or accompany monetary gains and losses under varying conditions of controlled expectation. All images were acquired on a 3 Tesla Siemens Trio MR imaging system; event-related curves were reconstructed and analyzed using an established General Linear Model provided by the BrainVoyager analysis package. An algorithm for acquisition of distortion matched images developed at McLean Brain Imaging Center was employed to ensure correct registration of functional maps with brain structures in regions of severe magnetic field inhomogeneity. Preliminary analysis suggested that the faces task had relatively focal manifestations in medial prefrontal cortex and monetary reward had more diffused cortical and subcortical effects (including nucleus accumbens). A complete analysis including sex differences in brain activations in response to male vs. female faces will be presented.

34. Venotrolateral Prefontal Abnormalities May Underlie Depression Risk among Coronary Disease Patients

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Background: Although the co-morbidity of depression with coronary artery disease is well established, the pathophysiologic mechanisms possibly underlying this association are poorly understood. In this study, we sought to explore to what extent the presence of coronary artery disease[CAD] affects the phenotypic profile and the in vivo neurobiology of depression as measured by structural MRI and Proton MR spectroscopy. Specifically, in view of their involvement in affect regulation, we examined the possible pathophysiologic role of dorsolateral and ventral prefontal cortex (DLPFC and VPFC). **Methods:** Subjects included consenting adults of both genders, ages 40-65 with either a current MDD(n=15) or CAD(n=3) and healthy controls (n=13) age 40-65 without cardiac or mood disorders, who match the patient-subjects on the basis of gender and age (within 3 years). Mood and anxiety symptoms were assessed using both standard measures of current symptomatology (HRSD and IDS) and lifetime measures of mood and anxiety spectrum conditions. All subjects underwent an integrated MRI/1H MRS study and the UPMC MR Research center. 3D gradient echo imaging (Spoiled Gradient Recalled Acquisition SPGR) in the coronal plane was emloyed to obtain 128 images covering the entire brain. Morphometric measurements of the VPFC and DLPFC were conducted by trained and reliable raters blind to clinical information and according to methods established inn this laboratory. **Results:** With respect to both current and lifetime mood and anxiety symptoms, the MDD and MDD+CAD groups were quite similar and distinct from the CAD only and control subjects. However, this was not true for the measures of brain pathology. Analyses of covariance (ANCOVA) with age and intracranial volume as covariates revealed a significant group effect, with all patient groups showing significant reductions in right VPFC($p<.007$). Patients with comorbid CAD and MDD showed the smallest VPFC volumes. When examined separately, right lateral VPFC (VLPFC)showed a robust effect ($p<.001$), but not the right medial VPFC. No group differences were seen with DLPFC volumes. **Discussion:** This is, to our knowledge, the first study to examine neuroanatomical correlates of co-morbid mood disorder in coronary disease. Our observations of decreased VLPFC volumes are consistent with functional imaging showing alterations in VLPFC activity in MDD. Decreased VPFC volumes were seen in both depression groups, suggesting that anatomic alterations in this brain region may underlie the etiologically heterogeneous depressive syndrome. Microvascular lesions in VPFC regions in CAD patients may be one of the etiological mechanisms that contribute to such propensity.

35. Cortical Gray Matter Volumes in Pediatric Bipolar Disorder

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Introduction: Cortical gray matter volume deficits have been described in adults with bipolar disorder (BPD). However, the presence of such deficits is less well-established in children with BPD. Based on the adult literature, we hypothesized that children with BPD would have cortical gray matter deficits in the frontal and temporal lobes. **Methods:** Thirty-two youth with DSM-IV BPD (ages 6-16 years) and 15 healthy controls (C) underwent structured and clinical interviews, neurological exams, neurocognitive testing and MRI scanning on a 1.5 Tesla, General Electric Signa Scanner. Image parcellation divided the neocortex into 48 gyral-based units per hemisphere, and these units were combined into frontal (FL), temporal (TL), parietal (PL), and occipital (OL) lobes. Volumetric and symmetric differences were examined using two-way (diagnosis and sex) univariate analyses of variance, covarying for age and total cerebrum. Subsequent analyses of four functional units of the PL (post central gyrus, precuneus, superior parietal lobule, inferior parietal lobule) were done using the same statistical approach. **Results:** Relative to controls, the BPD youth had a trend towards a smaller PL ($p=0.053$). Analysis of functional subsections of the PL indicated that there was a trend towards a difference in the left precuneus portion of the PL (an area with strong connections with the dorsolateral prefrontal cortex) ($p=0.06$, BPD< C) and a significant difference in the total post central gyrus ($p=0.04$, BPD< C). **Conclusion:** These findings are consistent with reports of cortical gray matter volume deficits in adults with BPD. However, children with BPD showed deficits in the PL cortical gray rather than in the frontal and temporal lobes as reported in adult studies. Additionally, the PL follow-up analyses suggest that areas subserving primary somatosensory processing and playing a role in attentional control, detection of response conflict, response selection and episodic memory retrieval are affected in children with BPD. Further replication of these findings with larger numbers is indicated.

36. Insula and Gustatory Inputs to the Caudal Limbic Striatum in the Primate

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The ventral striatum plays an established role in goal-directed behaviors based on inputs from the amygdala, and other brain regions that mediate emotional processing. Increasing evidence in rodent and primate models indicate that subregions of the striatum caudal to the ventral striatum may also mediate limbic-driven behaviors. We previously found that the central ventral putamen, lateral amygdalostriatal area and caudal ventral putamen which surrounds the amygdalostriatal area in the primate receive strong inputs from

the amygdala . This entire area can thus be considered a limbic territory of the striatum. In the present study we sought to determine whether the insula, another structure involved in emotional processing, also projects to these regions. Previous studies indicate that the anterior half of the insula innervates the classic ventral striatum, however, there are few data with respect to the caudal limbic striatum. We used retrograde studies to determine the extent to which specific subdivisions of the insula influence caudal ventral striatal subregions in the primate. Results were verified with anterograde tracer injections into the insula. The agranular and dysgranular insula have a strong input through out the caudal ventral striatal regions that receive input from the amygdala. In contrast, the granular insula makes a modest contribution only to the caudal ventral striatum. The majority of agranular inputs originate in the lateral rostral agranular insula on the caudal orbital surface, and ventral agranular insula. The dysgranular insula projects robustly to all caudal ventral striatal subregions. The gustatory cortex, a paralimbic area adjacent to the agranular insula, also has strong inputs, which overlap those from the insula, in the caudal ventral striatum. Taken together, caudal ventral striatal areas that are limbic-related by virtue of amygdaloid afferents receive significant innervation by the anterior insula. The anterior insula is interconnected with the amygdala, and has recently been implicated in mood induction paradigms. Afferents from the anterior insula, along with those from the amygdala, further support to the idea that the limbic striatum exists along a rostrocaudal continuum.

37. Correlations between the Neurochemical Profile Determined with Proton Magnetic Resonance Spectroscopy at 11.7 T and Dopamine and Serotonin Turnover in Rat Brain: Effects of Challenge with Serotonergic Agents

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While proton magnetic resonance spectroscopy (1H-MRS) is a powerful clinical tool to assess neurochemistry in vivo and MRS-visible neurochemicals represent a unique measurement in intact tissue (i.e. not a tissue extract or a microdialysis sample), their physiological significance remains to be determined. Therefore we sought to determine potential relationships between the MRS-derived metabolomic profile in rat brain and conventional measures of monoamine turnover after a pharmacological challenge. Male rats were treated with saline, the 5HT2 agonist DOI (5 mg/kg sc), or the SERT substrate MDMA (10 mg/kg sc) and sacrificed 60 or 20 min (respectively) later. Regions of interest (2.0x2.5mm punches, ~4mg) from monoamine projection fields were obtained bilaterally and the intact tissue subjected to high-resolution magic angle spinning 1H-MRS (4200Hz, 4C) with a Bruker 500 MHz (11.7T) using a CPMG pulse sequence. Absolute metabolite concentrations (mmolar) were determined with the LCModel using the H2O content measured in each tissue. The contralateral punch from each slice was sonically disrupted in perchloric acid, centrifuged and the supernatant analyzed directly for monoamines and metabolites with an ESA coulometric HPLC-EC. In the anterior medial dorsal striatum, DOI treatment significantly increased DA turnover (ratios), alanine, and glycine whereas 5HT turnover was decreased. MDMA treatment increased 5HT turnover, GABA, and glutathione whereas DA turnover was decreased. Multivariate analysis of principle components readily separated drug treated animals consistent with the changes observed with univariate analysis. Pearson correlation analysis revealed significant relationships in each group: DA turnover correlated with glycine, glutamine, and 1/aspartate in controls; DA turnover correlated with 1/aspartate and 1/glutamate after MDMA treatment; and DOI treatment eliminated correlations between the two measures. When drug treatment results were analyzed combined with controls, MDMA treatment was associated with significant correlations between DA turnover, 1/aspartate, 1/glutamate, 1/glutathione, and 1/alanine; 5HT turnover was correlated with glutathione. Analysis of the control-DOI data set revealed correlations between DA turnover, alanine, and glycine; 5HT turnover was correlated with glutamine. The results demonstrate the utility of a dual analytical approach (HPLC and MRS) and multivariate analysis of 1H-MRS derived metabolic profile to determine potential physiological relationships of 1H-MRS visible neurochemicals. Moreover, MDMA-induced decreases in DA turnover are associated with increased MRS-visible GABA and DOI-induced increases in DA turnover are associated with decreased MRS-visible glutamate. The causality of these relationships, as well as their robustness and regional specificity, remain to be determined. Finally, the results demonstrate the ability to explore neuronal circuitry using multivariate analysis of multimodal changes in neurochemical profiles. Supported by NIDA 16736 (MPG) and the MJ Fox Foundation for Parkinsons Research.

38. XXY (Klinefelter Syndrome): A Pediatric Quantitative Magnetic Resonance Imaging Study

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BACKGROUND: 47,XXY, or Klinefelter Syndrome (KS), the occurrence of two X-chromosomes in males, is the most common sex chromosome aneuploidy. XXY is associated with variable but characteristic physical and cognitive/behavioral features. The most consistent physical finding in XXY is hypogonadism. The most consistently documented aspect of cognitive impairment is language-based learning disorders; other reported deficits include impaired auditory processing, attentional difficulties, executive dysfunction, and motor delays. Visual-spatial processing abilities may be relatively preserved. Prior MRI studies of XXY subjects have been small and in older subjects. The objective of this study is to explore the neuroanatomical substrates of these cognitive/behavioral features during development. **METHODS:** Magnetic resonance imaging (MRI) brain scans and IQ testing were performed on 42 subjects with XXY (age range 5.3 to 26.0 years) and 87 healthy XY age-matched control males. MR images were acquired using a 3D-SPGR sequence on a 1.5T scanner (124 axial slices, 1.5mm thick). Scans were registered into standardized stereotaxic space, corrected for non-uniformity artifacts, and segmented using a neural net classification system. White and gray matter surfaces were fitted using a surface deformation algorithm resulting in two linked surfaces of 81,920 polygons each. Cortical thickness was defined as distance between corresponding gray and white matter surface vertices. Tissue classification information was combined with a probabilistic atlas to provide selected region of interest measures. Demographic differences between the groups were assessed with independent samples t-tests. Brain morphometric data was analyzed using both ANOVA and ANCOVA adjusted for total cerebral volume. **FINDINGS:** Lateral ventricle volume was approximately 34% larger and total cerebral volume (TCV) was approximately 7% smaller in subjects with XXY. All regional volumes except parietal white matter were also significantly smaller in the XXY group. When adjusted by ANCOVA for TCV, frontal and temporal gray matter remained significantly smaller in the XXY group. Parietal gray matter was not significantly different after ANCOVA while parietal white matter was significantly larger in the XXY group, indicating a relative sparing of this region. The caudate nucleus was approximately 10% smaller in the XXY group and remained significantly smaller after ANCOVA. The cerebellum was approximately 5% smaller in the XXY group and was not significantly different after ANCOVA. The midsagittal corpus callosum area was not significantly different between groups with or without ANCOVA. The cortex was strikingly thinner in the XXY group in three areas, (1) left inferior frontal, subserving executive functions and inhibition, (2) temporal, subserving functions related to language and social skills, and (3) superior motor, subserving functions of fine and gross motor skills. **INTERPRETATION:** The brain

imaging findings of preferentially affected frontal, temporal, and motor regions and relative sparing of parietal regions are consistent with observed cognitive/behavioral strengths and weaknesses for XXY subjects. These results suggest that both educational and therapeutic strategies should employ a more syndrome-specific approach that includes visual and hands-on learning as well as attention to early deficits in speech and auditory memory. It should be emphasized that these are group findings and do not imply that all individuals with XXY will have these brain/behavior features. However, exploring group differences between XY and XXY males may increase our understanding the effects of the sex chromosomes and hormones on brain development.

39. Dynamic Mapping of Cortical Brain Development in Pediatric Bipolar Illness

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Sponsor: Judith Rapoport

We report the first quantitative time-lapse movie of cortical development in pediatric bipolar illness, reconstructed from serial brain MRI scans of children with psychosis NOS who became bipolar I at 2-8 year prospective follow up. Prior MRI studies of gray matter (GM) changes in Bipolar Illness have shown inconsistent results with side to side differences although majority point to the abnormalities in fronto-striato-limbic circuitry. There are no longitudinal studies in pediatric mood disorders where the scans were obtained before and after the onset of Bipolar Illness. Applying novel cortical pattern matching algorithms to longitudinal brain MRI scans obtained before and after the onset of Bipolar I illness, we have created 3-D time lapse sequence of cortical development in the Bipolar I Illness. Twenty-four 3D (1mm isotropic) T1-weighted fast SPGR MRI scans were acquired from 8 children and adolescents, scanned repeatedly every 2 years, before and after the onset of bipolar illness, and compared with 42 scans from 14 age and sex matched healthy controls prospectively scanned at same time points. For both groups, 3D maps localizing brain changes were derived using gyral anatomy across subjects and time. A quadratic statistical model, with random effects, was fit to the profile of gray matter density against time, at each of 65,536 cortical points. Ratio maps of GM density of bipolar subjects over healthy controls were created and animated to create a time-lapse movie. This revealed significant regional GM change across the brain surface in bipolar subjects with side to side differences. The prefrontal cortical regions, temporal poles and inferior parietal cortex on the left side appeared to enlarge with the onset of bipolar illness, while these regions on the right side showed reduction in GM volume. The anterior and subgenual cingulate cortices also showed GM loss prominently on the right side. Our results indicate that the children with Bipolar Illness, despite being on similar medications, follow a different brain developmental trajectory compared to the children with schizophrenia. These results also highlight the importance of prefrontal and corticolimbic circuitries in the pathogenesis of bipolar illness.

40. Hormones Modulate Brain Activity in Affective Arousal in Normals: Implications for Sex Differences in Psychiatric Disorders

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Sponsor: Carl Salzman

Numerous behavioral studies have reported associations between mood and menstrual cycle status, independent of cognitive function and correlated with autonomic nervous functioning, particularly increased negative emotions & greater autonomic responsivity when estrogen is low. However, there are no imaging studies of the role of hormones in brain activity associated with affective regulation. An understanding of how hormones may mediate brain activity involved in affective arousal is important for an understanding of how this may go awry in a number of major psychiatric disorders. This fMRI study investigated the associations between brain activity in regions implicated in aversive affective arousal and hormonal status in normal women at two points in the menstrual cycle and in men. Brain regions of interest (ROIs) included nuclei in the hypothalamus, amygdala and brainstem, and frontoorbital cortex and anterior cingulate gyrus, brain regions involved in affective arousal and the hypothalamic-pituitary-adrenal (HPA) system. We hypothesized greater activation in women during early follicular compared with ovulation and that these ROIs in men would activate similarly to women in the early follicular phase. Twelve normal premenopausal women and ten men, selected to be comparable to the women sociodemographically, were recruited from a normal population study to participate and scanned twice (women at early follicular & ovulation & men, two weeks apart). Subjects undergoing fMRI were presented with slides from the International Affective Picture System (IAPS) designed to induce an emotion of negative valence and high arousal or neutral valence and low arousal; galvanized skin response (GSR) & heart rate were also collected. Using ROI analyses with SPM99, analyses were performed within each menstrual condition, comparing conditions, and comparing men to each condition. When activations during the two cycle conditions were directly compared, significant increases in BOLD signal changes (5-voxel minimum, at p=.005) in hypothesized central amygdala (effect size (ES)=3.38), ventromedial & paraventricular (PVN) nuclei (ES=3.36), frontoorbital cortex (BA47; ES=3.03), anterior cingulate (BA32; ES=2.80), and peripeduncular brainstem nucleus (ES=3.17) were found at early follicular compared to ovulation. Increased activations in these ROIs during early follicular were significantly correlated with autonomic arousal. Activations in men were similar to women during early follicular. Thus, findings demonstrated activation of brain regions implicated in agonistic behavior, or the "stress response", and HPA activity, and correlated with autonomic arousal. Further, we demonstrated significant BOLD changes at two points in the menstrual cycle, suggesting gonadal hormonal effects on BOLD changes in brain regions associated with agonistic behavior. Our findings suggest that estrogen has a moderating effect on a hyperaroused state in women, consistent with animal studies demonstrating an inhibitory role of estrogen on neuronal activity in the hypothalamus. Evidence from our current studies on the role of neuroendocrine dysfunction in mediating affective dysregulation in major psychiatric disorders with known sex differences will be discussed.

41. Temperamental Resiliency Modulates the Effects of Early Stress on Reward-Related Circuitry

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Sponsor: John Greden

Repeated exposure to stress early in life has lasting effects on stress-related neurobiological systems, including the HPA axis, serotonin, dopamine, and brain memory systems (hippocampus, amygdala and prefrontal cortex), and increases the risk of later psychiatric disorders, including substance abuse and depression. Temperamental resiliency is the ability to adapt flexibly to stress, reflecting individual differences in heritable personality tendencies, and is believed to serve as a moderator of risk for psychopathology. In the present

study we investigated the effects of temperamental resiliency on brain responses to negative affective stimuli in adolescents with high or low levels of early-life stress. We used fMRI in a sample of 26 adolescents drawn from the ongoing University of Michigan/Michigan State University Longitudinal Study of alcoholic probands and matched control families. Early stress was measured for each participant using scores from the Coddington's Social Readjustment Rating Scale. This questionnaire is filled out by the parents of each participant every three years, starting when the participant is 3 to 5 years old. It inquires about life events that occurred during the past 6 and 12 months of the child's life, and whether that event was positive or negative for the child. Temperamental resiliency was measured using the California Child Q-sort which is completed by a test administrator who knows the child and the family. It involves 100 statements that portray a variety of behavioral adaptations and the administrator sorts these into a normally distributed pattern that ranges from the most to the least salient descriptors of the child's behavior. We found that those adolescents who had high levels of early-life stress and also high resiliency had increased activity in the ventral striatum and extended amygdala in response to negative words compared with those who had high stress but low resiliency. This difference was not observed in those with low levels of early-life stress. These data provide important information on the early neurobiological processes associated with the later development of psychopathology in adolescence and early adulthood and may have relevance for early intervention and prevention.

42. In Vivo Evaluation of A New PET Radioligand for the Metabotropic Glutamate 1 Receptor

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Sponsor: Marc Laruelle

Introduction: The metabotropic glutamate subtype 1 receptor (mGlu1) is an important protein in the regulation of glutamate transmission in the brain. Over-stimulation of this receptor has been implicated in a number of neuropsychiatric disorders such as ischemia, epilepsy and anxiety. However, elucidation of this receptor subtype's function and its involvement in diseases has been hampered by the lack of selective radioligand. The goal of this study was to label with C-11 the potent and selective mGlu1 receptor antagonist R176898 (Ki 0.5 nM for mGlu1), and evaluate its potential as a PET radioligand for the in vivo imaging of mGlu1 receptor. **Methods:** [C-11]R176898 was prepared by Stille coupling of its trimethyltin precursor with [C-11]methyl iodide. Biodistribution studies in rats were performed under control conditions and with blocking agents. MincroPET imaging experiments were conducted with the Concord R4 microPET camera, following injections of high and low specific activity [C-11]R176898. **Results:** Preparation of [C-11]R176898 was carried out by reaction of the trimethyltin precursor with [C-11]methyl iodide, with Pd_2dba_3 and tri-(o-tolyl)phosphine as catalysts. The final product was produced in high radiochemical yield (>30%), high specific activity, and >99% radiochemical purity. Ex vivo biodistribution study in rats indicated a high uptake of [C-11]R176898 in the brain (%ID/g >1 at 10 min after injection). The highest activity level was found in the cerebellum, followed by hippocampus, striatum, frontal cortex, and medulla, in a rank order consistent with the distribution of mGlu1 receptor in rat (1). At 30 min post-injection, the cerebellum/medulla activity ratio was ~5, indicating a high degree of specific binding. Moreover, binding in mGlu1 receptor-rich regions such as cerebellum, hippocampus, and striatum was reduced to the level in the medulla by pre-treatment of the rats with R176898 or R206775, another selective mGlu1 antagonist (2 mg/kg each), but unaffected by MPEP (2 mg/kg), a selective mGlu5 antagonist, thus underlining the binding specificity and selectivity of [C-11]R176898 to the mGlu1 receptor in the rat brain. PET imaging experiments in a rat confirmed the findings of ex vivo biodistribution studies. Whe the rat was injected with high specific activity [C-11]R176898, radioactivity level rapidly increased in the cerebellum and peaked at ~10 min after injection. Moderate activity levels were also found in the hippocampus and striatum, and lower levels in the cortex. When the rat was given low specific activity [C-11]R176898, activity uptake was homogeneous across brain regions, indicating a blockade of the [C-11]R176898 binding sites by the cold compound R176898. **Conclusions:** Ex vivo distribution studies and in vivo PET imgaing experiments in rats demonstrated that binding of the new PET radioligand [C-11]R176898 in the rat brain is specific and selective to the mGlu1 receptor. It is therefore conluded that [C-11]R176898 is a suitable PET radioligand for the in vivo labeling of mGlu1 receptor in rats. 1. Mutel V et al (2000) J Neurochem 75:2590

43. Relationship of 5-HT1A and 5-HT2A Activity to Behavioral Inhibition in Healthy Women

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Background: Recent brain imaging studies, using monoamine radioligands in healthy subjects, have found negative relationships between 5-HT1A receptor binding and aggression (Parsey et al 2002), or self-transcendence (Borg et al 2003), or anxiety (Tauscher et al 2001) in frontal, temporal, and cingulate cortical regions, as well as negative correlations with 5-HT2A receptor binding and harm avoidance (HA) in frontal and parietal regions (Moresco et al 2002). **Methods:** We tested such relationships with the Temperament and Character Inventory (TCI) and the Spielberger State-Trait Anxiety Inventory (STAI) in 24 healthy women (HW) (age: 24.5 + 5.7 years, BMI: 21.8 + 1.5 kg/m2). PET and [11C]WAY100635 binding potential (BP) was used to assess pre- and postsynaptic 5-HT1A receptors in 16 HW and [18F]altanserin BP was used to assess postsynaptic 5-HT2A receptors in 20 HW. **Results:** HW showed significantly ($p < .05$, corrected for multiple comparisons) negative relationships between [11C]WAY100635 BP and novelty seeking or self-transcendence in frontal, temporal, cingulate, and parietal regions. No significant relationships were found for behavior and brain regions for [18F]altanserin BP. However, there were significant negative interactions between novelty seeking and a ratio of [11C]WAY100635 BP to [18F]altanserin BP in the medial orbital frontal cortex ($r = -.72$; $p = .01$), sub-and pregenual cingulate ($r = - .62$; $p = .03$ and $r = -.74$; $p = .006$ respectively), lateral temporal cortex ($r = -.74$; $p = .005$) and parietal cortex ($r = -.65$; $p = .02$). **Conclusion:** These findings add to a growing literature that raise the possibility that increased 5-HT1A receptor activity is associated with behavioral inhibition in healthy human subjects. In comparison, high novelty seeking, aggression, or self-transcendence may reflect a loss of inhibition. We also found that interactions between [11C]WAY100635 and [18F]altanserin binding were substantially associated with novelty seeking. Since cortical 5-HT1A and 5-HT2A receptors are co-localized and interact to control descending excitatory input into limbic and motor structures (Amargos-Bosch et al 2004), such interactions may modulate the expression or inhibition of a range of behaviors. For example, mixed 5-HT2A/1A agonists, e.g. psilocybin, seem to disrupt the 5-HT1A/2A balance by driving 5-HT2A activity, and thus resulting in excessive neuronal output contributing to extremes of disinhibition and disorganization.

44. Evaluation of a Benzodiazepine Receptor Agonist PET Radioligand, [11C]Triazolam, for Response to Pharmacologically Induced GABA Concentration Changes in Baboon Brain

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Sponsor: Herbert Pardes

Introduction: In vitro studies have suggested that agonist but not antagonist ligands at the benzodiazepine receptor (BDZR) site of the GABA-A receptor complex may show sensitivity to GABA levels by demonstrating concentration-dependent changes in affinity. These studies suggest that the established antagonist PET radioligand [11C]flumazenil does not respond to GABA concentration variations. An agonist ligand, [11C]triazolam, has previously been developed [1] and its properties evaluated [2] including test-retest reliability, blocking studies, and tracer kinetics modeling. The purpose of the current study was to evaluate in vivo response of this ligand to pharmacologically induced GABA level increase in baboon brain. **Methods:** Radiochemistry, anesthesia, arterial input function determination, region of interest (ROI) definition, and tracer kinetic modeling determination of total distribution volume, VT, for [11C]triazolam were as previously described [2]. Four 2-scan sessions each consisting of a 90-minute baseline scan followed immediately by i.v. administration of 300 mg/kg of the GABA-elevating anticonvulsant medication gamma-vinyl GABA (GVG), followed 3 hours later by the second scan (8 scans) were performed in 3 male baboons. **Results:** Injected dose, specific activity, and plasma clearance of radioligand were not different by repeated measures ANOVA between baseline and post-GVG scans. High test-retest reliability was previously reported across ROIs (centrum semiovale, brainstem, striatum, temporal cortex, frontal cortex, occipital cortex): VT variability averaged $5.90 \pm 3.51\%$ across regions and intraclass correlation coefficient was greater than 0.99 for all regions [2]. These ROIs exhibited no significant changes in VT induced by GVG administration (repeated measures ANOVA, p values ranging from 0.38 for occipital cortex to 0.52 for striatum). **Conclusions:** These studies failed to show an affinity shift of [11C]triazolam for the BDZR under pharmacologically induced elevation of GABA levels in baboon brain. The main study limitation was performance of the scans under conditions of general anesthesia with isoflurane, which may mask the GABAergic effects of GVG. Definitive evaluation of this or other agonist BDZR PET radioligands for responsivity to GABAergic tone will require studies with non-GABAergic anesthesia or no anesthesia. References: [1] Bottlaender M, Brouillet E, Varastet M, Le Breton C, Schmid L, Fuseau C, Sitbon R, Crouzel C, and Maziere M. J Neurochem 62: 1102-1111 (1994); [2] Kegeles LS, Hwang D-R, Waterhouse RN, Huang Y, Narendran R, Talbot PS and Laruelle M. J Nucl Med 44: 222P (2003); Grant support: NIMH, Lieber Center, Ritter Foundation.

45. Dissociation of the Effects of Childhood Trauma and Major Depression on the Neural Correlates of Emotional Memory

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Enhanced memory for emotional stimuli represents an evolutionary and social advantage, and the theoretical basis of psychopathology related to mood and anxiety disorders. As part of the Emory Conte Center studies of early life stress (ELS) we extended a previous $[^{15}O]H_2$ positron emission tomography (PET) study of neural processes related to emotional memory (Hamann et al., 2:289,1999) to a comparison of groups of adult women with/without histories of childhood abuse (+ELS/-ELS) and with/without current major depression and PTSD (+MDD/-MDD). PET images were acquired during the experiential processing of sets of visual images that were emotionally positive or negative (IAPS), or nonemotional neutral or interesting. Co-acquired behavioral data included ratings of the degree of emotional arousal and valence, and interest of the viewed image sets, and short-term (~10 min) and long-term (1 week) recognition memory for the viewed images. The +ELS and -ELS groups differed markedly in the neural response to the negative images with the +ELS group demonstrating a robust activation (relative to the neutral images) in the amygdala, hippocampus, hypothalamus, fusiform gyrus and the orbital and dorsal medial prefrontal cortex; the groups did not differ for the positive images. These results are consistent with the association of ELS with an exaggerated perceptual and self-referential processing of negative, but not positive emotional stimuli. Comparison of the +ELS/+MDD and +ELS/-MDD groups indicated that the +ELS effect on neural processing was attributable to the current presence of a MDD/PTSD diagnosis. These results suggest that MDD is associated with an exaggerated neural response and negative affective processing bias, perhaps modulated by a history of childhood abuse. Supported by NIMH058922

46. Emotion Processing in Borderline Personality Disorder: A Functional MRI Perspective

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Sponsor: Jack Green

Emotional instability is a core feature of borderline personality disorder (BPD). It is associated with highly disabling symptoms of BPD, such as suicidality, inappropriate anger, stormy relationships and identity disturbances. The biological underpinnings of the emotional instability in BPD are poorly understood. We employed functional MRI to compare patterns of regional brain activation in BPD patients and healthy volunteers as they process positive and negative emotional stimuli. Method: Blood oxygen level dependent (BOLD) fMRI images were acquired while eleven BPD patients and nine healthy volunteers viewed emotion inducing pictures of negative and positive emotional valence, selected from the International Affective Pictures System (IAPS). Activation data were analyzed with SPM99 ANCOVA models to derive the effects of diagnosis and stimulus type, as well as covariance with disease severity (quantified as self-reported levels of affective instability). Results: BPD patients demonstrated more extensive activation when viewing negative compared to positive pictures, and this difference was significantly greater than in controls. Greater activation to negative stimuli was observed in a network including the ventrolateral prefrontal cortex (BA47), the anterior and medial frontal cortex (BA9, BA10), and the cerebellum. Greater response to negative stimuli in BPD patients was significantly correlated with emotional instability, in the cingulate gyrus, fusiform gyrus, hippocampal and amygdala regions and precuneus. Conclusions: These findings suggest that BPD patients with affective instability process emotional stimuli via differently allocated brain networks than healthy control subjects. BPD patients appear to show greater activation of cerebellar structures and of brain regions involved in self-referential activity than do healthy volunteers when processing negative emotional pictures.

47. Developing Functional MRI Detection of Deception

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Sponsor: Mark George

Introduction: Deception, defined as the purposeful misleading of another, is ubiquitous in society. In two previous studies, we have

shown five areas of the brain (right orbitofrontal, anterior cingulate, middle frontal, inferior frontal and left middle temporal) that are consistently more active when telling a lie versus telling the truth at the group level of analysis (Kozel et al 2004a; Kozel et al 2004b). Unfortunately, at the individual level, the results were not consistent. Others have also found group, but not individual, differences in deception (Ganis et al 2003; Langleben et al 2002; Lee et al 2002; Spence et al 2001). In an attempt to improve the predictability of individual results, we have acquired data with 30 subjects in which to build a model to reliably distinguish deception from truth. This model is now being tested in a subsequent group of 30 subjects. **Methods:** Healthy men and women age 18 to 50 years were recruited. Subjects were initially consented and screened using SCID, urine drug test, pregnancy test, history, physical and Annette Handedness scale. For the imaging portion of the experiment, subjects were given a choice of two objects to "steal." They took one of the objects and placed it in a locker. Subjects were then scanned while being visually presented with a series of questions. The questions were regarding whether they took either object, as well as neutral and control questions. Subjects answered yes or no using a response glove. The BOLD fMRI scans (Philips 3T, EPI with SENSE factor of 2, TR 1.867, FOV 208, matrix 64x64, 36 axial 3 mm slices) were acquired while the subjects read and answered the questions using IFIS. Functional MRI analysis was performed using SPM2. Functional imaging dating was realigned and unwarped, slice timing corrected, spatially normalized and spatially smoothed. Individual t-maps were generated for various contrasts including Lie minus True, Lie minus Neutral, True minus Neutral, Lie minus Control and True minus Control as well as the inverse of these contrasts. To build the model, a random effects group analysis of Lie minus True was used to determine significant ($p<0.05$, FDR, $k>20$) clusters. Applying these clusters as regions of interest for each individual subject's contrast of Lie minus True, 3 of the 11 significant clusters accounted for 26 of 30 subjects having a significant activation. These three clusters were chosen as regions of interest to apply to individual t-maps of contrasts Lie/Truth minus Neutral/Control. **Results:** For the model building stage, 30 subjects (13 women, 1 left handed, average age 30.4 ± 8.3 years) were scanned. The group analysis of Lie minus True had significant ($p<0.05$, FDR, $k<20$) activation in the 5 regions previously identified. The three clusters identified as having the best predictive value were located in the right anterior cingulate, right orbitofrontal/inferior frontal and right middle/inferior frontal regions. Using these clusters as regions of interest, we were able to differentiate lies from truth using a subtraction technique with 93% sensitivity and 93% specificity. **Conclusion:** The principle finding of the first half of this study is that a model can be developed which could potentially predict deception with high sensitivity and specificity. Because these data were used to build the model; however, they cannot be used to test the model. The subsequent 30 subjects being scanned will be used to test the sensitivity and sensitivity of this method in a healthy population. These results will be presented.

48. Neurodevelopment of Fronto-temporal Connectivity: A DTI Study of Normal Adolescence

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Sponsor: Past Travel Awardee, Memorial, 2003

Background: With the recent introduction of diffusion tensor imaging (DTI), increasing attention has been paid to white matter (WM) abnormalities in schizophrenia. However, there have been no DTI studies specifically examining WM neurodevelopment in normal adolescence, when schizophrenia begins to manifest. In the present cross-sectional study, DTI was used to examine changes in WM microstructure during adolescence. It was hypothesized that fractional anisotropy (FA) would increase with age in the critical fronto-temporal connections that have been found to be aberrant in schizophrenia. **Subjects:** Subjects were 25 adolescents (15F/10M), ranging in age from 11.8-20.4 years (Mean/SD=15.2/2.1). Male and female subjects did not differ in age ($p>.65$). All were free of any history of psychotic disorders, major depression, and substance abuse/dependence, were neurologically normal, were not taking psychotropic medications, and had no first degree relatives with psychotic illness. **Methods:** Subjects were scanned on a 1.5 Tesla GE EchoSpeed MR scanner, using a pulsed gradient, spin-echo, single-shot echo-planar imaging method (TR=6s/TE=106ms; matrix=128; FOV=24cm; b=860s/mm2; NEX=4; 18 5mm contig. AC/PC-aligned slices). Diffusion was measured along six non-collinear directions, and an acquisition without diffusion weighting (b=0) was also acquired. After correction for eddy current distortion and movement, FA was computed for each voxel following derivation of eigenvalues/eigenvectors from the tensor; FA maps were then warped into Talairach space, using transformation parameters obtained from high-resolution 3D anatomic images (Ardekani et al., Neuroreport, 14:2025-2029). Spatially normalized FA maps were reconstructed with 1mm isotropic voxels and smoothed (6mm Gaussian). Voxelwise analyses of the relationship of age to these FA maps were conducted in SPM2 (simple correlation model). Nonlinear effects were modeled using the square and square root of age. Threshold for statistical significance (height) was set at $p<.001$ (min.100 contig. voxels). Significant regions were identified using the fiber tract atlas of Wakana et al. (Radiology, 230: 77-87). **Results:** Statistically significant, positive correlations of FA with age were obtained in three fronto-temporal association tracts: left and right uncinate fasciculus and left arcuate fasciculus. The left inferior longitudinal fasciculus was also positively correlated with age. At slightly lower thresholds, age was correlated with FA along the inferior fronto-occipital / longitudinal fasciculi bilaterally, running posteriorly through the temporal lobe from the uncinate to the arcuate. The only other significant result was obtained in right prefrontal cortex (superior corona radiata / paracingulate gyrus). Results did not change with nonlinear age terms. No statistically significant inverse correlations between FA and age were found. **Conclusions:** Findings suggest that WM coherence increases in fronto-temporal association fibers, particularly in the left hemisphere, across the adolescent years. These fibers, which connect critical brain regions such as Broca's and Wernicke's areas, are essential for normal language development. Combined with the prefrontal/ paracingulate region, these are precisely the WM tracts that have been reported to be abnormal in DTI studies of schizophrenia, which may represent a failure of normal neurodevelopmental processes of adolescence.

49. HPA Axis Dysregulation in Panic - Accumulating Evidence for a Non-Hypothalamic Source

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Sponsor: Israel Liberzon

Background: Evidence from animal work indicates that CRH is an important neurotransmitter in central circuits that mediate anxiety. This suggests a possible role for CRH and the HPA axis in the pathophysiology of anxiety disorders such as panic. There is evidence of HPA axis dysregulation in some studies of panic patients, but results have been inconsistent, suggesting that HPA axis dysregulation may not play a primary, etiologic role. Panic patients have shown inconsistent responses to CRH infusion and dexamethasone suppression, no HPA response in some laboratory panic models, and possibly elevated baseline ACTH levels in some challenge paradigms. We have examined HPA axis activity in a resting state paradigm and 2 challenge models. Our cumulative data suggest that any HPA axis dysregulation that may be found in panic patients likely comes from non-hypothalamic sources. **Methods:** Panic patients

were studied in three contexts: (1) at rest over a full circadian cycle, (2) before and after activation by a panicogenic respiratory stimulant (doxapram) that does not directly stimulate the HPA axis, and (3) before and after a CCK-B agonist that is panicogenic and does directly stimulate the HPA axis. **Results:** Panic patients had elevated overnight cortisol levels, which correlated with degree of sleep disruption. Overall ACTH and cortisol levels were higher in the doxapram challenge paradigm than in the resting state study, and this paradigm-related elevation was exaggerated in panic patients; but doxapram itself was able to elicit panic without associated HPA axis activation. Panic patients appear to have an exaggerated ACTH response to pentagastrin when it is given in a single visit design, but they appear to have normal HPA axis responses when given prior exposure to the experimental context or psychological preparation to reduce novelty and enhance coping. **Discussion:** All of the HPA axis abnormalities detected in 4 experiments using 4 different samples of panic patients can be attributed to exaggerated HPA axis reactivity to novelty cues. Novelty is one of a number of contextual cues known from animal work to activate the HPA axis. The hypothesis that HPA axis dysregulation in panic disorder may be due to hypersensitivity to contextual cues should be examined experimentally. A model in which such hypersensitivity may be created by abnormalities in supra-hypothalamic inputs to the HPA axis should be further explored.

50. The Neuronal Tryptophan Hydroxylase Gene (TPH2): Post Mortem Expression Analysis in the Human Brain and Molecular Genetic Studies in Depression and Suicidal Behavior

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The Tryptophan hydroxylase (TPH) gene is widely discussed as a candidate gene in many psychiatric disorders, which implicate disturbances of the serotonergic system. Numerous studies about genetic variants or different expression levels of the TPH gene in depression, schizophrenia, alcoholism, drug abuse, aggression and sucidality have been reported, but non of them have led to convincingly confirmed results. Until recently only one gene encoding TPH (TPH1) was described for vertebrates. Recently a second TPH isoform was identified in mice, designated as TPH2 or neuronal TPH, which was shown to be exclusively present in the mouse brain. In human post mortem studies we were recently able to demonstrate for the first time that TPH2 is also expressed in the human brain (frontal cortex, thalamus, hippocampus, hypothalamus and amygdala), but not in peripheral tissues such as heart, lung, kidney, duodenum, liver and adrenal gland. Further results of our study show that the mRNA expression of TPH1 and TPH2 is nearly identical in these regions except in the raphe nuclei and the pituitary. In raphe nuclei, the major locus of the serotonin producing neurons, TPH2 was the predominately gene (up to 10 fold increase), whereas in the pituitary TPH1 mRNA was expressed at up to 20 fold higher. These results suggest a priority role of the TPH2 isoform in 5-HT related behavior. This observations could be supported by SNP-, LD- and haplotype analysis with 300 depressed patients, 263 individuals who committed suicide and 265 healthy controls. Due to some preliminary positive results within a SNP screening over the whole gene we performed detailed analysis with 10 SNPs in the TPH2 gene spanning approximately 28 kb between exon 5 and exon 7. Significant association was detected between one SNP and MD, as well as suicidal behavior (global $p < 0.01$). Haplotype analysis produced additional support for association (global $p < 0.001$). This is the first report of an association between polymorphisms in the TPH2 gene and major depression, as well as completed suicide. Our finding opens up new research strategies for the analysis of psychiatric disorders with altered serotonergic function and might be a hint on the repeatedly discussed duality of the serotonergic system. Additionally, numerous genetic studies with the TPH1 gene in relation to psychiatric disorders, especially in sucidality have to be re-evaluated using genetic variants within the TPH2 gene. In conclusion further studies of this new TPH2 isoform in psychiatric disorders are needed to clarify the role of TPH2 in the pathophysiology of psychiatric diseases. This project is supported by the German Federal Research Ministry within the promotional emphasis "Competence Nets in Medicine".

51. Valproate Inhibits Myo-Inositol-1-Phosphate (MIP) Synthase

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Sponsor: RH Belmaker

Background: Although there is a plethora of biochemical and cellular effects of the two dissimilar mood-stabilizers lithium (Li) and valproic acid (VPA), their therapeutic mechanisms are unknown. Both drugs reduce intracellular inositol in mammalian brain and in yeast, but while lithium causes a parallel increase in inositol-1-phosphate, studies in yeast have shown that valproate causes a decrease in this metabolite. This suggested to us that myo-inositol-1-P (MIP) synthase, the rate-limiting step in inositol biosynthesis, may be the site of valproate's action on inositol metabolism. **Results**: Valproate inhibits MIP synthase activity in postmortem human brain homogenate with a Ki of 0.21 mM (0.35 mM is the lowest plasma therapeutic level). The effect is not obtained with other anticonvulsant mood stabilizers, typical and atypical antipsychotics and tricyclic antidepressants. Accordingly, only VPA upregulates expression of the yeast INO1 gene coding for MIP-synthase. In the rat neuron growth cones model Li and VPA show an additive effect, as occurs in the clinical use of these two drugs. The antiepileptic VPA derivative N-methyl-2,2,3,3,-tetramethyl-cyclopropane carboxamide (M-TMCD) reduces in vitro human brain MIP synthase activity and has an effect similar to VPA on rat neurons, whereas another VPA derivative, valpromide (VPD), poorly affects the activity and has no effect on neurons. Chronic lithium in food caused 33% upregulation of hippocampal MIP synthase expression and acute i.p. VPA resulted in a two-fold upregulation of frontal cortex MIP synthase expression. **Conclusion**: The study is a further example of the heuristic nature of Berridge's inositol depletion hypothesis. It suggests that inositol depletion may be the first event in the therapeutic mechanism of mood stabilization by Li and VPA, albeit, through inhibition of different enzymes, thereby offering a conceptual unification of how both drugs work in manic-depressive illness.

52. Probing Inflammatory Signaling Pathways in IFN-alpha-treated, HIV/HCV Co-infected Patients using Flow Cytometry

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Sponsor: Past Travel Awardee, Aventis, 2002

Objectives: There has been increasing interest in the role of inflammatory cytokines in the development of behavioral changes in patients with immune-related disorders, including patients infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Cytokines act through their receptors to stimulate inflammatory signal transduction pathways including activation of p38 mitogen activated protein kinase (MAPK) and NFkB. To further explore the relationship between behavioral changes and inflammatory signaling pathways, novel techniques must be developed to probe signal transduction in vivo. **Method:** Work in our laboratory is focused on the development of flow cytometric techniques to quantify p38 MAPK signaling in HIV/HCV-co-infected patients undergoing IFN-alpha treatment. IFN alpha is a potent inducer of

the inflammatory cytokine network and is associated with a high rate of behavioral changes, including depression, anxiety, fatigue, sleep disturbances and cognitive dysfunction. In preliminary studies, HT22 mouse hippocampal cells were treated with interleukin (IL)-1 alpha (1000U/ml), and p38 was measured using fluorochrome-conjugated antibodies to p38. **Results:** IL-1-alpha treatment was associated with a marked induction of p38-associated flourescence, which progressively increased from 30-120 minutes. This effect was inhibited with concomitant administration of the cAMP specific, Type IV phosphodiesterase inhibitor, rolipram (also previously used as an antidepressant). **Conclusions:** These results suggest that flow cytometric techniques can be a useful tool to explore the complex interactions between inflammatory signaling pathways and behavior in patients with infectious diseases including HIV/HCV co-infection. In addition, such techniques may help identify novel treatment strategies to reverse increased inflammatory activity in these individuals.

53. Remission and Maintenance Effect of Risperidone Augmentation for Older Patients with Resistant Depression

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Background: Both older age and medical comorbidity have been reported to be indicators of nonresponse to antidepressants. Thus resistant depression may be especially prevalent and challenging in older adults. Risperidone augmentation of citalopram for patients with resistant depression was evaluated in a multisite international study that included older patients. **Methods:** Inclusion criteria were adults aged 18-85 years; a DSM-IV diagnosis of major depressive disorder; and a HAM-D score ≥20. This analysis focuses on patients aged ≥55 years. All patients had failed at least one trial of an antidepressant in the current episode. In the open-label phase, older patients received citalopram monotherapy (20-40 mg) for 4-6 weeks to confirm nonresponse (defined as <50% reduction in HAM-D scores). Full nonresponse was defined as <25% reduction in HAM-D scores. All nonresponding patients were eligible to receive citalopram augmented with risperidone (0.5-1 mg) for 4-6 weeks. Patients who achieved symptomatic remission (HAM-D ≤7 or CGI-S 1 or 2) after 4-6 weeks of risperidone augmentation could then enter a 24-week double-blind phase to evaluate maintenance of effect, during which they received citalopram augmented with risperidone or placebo. Relapse during the double-blind phase was defined as a CGI-change score of 6-7, HAM-D score ≥16, discontinuation due to lack of therapeutic effect, or deliberate self-injury or suicidal attempt. **Results:** The patients' mean age was 63.4 ± 8.0 years and 56% were women. The mean duration of the current episode of depression was 2.0 ± 4.3 years; the mean duration of overall illness was 23.6 ± 15.0 years; 61% of subjects had received 2 or more antidepressants during the current episode. Of the 101 patients who completed citalopram monotherapy, 93 (92%) met the criterion for citalopram nonresponse; 89 (96%) of these completed open-label risperidone augmentation. In the open-label phase, sixty-three patients (68%) achieved remission and chose to enter the 6-month double-blind maintenance phase (n=32 risperidone augmentation; n=31 placebo augmentation). Median time to relapse was 105 days in the risperidone group and 57 days in the placebo group (P=0.069, Wilcoxon). Fifty-six percent of the patients in the risperidone augmentation group and 65% in the placebo augmentation group met study-specific relapse criteria. The majority of patients (n=40/63) who entered the double-blind maintenance phase were fully nonresponsive to citalopram monotherapy (<25% reduction in HAM-D scores). In these patients, the median time to relapse was 142 days with risperidone augmentation compared with 35 days with placebo augmentation (P=0.068, Wilcoxon). Treatment was well-tolerated; headache was the most common adverse event (n=3, risperidone group). **Conclusions:** In this population of older patients with poor response to standard treatments, these data suggest that risperidone augmentation resulted in symptomatic remission in a substantial number of patients and a clinically meaningful delay in time to relapse. A limitation of this study is the small number of older subjects participating in the trial. Supported by Janssen Medical Affairs, L.L.C.

54. A Placebo-Controlled Trial of Escitalopram and Sertraline in the Treatment of Major Depressive Disorder

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Escitalopram and sertraline are selective serotonin reuptake inhibitor (SSRI) antidepressants. The objective of this study was to evaluate the safety and efficacy of escitalopram and sertraline to placebo in the treatment of major depressive disorder (MDD). Outpatients (ages 18-65 years) with DSM-IV-defined MDD (MADRS≥22) were eligible to participate in this randomized, double-blind, placebo-controlled, multicenter, flexible dose trial. The study consisted of a one-week single-blind placebo lead-in, followed by an eight-week double-blind treatment period, in which patients were randomly assigned to escitalopram (10-20 mg/day), sertraline (50-200 mg/day), or placebo treatment. Dosing began at escitalopram 10 mg/day or sertraline 50 mg/day and was flexibly adjusted after one week of double-blind treatment. The primary efficacy endpoint was the mean change from baseline to Week 8 in MADRS total score using the LOCF approach. Response was defined as ≥50% improvement from baseline MADRS score, and remission as MADRS≤10. A total of 403 patients received double-blind study drug, of whom approximately 80% completed treatment. Baseline MADRS score was approximately 30 for each treatment group. Both escitalopram and sertraline led to statistically significant improvement relative to placebo in MADRS scores at endpoint, for both LOCF and Observed Cases analyses. There were no differences between active treatment groups in MADRS scores at endpoint. Response rates for both active groups (escitalopram 60%, sertraline 62%) were significantly greater than for placebo (42%) at endpoint (LOCF, $p<0.01$ active drug vs. placebo). Remission rates were also significantly higher for the active treatment groups (escitalopram 46%, sertraline 46%) than for placebo (27%, LOCF, $p<0.01$ active drug vs. placebo). There were no differences between any treatment groups in the rate of discontinuation due to adverse events (placebo 3%, escitalopram 6%, sertraline 4%). Both escitalopram and sertraline groups displayed significant improvement in efficacy relative to the placebo-treated group at endpoint, and were well tolerated.

55. Clinical Correlates of Triiodothyronine (T3) Augmentation of SSRI Treatment in Patients with Unipolar, Non-psychotic Major Depression

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The thyroid hormone, triiodothyronine (T3) is frequently used by clinicians to augment the effect of antidepressants in patients who manifest an inadequate response to treatment. The intervention has some support from controlled studies on the effect of T3 in patients who have not responded to tricyclic antidepressants (TCAs), as indicated by the meta-analysis of Aronson et al (Arch Gen Psychiatry. 1996; 53:842-8). An effect of T3 to accelerate the onset of action of TCAs was supported by the meta-analysis of Altshuler et al (Am J

Psychiatry. 2001;158:1617-22). It is unclear which patients will benefit from T3 augmentation, to what extent the effect is related to thyroid function and whether there is, indeed, a differentially positive effect in female patients as was suggested by the meta-analysis of Altshuler et al (2001) and supported by the algorithm-based study of Agid and Lerer (Int J Neuropsychopharmacology. 2003; 6:41-49). We have analyzed data from an ongoing randomized, double blind, controlled trial comparing the antidepressant effect of sertraline (50mg\day for 1 week and 100mg per day thereafter if tolerated) plus T3 (20-25mcg per day for 1 week, 40-50mcg. per day thereafter if tolerated) and sertraline plus placebo, for 8 weeks, in patients with unipolar, non-psychotic, major depression. 36 patients have been randomized to sertraline plus T3 (SERT-T3) and 28 to sertraline plus placebo (SERT-PLAC). Response was defined as a decrease of 50% or more in 21 item Hamilton Depression Scale (HAM-D) scores and remission as a HAM-D score of 7 or less at the end of the trial (last observation carried forward). Comparing the 29 patients who responded to sertraline plus T3 to the 7 patients who did not, there was no evidence for an influence of gender on response (SERT-T3 responders 51.7% female, non-responders 57.1%; $p>0.1$) nor of baseline thyroid function (TSH levels in SERT-T3 responders 1.75U [SD 1.04] non-responders 1.94 [SD 0.60] $p>0.1$) or severity of depression (HAM-D in SERT-T3 responders 19.6 [SD 3.9] non-responders 20.2 [SD 3.8] $p>0.1$). However, SERT-T3 responders received on average a significantly higher overall dose of T3 during the trial (SERT-T3 responders 36.4mcg [SD 6.5], non-responders 27.5mcg. [SD 7.7], $t=2.9$, $p=.006$). In the overall sample (including the group treated with SERT-PLAC) there was a small but significant relationship between improvement in HAM-D scores over the course of the trial and change in TSH levels ($r=0.29$, $p=.03$) but this was not significant in the SERT-T3 group alone. There were no significant differences between responders and non-responders to SERT-PLAC on any of the variables examined. These findings suggest that contrary to previous reports, male depressed patients respond as well to T3 augmentation as do female patients. Furthermore, the antidepressant augmenting effect of T3 may be dose related. [Supported by a grant from the Stanley Medical Research Institute]

56. Serotonin And Dopamine Candidate Genes In OCD Symptom Subgroups

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Sponsor: Travel Awardee, ADAA, 2004

Finding susceptibility genes for obsessive-compulsive disorder (OCD) may be complicated by genetic heterogeneity. It has been proposed that symptom subtypes are more etiologically homogenous and therefore should be targeted in genetic studies, particularly the symmetry/ordering phenotype which appears to be highly heritable. We set out to determine if variants in selected candidate genes were more likely to be associated with symmetry/ordering symptoms in families of OCD probands compared with other core symptoms. We genotyped 87 nuclear families for selected serotonergic and dopaminergic candidate genes: the serotonin transporter (5HTT), serotonin 2A (5HT2A), and the Dopamine 4 receptor (DRD4). Participants were assigned to symptom subgroups based on target symptoms identified on the Yale-Brown Obsessive-Compulsive Scale (YBOCS). The analysis for genetic association was conducted using the Family Based Association Test (FBAT). For the symmetry/ordering subtype, a statistically significant association was found only for transmission of 5HTT ($p=0.04$), a result which was not obtained when examining the sample as a whole or for the other subtypes. These results were not corrected for multiple comparisons. Overall, these findings provide preliminary evidence that the phenotype of symmetry/ordering may be associated with 5HTT, although further replication in larger samples is needed.

57. Morbidity from Onset in First-episode Bipolar I Disorder Patients: The International 300 Study

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Several recent studies report surprisingly high levels of sustained morbidity, particularly of major and minor depression, in bipolar-I disorder (BPD) patients in mid-course, treated clinically. Since it is not known when such incompletely-treated morbidity arises, we analyzed data from the Harvard-McLean First Episode Project, pooled with similar data from two collaborating European centers, to estimate proportions of weeks in specific morbid states in 303 first-episode, type-I BPD patients (164 men, 139 women; aged 32 12 years at intake) during systematic follow-up for 24 months from hospitalization for a first mania, and treated clinically. DSM-IV diagnoses of the primary disorder and of each episode were based on investigator-consensus from SCID examinations at baseline and 24 months, and all other available clinical assessments; morbid states not meeting DSM-episode criteria were considered "subsyndromal." Total percent-time-ill in episodes of mania/hypomania, major depression, mixed-states, or psychosis averaged 25% in men and 23% in women. All additional subsyndromal illness accounted for another 18% of time in men and 13% in women, for overall totals of 43% and 37% time-ill. Overall, morbidity for episodes ranked: hypomania/mania 10% > major depression 7% > mixed-states 8% > psychosis 0.2%; and subsyndromal morbidity ranked: dysthymia 11% > mixed-symptoms 4.5% (total, 40%). There was thus a 3-fold excess of depressive-dysphoric (30%) vs. manic-hypomanic-psychotic (10%) morbidity from the start of type-I BPD. The findings generally accord with reports on mid-course BP-I morbidity during ongoing treatment, and underscore the need to recognize and better-manage BP depression.

58. Withdrawal From a High Fat Diet: Obesity as a Stress-Sensitive Disease of Addiction

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Sponsor: Past Travel Awardee, BMS, 2002

We are interested in determining the genetics and mechanism by which increased stress susceptibility leads to dietary fat activation of brain reward centers causing food addiction and obesity. Obesity in America is currently at epidemic proportions and the fastest growing cost to our healthcare system. It has been estimated that 1 in 4 Americans will develop Type II Diabetes within the next decade as a consequence of this pervasive disease. Stress and the susceptibility of the individual to stress are key factors in the onset of such an addiction. While the genetics of stress sensitivity have not been extensively examined, studies indicate a major involvement of the corticotropin-releasing factor (CRF) family of ligands and receptors. Actions of CRF occur via stimulation of its first receptor (CRFR1), while ligand activation of the second CRF receptor (CRFR2) may function as a modulator of CRFR1 activity. Our CRFR2-deficient mice are a valuable model of increased stress sensitivity. In order to categorize dietary fat as a drug capable of activating reward centers, we have given mice a chronic high fat diet (45% fat by calories) and examined the expression of key components in the striatum of these mice as indicators of dopamine receptor activation. Additionally, striatal dopamine receptor occupancy following fat exposure has been quantified using GTP incubation prior to radioligand exposure. In addition, we have examined withdrawal aspects of a chronic high fat diet and demonstrated potent increases in 24 hr and 7-day withdrawal stress responsivity. Animals withdrawn from high fat also showed significant increases in locomotor activity and anxiety-like behaviors compared to animals withdrawn from a lower fat diet. Biochemically, downstream

dopamine signaling was significantly depleted in the striatum of mice following high fat withdrawal. Both phospho-DARPP32 and phospho-CREB levels were significantly decreased in the high fat group in both wild type and stress-sensitive CRFR2-deficient mice. The studies suggest that dietary fat can function as a drug of addiction in activation of reward pathways and presentation of withdrawal symptoms during its removal. Our results support the addictive property of dietary fat and suggest that obesity treatment may benefit from being managed as a disease of addiction. Future studies will further investigate dietary fat application necessary for stimulation of neurocircuitry in establishment of reward.

59. Escitalopram in the Treatment of Anxiety Symptoms Associated with Depression

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Sponsor: Murray B. Stein

Comorbidities are common in real life, and it is important to examine comorbid depres-sion/anxiety. In the present paper, the effect of the selective serotonin reuptake inhibitor escitalopram in treating the symptoms of anxiety in patients with major depression was investigated. Data from four previously published escitalopram studies that included a placebo arm were analyzed. Two of the studies also included a comparison with citalopram. In all studies, anxiety was assessed using the "Inner Tension" item (item 3) of the Montgomery-Asberg Depression Rating Scale. In two of the studies, anxiety symptoms were also assessed, either continuously over time or at baseline and endpoint, by using the Hamilton Rating Scale for Anxiety (HAMA), the "Anxious Mood" item of the HAMA (item 1), the Psychic Anxiety subscale of the HAMA (items 1-6 and 14) and the Anxiety/Somatization subfactor (items 10-13, 15, and 17) of the Hamilton Rating Scale for Depression. In all comparisons, mean improvement for escitalopram was significantly greater than for placebo. In some comparisons, escitalopram showed numerically higher improvement scores than citalopram. Thus, anxiety symptoms in depressed patients can effectively be treated with escitalopram.

60. Identification and Characterization of a Gene Predisposing to Both Bipolar and Unipolar Affective Disorders

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We have previously reported linkage analysis results that pointed to the localization of a gene for susceptibility to bipolar disorder (BP) in the chromosome12q23-24 region. These results were supported by follow-up analysis using 20 polymorphic microsatellite markers distributed over 7.7Mb of genomic sequence on 12q24.31. Moreover, association studies with these markers revealed significant allelic associations with BP for two loci, NBG6 ($p=0.008$) and NBG12 ($p<0.001$). We identified and genotyped polymorphisms in close to 40 genes around these markers. We were lead to focus on three adjacent candidate genes that overlapped NBG6 and had similar functional roles in cell signaling mechanisms. Mutation analysis in regulatory and coding regions of these three candidate genes allowed us to identify 105 variants, of which twenty-seven are found in coding regions. Forty-four SNPs were genotyped in the Quebec case/control sample (BP affected=213, control=214) to perform association studies. We identified five SNPs that gave significant association with either allelic association, genotypic association or both. In one of the genes, three of these polymorphisms are located in the intracellular C-terminal domain of the protein product, a domain known to be critical for protein function. The two other associated SNPs were found in the two adjacent genes and it is to be expected that SNPs in these proximal genes would be in LD. Using a sliding-window strategy with 15 successive SNPs, we observed significant haplotypic association ($p<0.001$) overlapping this genomic region. Further SNP-based association studies on this gene with a larger case/control sample (largely unipolar; BP/UP affected=315, control=220) of European origin demonstrated significant associations as well. Together, our data strongly suggests that, alone or in combination, polymorphisms in this gene can confer predisposition to BP/unipolar affective disorders. To confirm the role of this gene in affective disorders, we have performed functional and biological studies. The gene product is localized in hippocampus and is down-regulated by stress and up-regulated by antidepressant therapy. A reduction of gene expression in mice by small interfering RNA lead to a significant increase in passive behavior in the Porsolt forced swim test, which is generally construed as depressive-like behavior. Gene activity can also be regulated by known agonists/antagonists and while antagonists have no effect on behavior, treatment of mice with agonists reverses depressive-like behavior. Together these results clearly indicate the identification of a novel gene involved in the susceptibility to affective disorders and indicate new therapeutic approaches.

61. TDT Analyses Suggest Two Distinct Haplotypes in G Protein Receptor Kinase-3 (GRK3) are Associated with Bipolar Disorder

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Sponsor: John Kelsoe

In a genome-wide linkage survey we have previously shown evidence indicating chromosome 22q12 contains a susceptibility locus for bipolar disorder (BPD). Two independent family sets gave lod scores of 2.19 and 2.72 at or near marker D22S419 which lies 20 kb centromeric to the gene G protein receptor kinase-3 (GRK3). GRK3 is an excellent candidate susceptibility gene for BPD since GRKs play key roles in the homologous desensitization of G protein-coupled receptor signaling. GRK3 has been demonstrated to desensitize many G protein-coupled receptors, including CRF, dopamine D1, adrenergic, muscarinic, histaminic and opioid receptors. In 2002 we reported an association study indicating GRK3 may be a risk gene for BPD (Barrett TB, et al. Molecular Psychiatry). In that study we sequenced the putative promoter region, exons, and intron flanking each exon, in 14 affected individuals selected from families showing evidence for linkage between the GRK3 region and BPD. We found six variants in the 5-UTR and promoter region, but no coding or obvious splice variants. Transmission disequilibrium data from two triad sets indicated a variant in the promoter region (P-5) was associated with BPD. In 329 northern European Caucasian triads the transmission to non-transmission ratio was 26:7.7, chi-square = 9.6, $p = 0.0019$. However, these six promoter SNPs were present at only low to moderate frequency. Altogether they tagged only ~25 % of the founding chromosomes, and, hence, provided only modest power to detect overall association between GRK3 and BPD. To identify additional variants for use in association studies we have now sequenced a 30 kb genomic segment of GRK3, centered on the promoter and first exon, in 25 individuals with BPD. 50 variants were identified, half of which were present in three or more subjects. A subset of these variants was then genotyped in 181 Caucasian nuclear families. TDT analyses using Unphased identified an overtransmitted haplotype, defined by two SNPs located upstream of the promoter region, for which the transmission to non-transmission ratio was 119:80, $p = 0.0059$. This haplotype was found on an entirely different set of chromosomes from the previous set of haplotypes de-

fined by SNPs in the promoter region. This haplotype was present on 18 % of the founding chromosomes in these families. The P-5 haplotype, by comparison, was present on ~2 % of founding chromosomes. The data from these studies provide evidence that two distinct haplotypes (and possibly two different underlying mutations) in the gene GRK3 are associated with BPD. One of these haplotypes is relatively common. These new findings add support for the hypothesis that a dysregulation in GRK3 expression alters signaling desensitization and thereby predisposes to the development of bipolar disorder.

62. Serotonin Metabolism During Self-induced Sadness and Happiness in Professional Actors

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Sponsor: Theodore Sourkes

Much of the evidence indicating that brain serotonin (5-HT) neurotransmission involvement in emotion regulation arises from the study of clinical populations. The objective of the present experiment was to investigate aspects of serotonin neurotransmission, using Positron Emission Tomography (PET), during voluntary self-induced sadness and happiness in healthy volunteers. Seven trained professional actors were scanned, on separate days, under three conditions, sadness, happiness, and a neutral emotional state, using 11C-α-methyl-L-tryptophan (11C-αMTrp) as a tracer, a 5-HT precursor analog. This method has been shown to provide a valid estimate of serotonin synthesis capacity (SSC), through the measurement of the unidirectional trapping of 11C-αMTrp in serotonergic neurons. After each scan, subjects rated on a scale from 0 (not at all) to 10 (extremely), the intensity of the target emotion and indicated the percentage achievement of the task. All subjects experienced emotions of high intensity and reliably performed the task. Image analysis (SPM99) of SSC contrasted emotional conditions to the neutral condition and revealed significant differences ($p < 0.01$, corrected). Brain regions showing a decrease in SSC were widespread during happiness, extending from the putamen to cortical areas (BA 2, 4, 7, 11, 20, 24/32, 47) and the cerebellum, yet were restricted to cortical regions (BA 4, 7, 22, 40, 47) during sadness. Brain regions revealing increased SSC were localized within the globus pallidus, the brainstem, and cortical areas (BA 3, 4) during happiness, and within the thalamus and cortical areas (BA 3, 11, 19, 21, 40) during sadness. These preliminary observations suggest that different patterns of brain SSC may be associated with distinct self-induced emotions. Supported by CIHR and NSERC.

63. Resolution of Depression is Associated with Increased Natural Killer Cell Activity among HIV-seropositive Women

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Sponsor: Dwight Evans

Objective: Depression is a potential risk factor for morbidity and mortality among numerous medical conditions, including HIV disease, and is also associated with immunologic alterations including diminished natural killer (NK) cell activity. This study examined whether improvements in depression are related to increases in NK cell activity among HIV-seropositive (HIV+) women. **Method:** HIV+ women were recruited as part of a longitudinal cohort study and underwent comprehensive medical and psychiatric evaluations during a two-year period. Fifty-seven women had NK cell activity and depression data measured at two time points and were examined for associations between changes in depression status and alterations in NK cell activity over time. **Results:** Among the 57 HIV+ women, improvement in depression diagnostic status and decreases in the 17-item Hamilton Depression Rating Scale were significantly associated with increases in NK cell activity over time, as measured in lytic units (LUNK). Eleven women (19.3%) had a major depression diagnosis that resolved over time, and this group also had a significant increase in LUNK cell activity during this period. **Conclusions:** Depression may impair natural killer cell acitivity which is important in innate immunity and HIV/AIDS immune defense. These alterations in NK cell activity are reversible with the resolution of a depressive episode. NK cell activity is involved in the host defense against HIV disease and is an immune measure relevant toward understanding the relationship between depression and morbidity and mortality in HIV/AIDS.

64. Distribution of Serotonin-1A Autoreceptors in the Dorsal Raphe Nucleus of Depressed Suicide Victims

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Sponsor: Efrain Azmitia

Serotonergic dysfunction is present in mood disorders and suicide. The 5-HT1A receptor is a somatodendritic inhibitory autoreceptor on serotonin synthesizing neurons in the dorsal raphe nucleus (DRN). Studies of 5-HT1A autoreceptor binding in the DRN in suicides and controls report conflicting results. We determined whether the anatomical distribution of 5-HT1A receptor Binding Density (BD), Binding Area (BA) and Binding Capacity (BC) in the rostrocaudal extent of the DRN differs between suicides and controls and whether sex differences contribute to suicide vs. control differences on these measures. Postmortem quantitative receptor autoradiography of [3H]8-hydroxy-2-(di-n-propyl)aminotetralin (3H-8-OH-DPAT) in brainstem tissue sections was carried out in drug-free suicide victims (n=10) and controls (n=10). Comparable anatomical levels through the brainstem in the rostral to caudal direction were identified. The tissue section with the maximum DRN BA (mm2) was identified (0 mm) and used to align all the other 1 mm-spaced sections across subjects. For statistical analysis, the DRN was divided into 6 rostrocaudal levels relative to the section with peak cross section area: -3 mm, 0 mm, 3 mm, 6 mm, 9 mm, 12 mm. 5-HT1A receptor BD (fmol/mg tissue) varied rostrocaudally along the DRN ($F= 11.08$ df= 5, 14; $p=0.0002$), with differences between suicides and controls ($F= 11.61$; df=5, 14; $p= 0.0001$). In suicides, [3H]8-OH-DPAT BD was higher than in controls at -3 mm ($F= 39.63$; df=1, 18; $p= 0.0001$), and lower than controls at 3 mm ($F= 5.75$; df=1, 18; $p= 0.0276$) and 6 mm ($F= 24.23$; df=1, 18; $p= 0.001$). [3H]8-OH-DPAT BD was not different between suicides and controls when averaged across all levels ($F= 2.192$; df= 1.0; $p= 0.173$). In both males ($F = 8.59$; df=5,6; $p= 0.0105$) and females ($F = 28.47$; df=5,2; $p= 0.0343$), significant differences in [3H]8-OH-DPAT BD between suicides and controls were found. Suicides had higher BD at the most rostral DRN level (-3 mm) in both males ($F= 23.69$; df=1, 10; $p= 0.0007$) and females ($F= 19.60$; df=1, 6; $p= 0.0044$). At the 6 mm level, BD was lower in suicides than in controls in males ($F= 17.61$; df=1, 10; $p= 0.0018$) and females ($F= 17.94$; df=1, 6; $p= 0.0055$). At the 3 mm level, BD was lower in suicides than in controls only in females ($F= 17.94$; df=1, 6; $p= 0.0055$). 5-HT1A receptor BA (mm2) varied along the DRN ($F= 14.85$ df= 5, 14; $p<0.0001$) but differently in suicides and controls ($F= 4.19$ df= 5, 14; $p=0.0154$). Overall, DRN [3H]8-OH-DPAT BA was smaller in suicides compared with controls

(F=14.76; df=1, 18; p= 0.0012), also within both males (F = 6.04, df=1, 10; p = 0.0339) and females (F= 9.07; df=1, 6; p= 0.0236). DRN 5-HT1A BC (fmol/mg tissue x mm2) in suicides and controls showed a rostrocaudal variation (F= 26.62 df= 5, 14; p< .0001), it was lower in suicides vs. controls (F=18.06; df=1, 18; p= 0.0005) and differed in male and female suicides (F=2.67; df=5, 12; p= 0.0277). BC was lower in suicides than in controls at the 6 mm level in both males (F= 6.31; df=1, 10; p= 0.0308) and females (F= 6.70; df=1, 6; p= 0.0413). Male suicdes had lower BC vs. controls at -3 mm (F= 12.82; df=1, 10; p= 0.0050), while female suicides had lower BC vs. controls at 0 mm (F = 14.54, df= 1,6; p= 0.0088). No effects of pH (range 6.23 to 6.77), PMI (time in hours from death to freezing of brain tissue) or age were observed on 5-HT1A receptors BD, BA or BC. Less autoreceptor binding in the DRN of suicides may represent a homeostatic response to reduced local serotonin release, reducing autoinhibition and favoring more serotonin neuron firing. Supported by MH40210, MH62185.

65. Administration of Topiramate to Rats for Two Weeks Does Not Alter Brain Arachidonic Acid Release and Its Cyclooxygenase-Mediated Metabolism

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Chronic administration to rats of the mood-stabilizers lithium, valproate and carbamazepine at therapeutically relevant concentrations has been shown to down-regulate the expression of certain enzymes involved in brain arachidonic acid (AA) release and cyclooxygenase-mediated metabolism. Open trials with the anticonvulsant topiramate suggest that this drug also may be effective in the treatment of bipolar disorder. To see if topiramate had effects on AA metabolism similar to those observed with lithium, valproate and carbamazepine, we administered topiramate to rats for 14 days at 20 mg/kg p.o. twice daily. Compared with p.o. vehicle, topiramate treatment did not significantly change the brain activity or protein level of cytosolic phospholipase A_2 ($cPLA_2$), secretory $sPLA_2$ or Ca^{2+}-independent $iPLA_2$. Additionally, brain protein levels of cyclooxygenase (COX)-1, COX-2, 5-lipoxygenase and cytochrome P450 epoxygenase were unchanged. These results suggest that topiramate does not modify expression the enzymes involved in brain AA metabolism that have been shown to be modulated by lithium, valproic acid, and carbamazepine. Our overall results suggest that if topiramate proves effective in bipolar disorder, it may not act by modulating brain AA metabolism.

66. The Impact of Lamotrigine Treatment on Depression in Bipolar I Disorder (5)

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Introduction: Subsyndromal and syndromal depressive symptoms in bipolar disorder cause significant functional impairment and subsyndromal depressive symptoms may increase the risk of depressive relapse. Long-term mood stabilizers may reduce the impact of depressive symptoms and may increase the number of days a patient spends in remission of depression. **Objective:** To assess the impact of long-term maintenance therapy with lamotrigine or lithium compared with placebo on the relative amount of time spent in remission vs. subsyndromal vs. fully symptomatic, as measured by mean Hamilton Depression Rating Scale (HAMD-17) scores. **Methods:** Pooled data from the two long-term maintenance trials (GW2003/2006) in bipolar I disorder were examined. After an 8 to 16 open-label phase in which lamotrigine was administered as either monotherapy or adjunctive therapy, patients were randomized to lamotrigine, lithium, or placebo. The relative amount of time spent in three levels of depression (in remission, defined as a HAMD-17 score less than or equal to 7; subsyndromal, HAMD-17 score=8 to 14; and fully symptomatic, HAMD-17 score greater than or equal to 15) was examined. **Results:** Patients treated with lamotrigine spent significantly more days in remission of depression compared to patients treated with placebo (128.7 vs. 84.5 days, p=0.006). Though not statistically significant, patients treated with lithium tended to spend more days in remission of depression than patients treated with placebo (117.0 vs. 84.5 days, p=0.058). Patients treated with lamotrigine or lithium were not significantly different from patients treated with placebo in terms of number of days with subsyndromal depression (lamotrigine: 29.4 vs. 21.9 days, p=0.180; lithium: 28.5 days vs. 21.9 days, p=0.271) or number of days with symptoms of depression (lamotrigine: 12.2 vs. 8.9 days, p=0.158; lithium: 10.2 vs. 8.9 days, p=0.605). **Conclusions:** Bipolar patients treated with lamotrigine spent significantly more days in remission as measured by the HAMD scale over 18 months of treatment compared to placebo. Furthermore, patients spent substantially more days in remission than symptomatic. The number of days patients experienced subsyndromal or syndromal depressive symptoms was not significantly different for lamotrigine vs. placebo or lithium vs. placebo, suggesting that as planned, clinicians intervened promptly when patients experienced depressive symptoms. These results strongly support early intervention to prevent future depressive symptoms.

67. Treatment of Post-traumatic Stress Disorder with Phenytoin: An Open Label Pilot Study

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Background: Phenytoin (Dilantin) is an anticonvulsant used in the treatment of epilepsy. Its mechanism of action is incompletely understood but likely involves modulation of glutamatergic transmission. The neurobiology of posttraumatic stress disorder (PTSD) has been hypothesized to involve, at least in part, alterations in glutamatergic transmission in the hippocampus and possibly other brain regions like frontal cortex. The purpose of this study was to assess the effects of phenytoin on symptoms of PTSD. **Methods:** Phenytoin was administered in an open label fashion for three months to 9 adult male and female patients with PTSD related to a variety of traumas including early abuse, combat, and car accidents. Dosage was adjusted to maintain the therapeutic blood levels used in the treatment of epilepsy. Subjects were assessed before and after treatment for PTSD with standardized dimensional measures of disease severity including the Clinician Administered PTSD Scale (CAPS), the Hamilton Depression Scale (HAM-D), and the Hamilton Anxiety Scale (HAM-A). **Results:** Phenytoin treatment resulted in a significant decrease in PTSD symptoms as measured with the CAPS (65 pre versus 38 post treatment) with reductions in each symptom cluster of intrusions, avoidance and arousal ($p<0.05$). There were no significant decreases in symptoms of depression severity as measured with the HAM-D or anxiety symptom severity as measured with the HAM-A. **Conclusions:** These findings suggest that phenytoin may be efficacious in the treatment of PTSD, possibly mediated through its antiglutamatergic effects. Randomized controlled double-blind clinical trials are indicated to further evaluate this medication in the treatment of PTSD.

68. Effects of Phenytoin on Memory, Cognition and Brain Structure in Posttraumatic Stress Disorder: A Pilot Study
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Phenytoin (Dilantin) is an anticonvulsant used in the treatment of epilepsy. It is believed to act by modulation of glutamatergic transmission. Because the neurobiology of posttraumatic stress disorder (PTSD) has been hypothesized to involve alterations in glutamatergic transmission with subsequention neurotoxicity, we assessed the effects of phenytoin on cognition and brain structure in PTSD patients. Phenytoin was administered in an open label fashion for three months to 9 adult patients with PTSD related to a variety of traumas including early abuse, combat, and car accidents. Subjects underwent magnetic resonance imaging (MRI) for measurement of whole brain and hippocampal volume and neuropsychological testing of memory and cognition before and after treatment. Phenytoin treatment resulted in a significant 6% increase in right brain volume ($p<0.05$). Increased hippocampal volume was correlated with reductions in symptom severity as measured by the CAPS and improvements in executive function as measured by the Trails test. However treatment associated improvements in memory and cognition did not achieve statistical significance. These findings suggest that phenytoin treatment may be associated with changes in brain structure in patients with PTSD.

69. A Randomized, Double-blind, Placebo-controlled Trial of Citalopram in Outpatient Adults with Asthma and Major Depressive Disorder
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Sponsor: Martin Reite

Background: The impact of depression treatment on medical illness is of great interest. Asthma appears to be associated with higher rates of major depressive disorder (MDD) than the general population. However, no controlled studies have examined the treatment of MDD in patients with asthma. **Methods:** Ninty adult, outpatients with asthma and a current major depressive episode were randomized to receive citalopram or placebo on a flexible dosing schedule for 12 weeks. Depressive symptoms were assessed with the 17-item Hamilton Rating Scale for Depression (HRSD), and Inventory of Depressive Symptomatology Self-Report (IDS-SR30). Number of visits in which participants were taking systemic corticosteroids was quantified. Asthma-specific quality of life was assessed with the Asthma Quality of Life Questionnaire (AQLQ). Relationships between change in AQLQ and change in HRSD scores were explored. **Results:** A total of 82 participants returned for at least one post-baseline assessment and were included in the intent-to-treat sample. Sustained remission rates, defined as two consecutive assessments with HRSD scores ? 7 were significantly greater in the citalopram group ($p<0.05$). An observed case analysis found significantly lower HRSD scores in with citalopram at week 6 with a similar trend at week 12. The citalopram group, despite similar corticosteroid use at baseline and in the prior year, used significantly less systemic corticosteroids during the study ($p<0.05$). Improvement in depression was associated with improvement in asthma symptoms. HRSD responders had significantly greater improvement in AQLQ scores than non-responders ($p<0.05$). Change in AQLQ scores correlated significantly with change in HRSD scores ($p<0.05$) in both citalopram and placebo groups. HRSD remitters had greater reductions in AQLQ scores than non-remitters ($p<0.05$). **Conclusions:** Citalopram therapy was associated with rates of sustained remission from depression and less corticosteroid use than placebo. Improvement in depression was associated with improvement in asthma. Supported by NIH grant 1R21 MH63133 to ESB. Study medication provided by Forest Laboratories.

70. Double-Blind, Placebo-Controlled Study of Quetiapine in Bipolar Depression
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Objective: To evaluate the efficacy and tolerability of quetiapine as monotherapy for major depressive episodes in patients with bipolar disorder. **Methods:** 539 patients meeting DSM-IV criteria for bipolar depression (358 bipolar I, 181 bipolar II) were randomized to 8 weeks of double-blind treatment with quetiapine (fixed dose 300 or 600 mg/d) or placebo. The primary endpoint was change from baseline to endpoint in Montgomery-Asberg Depression Rating Scale (MADRS) total score. **Results:** Patients taking quetiapine 300 or 600 mg/d had a significantly ($P<0.001$) greater improvement in mean MADRS scores versus placebo at every assessment, starting with the first evaluation (Day 8) and sustained through endpoint (Week 8) (-16.7 and -16.4 vs -10.2). Patients taking quetiapine 300 or 600 mg/d also had significantly ($P<0.001$) greater improvements in mean Hamilton Rating Scale for Depression (HAM-D) scores versus placebo at every assessment from Day 8 to endpoint (-13.8 and -13.4 vs -8.5). Significantly ($P<0.05$) more quetiapine patients (both doses) versus placebo were considered responders (&#8805 50% decrease from baseline MADRS score) from Week 2 through the end of the study. Treatment-emergent mania did not differ between quetiapine and placebo (3% versus 4%). Common quetiapine adverse events (&#8805 10% and at least twice the placebo rate) were dry mouth (43%), sedation (31%), somnolence (26%), dizziness (20%), and constipation (11%). **Conclusions:** Quetiapine monotherapy (300 or 600 mg/d) is significantly more effective than placebo and well tolerated for the treatment of depressive episodes in patients with bipolar disorder. References: 1. Post RM, Leverich GS, Altshuler LL, et al. An overview of recent findings of the Stanley Foundation Bipolar Network (Part I). Bipolar Disord. 2003;5:310-319; 2. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry. 2002;159(4 Suppl):1-50.

71. Effects of the Association of Omega 6 Enriched Diet and Imipramine in Rats Submitted to the Forced Swimming Test
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Sponsor: ACNP Secretariat

Objective: Many studies have reported an association between polyunsaturated fatty acids (PUFA), especially decrease of omega 3 (Ω-3) and/or increase Ω-6/ Ω-3 ratio, and depression. Several aspects of the neurotransmission like metabolism, release, protein transporters and receptors function seem influenced by dietary PUFA. This controlled study verified the effect of the Ω-6 enriched diet on the behavior of rats treated with imipramine and submitted to the Forced Swimming Test (FST). **Methods and Results:** Wistar male rats were assigned to two groups and received, during six weeks, a control diet or Ω-6 enriched diet, with 10% of primrose oil. Thereafter, each group was subdivided and treated with vehicle or imipramine (10mg/Kg, i.p.) before undergoing the behavioral assessment. The animals were sacrificed and their blood collected for monoamine's assay in the four groups. The ANOVA showed diet differences among groups [$F(1,55)=5,24$; $p<0,02$]. The group treated with imipramine and control diet had an immobility time (67,60±9,45; n=15) in the FST, significantly lower (Duncan, $p<0,032$) than the control group

(100,33±11,79; n=15). The ANOVA of noradenaline (NA) plasma concentration showed differences among groups [F(1,36)=10,96; p<0,002]. The group which received imipramine and control diet had an increase of NA (2678,64 ±412,73; n=10) in comparison to the control group (1543,49 ±211,23; n=11; Duncan, p<0,018). There were no significant differences in the plasma concentrations of serotonin, adrenaline, L-Dopa and dopamine among groups. **Conclusion:** These results show that the Ω-6 enriched diet changed the rats behavior in the FST, inhibiting the effect of the imipramine. Financial support - Capes, CNPq and AFIP

72. Muscarinic Cholinergic2 Receptor Binding in Bipolar Disorder: Relation to Saliency of Affective Words

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Sponsor: Wayne Drevets

Introduction. The muscarinic-cholinergic system has been implicated in mood disorders by findings that, 1)cholinergic agonist administration exacerbates depressive symptoms, 2)muscarinic-cholinergic agonists, ACh releasing agents or acetylcholinesterase inhibitors induce exaggerated effects on REM density and latency in depressives versus controls, 3)both manic and depressed bipolar disorder (BD) subjects show increased pupillary sensitivity to the muscarinic agonist pilocarpine, 4)a M2 receptor polymorphism was associated with increased risk for Major Depressive Disorder (MDD) in females. The current study investigated muscarinic-cholinergic receptor binding in mood disorders using PET and [^{18}F]FP-TZTP, a muscarinic agonist that is relatively selective for M2-receptors. Because the cholinergic system plays major roles in learning the significance of emotional stimuli, the relationship between [^{18}F]FP-TZTP binding and performance on an affective word rating task was assessed. **Methods**. Central M2-receptor DV was measured in 21 currently-depressed subjects (8 BD, 14 MDD) and 13 controls (Mean±SD: Age HC 34±6; BD 32±5; MDD 36±7 yrs). A 120 minute dynamic PET scan in 3D mode was acquired using a GE Advance scanner with arterial blood sampling. To provide an anatomical framework for image analysis and partial volume correction of the PET data, MRI scans were obtained. Regional distribution volumes (DV) were obtained using a one-tissue compartment model. DV values were corrected for the plasma free fraction (f_1), and compared across groups using ANOVA. A subset of these subjects (8 BD, 13 MDD, 10 healthy controls) subjectively rated affective words. Pearson correlations between the affective word rating score and the [^{18}F]FP-TZTP DV were performed. **Results**. The MANOVA results indicated a trend toward a significant effect in primary visual cortex, orbital cortex and ventral striatum. The DV of BD subjects decreased by 21% in primary visual cortex (t=1.722; p=0.10), 18.7% in whole brain, 18.8% in orbital cortex and 13.7% in ventral striatum. In contrast, differences between MDD subjects and controls did not approach significance. The saliency score for affective word ratings was negatively correlated with whole brain [^{18}F]FP-TZTP DV for the BD subjects studied (r= -0.80; p=0.017). The correlation was not significant for healthy controls but there was a trend for a negative relationship in MDD subjects (r=0.53; p=0.06). **Conclusion**. [^{18}F]FP-TZTP binding trended towards being decreased in BD relative to MDD and control subjects. Because [^{18}F]FP-TZTP is a receptor agonist which is sensitive to endogenous ACh levels, a reduction in [^{18}F]FP-TZTP DV/f1 in BD subjects may reflect increased synaptic concentrations of acetylcholine. Alternatively, a lower DV could represent decreased M2-receptor density or affinity. Because M2-receptors are predominantly presynaptic-autoreceptors which regulate release of ACh, a decrease in these or their availability could conceivably lead to a lack of regulatory control over presynaptic ACh release. The inverse correlation between the DV of [^{18}F]FP-TZTP binding and the salience of affective words is noteworthy given the role of the cholinergic system in recognizing the saliency of experiential stimuli.

73. Risperidone Monotherapy in Bipolar Disorder: an Analysis of Standard and Sustained Remission Criteria

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Sponsor: Robert Hirschfeld

Background: Data suggest that achieving a low level of manic symptoms in bipolar disorder patients can reduce the risk of relapse and improve long-term functioning. This low symptom level has been referred to as a state of "remission" and defined as a Young Mania Rating Scale (YMRS) total score ≤12. However, this YMRS rating does not necessarily reflect an asymptomatic state or a sustained low level of both manic and depressive symptoms. This analysis examined risperidone and remission rates in patients with acute bipolar mania, using both the standard and more stringent criteria. **Methods:** Data are from two 3-week double-blind, randomized, placebo-controlled trials in patients with acute manic or mixed episodes of bipolar disorder and the subsequent 9-week open-label extension trial during which patients received risperidone. Measures include the YMRS, the Montgomery Asberg Depression Rating Scale (MADRS), and the Global Assessment Scale (GAS). Remission was defined by degree of symptomatology (YMRS total score ≤12 or ≤7), and by periods of time (at endpoint or sustained over time). Sustained remission was defined as these YMRS designations at any time point plus all subsequent time points. **Results:** In the 3-week studies, 155 patients received risperidone and 119 received placebo. According to the YMRS ≤12 criterion, 65% of risperidone patients and 38% of placebo patients met remission at endpoint ($P < 0.001$); sustained remission was achieved by 40% and 27%, respectively ($P<0.001$). According to the YMRS ≤7 criterion, 41% of risperidone patients and 15% of placebo patients were in remission at endpoint ($P < 0.001$); sustained remission was achieved by 23% and 8%, respectively ($P<0.001$). In the 9-week open-label study, all patients received risperidone. Among the patients who did not meet remission criteria during the double-blind phase, 68% met remission at endpoint according to the YMRS ≤12 criterion and 60% according to the YMRS ≤7 criterion. Rates of sustained remission were 53% and 46%, respectively. Overall rates of sustained remission during the 12-week study period (from double-blind baseline to open-label endpoint) were 62% with the YMRS ≤12 criterion and 53% with the YMRS ≤7 criterion. Mean MADRS total scores among patients who met overall sustained remission (either severity criterion) decreased significantly from double-blind baseline to open-label endpoint ($P<0.001$). Mean GAS scores in these patients improved from ~38 (poor functioning) at double-blind baseline to ~80 (good functioning) at open-label endpoint. **Conclusions:** Using both standard and more stringent remission criteria that consider both symptom severity and sustained symptom control, risperidone was associated with greater remission rates than placebo during the 3 weeks of double-blind treatment. Additional patients achieved remission during the 9 weeks of follow-up treatment with risperidone. Overall, over 50% of patients achieved sustained remission over the 12-week study period, with a decrease in depressive symptomatology and an improvement in functioning scores. These data suggest benefit of continued risperidone treatment in bipolar patients with acute manic or mixed episodes. Supported by Janssen Medical Affairs, L.L.C.

74. Open-Label Antidepressant Augmentation with Atomoxetine

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Sponsor: Lawrence Price

Background: Atomoxetine is a selective norepinephrine reuptake inhibitor (SNRI) currently approved for treatment of attention deficit hyperactivity disorder (ADHD). Other compounds that enhance synaptic norepinephrine, such as the tricyclic desipramine, have antidepressant effects. Reboxetine, a SNRI antidepressant available in Europe, has demonstrated efficacy both for monotherapy and as an augmentation agent. This case series study examined the role of atomoxetine for antidepressant augmentation. **Methods:** 15 adult outpatients with primary major depressive disorder received open-label atomoxetine augmentation following partial- or nonresponse to an adequate trial (minimum 8 weeks) of standard antidepressant pharmacotherapy. Atomoxetine (40 mg q d) was added to ongoing medication regimens and titrated according to clinical response. Clinician- and patient-rated symptom assessments were completed at each clinic visit. **Results:** Eleven (73%) patients completed a minimum of 6 weeks atomoxetine augmentation; 3 (20%) discontinued due to nausea, 1 discontinued due to lack of efficacy. Mean endpoint dose was 79.0 (SD 38.4; range 25-120) mg/d. Nine patients (60%) met criteria for positive categorical response. Mean IDS-SR symptom scores decreased significantly from baseline to endpoint ($p=.001$), and mean clinician-ratings of social and occupational functioning increased ($p<.0001$). No vital sign changes were detected, and the most common side effect was activation. A modest but significant drop in body mass index ($p=.025$) was observed, and a subset (40%) reported improvement in sexual function. **Conclusion:** More studies are warranted to evaluate the promising potential utility of atomoxetine for antidepressant augmentation.

75. A New Animal Model of Depression that includes an Anhedonic Measure and Gene Expression Changes in the Brains of Modeled Animals

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Depletion of serotonin and catecholamines induces an episode of depression preferentially in the individuals with a personal or a family history of mood-disorders and in individuals with the "s" allele of the serotonin transporter gene. These clinical observations indicate that, although monoamines are modulators of mood, lowered monoamine levels alone are insufficient to induce depression suggesting that there are other modulators of mood in addition to the monoamine neurotransmission systems. Based on these clinical data, we hypothesized that the ability to induce a depression-like episode in rodents by monoamine depletion would be highly dependent on the rodent strains used. We defined the depression-like episode in rodents as the manifestation of multiple behavioral deficits resembling the symptoms of clinical depression including that of anhedonia. Monoamine depletion was carried out in four different rat strains by treating the rats with the serotonin or catecholamine synthesis inhibitors, para-chlorophenylalamine (PCPA) or alpha-methylparatyrosine (aMPT), respectively. After the treatment rats were evaluated using the forced swim test. Both PCPA and aMPT increased immobility time and decreased swimming time only in Fisher 344 rats. Further evaluation of serotonin and catecholamine depletion in F344 rats showed that PCPA and aMPT also attenuated exploratory activity as measured by distance traveled and rearing behavior in a novel environment in this strain. We used sucrose preference as a measure of hedonic behavior. Sucrose consumption was decreased in the PCPA and aMPT treated F344 rats, an effect that was partially reversed by pretreatment with desipramine or fluoxetine. Examination of the gene expression profiles of "depressed" rats using cDNA microarray methodology showed that serotonin and catecholamine depletion in F344 rats altered the expression of genes in the hippocampus including the ATF-2, BDNF, and XBP-1. Previous studies have suggested that ATF-2, BDNF, and XBP-1 play roles in the etiology and the therapeutic mechanisms of mood-disorders. In summary, we found that vulnerability to the induction of depression-like episode in rats is strain dependent and that serotonin and catecholamine depletion induces depression-like episode in F344 rats. Furthermore, the depression-like episode is accompanied by alterations in the expression of genes that have been suggested to be associated with mood disorders. This behavioral paradigm represents a new animal model to investigate the neurobiology of depression. This paradigm allows the investigation of potential new sites of action for novel antidepressants that would not depend on the availability of monoamines for an initial mechanism of action.

76. Behavioral Deficits of ERK1 Knockout Mice in Mood Disorder-related Animal Tests

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Neurotrophic factors (such as NGF, BDNF and NT-3) and other neuroactive molecules activate the ERK pathway and through this pathway produce their effects on neurogenesis, neurite growth and neuronal survival. The ERK pathway also modulates synaptic plasticity, neurotransmitter release, learning and memory, and circadian rhythms. We previously found that lithium and valproate increased levels and functions of AP-1 transcription factors and increased levels of the neurotrophic-neuroprotective protein Bcl-2. The ERK pathway is one of the signaling pathways that regulates Bcl-2 and AP-1 expression and functions. Following these clues, we found that lithium and valproate activated the ERK pathway in rat frontal cortex and hippocampus, cultured rat cortical neurons, and human derived neuronal cell lines. Valproate, in an ERK pathway-dependent manner, promoted neurite outgrowth and neurogenesis in cultured cortical cells. Both lithium and valproate promoted hippocampal neurogenesis in adult animals. These data suggest that antimanic mood-stabilizers may alleviate mood disorder-associated pathological changes such as the reduction of cerebral grey matter as well as the atrophy and loss of neuronal and glial cells, which have been described in recent human brain imaging and postmortem studies of bipolar patients.
We also examined the role of the ERK pathway in models related to the pathophysiology of bipolar disorder. We found that the ERK pathway inhibitor SL327 induced hyperactivity in the forced swim test and the open field test. In the present study, we examined the effects of genetic manipulation of the ERK pathway on mood-related behaviors. We found that knocking out one of two ERK encoding genes, ERK1, reduced the function of the ERK pathway in the brain and resulted in multiple behavioral deficits in behavioral tests associated with mood disorders. The ERK1 KO mice showed reduced immobility time and increased swimming time in the forced swim test, increased locomotor activity and rearing behavior in the open field test, increased numbers of entries to each arm in the elevated plus maze test, and increased home cage activity as monitored by several weeks of wheel running. As well, these mice were supersensitive to amphetamine challenge. Lithium stimulated the function of the ERK pathway and attenuated the amphetamine response in the ERK1 KO mice. In summary, we found that antimanic mood-stabilizers activated the ERK pathway and promoted neurobiological functions of the ERK pathway in cultured neuronal cells and in rodent brains. Disabling the ERK pathway chemically or genetically caused multiple behavioral deficits in mood disorder-related animal tests. Lithium treat-

ment partially reversed these behavioral deficits. The evidence obtained thus far in animals are coherent and indicate that the ERK pathway is a critical mediator of the pathophysiology of bipolar disorder. The roles of the ERK pathway in the etiology and pathophysiology of bipolar disorder should be further studied in humans.

77. Chronic Infusion Of Ovine CRF Or Urocortin II Into Rat Dorsal Raphe Alters Exploratory Behavior But Not Serotonin Autoreceptor Expression

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Sponsor: Past Travel Awardee, BMS, 2002

Corticotropin releasing factor (CRF) peptides play key roles in integrating neural responses to stress. Both CRF-R1 and R2 receptors are found in the serotonergic dorsal raphe nucleus. While chronic stress and serotonergic dysfunction have been strongly implicated in human mood and anxiety disorders, little is known about the effects of chronic CRF receptor activation in dorsal raphe. We used osmotic minipumps to infuse into rat dorsal raphe 1ng/hr ovine CRF, 1ng/hr urocortin II (UCNII), or vehicle alone for 6d. On day 5, rats were allowed to enter and explore an open field for 15 min. The following day, a novel object was placed in the center of the same field, and the animals again allowed to enter and explore the field for 15 min. Immediately after testing, animals were euthanized and brains frozen. Dorsal raphe expression of 5-HT^{1A} and 5-HT^{1B} autoreceptors was examined across the AP axis by in situ hybridization. While neither 5-HT^{1A} nor 5-HT^{1B} expression changed, exploratory behavior was significantly altered. Animals receiving ovine CRF displayed significantly longer latencies to touch the novel object, fewer touches, and markedly less vigorous exploratory climbing behavior. Animals receiving UCNII demonstrated decreased climbing behavior, but no alterations in either latency to touch or touch number. Thigmotaxis was not altered in either treatment group during the first open field exposure. During novel object exposure, animals infused with ovine CRF spent less time in the center and more time on the sides, and trended towards more time spent in the corners. Similar, though mostly statistically insignificant changes were found in animals infused with UCNII. These findings demonstrate that chronic exposure of the dorsal raphe to low dose CRF receptor agonists decreases exploration of a novel object, without altering serotonin autoreceptor expression.

78. Low Field Magnetic Stimulation: Mood Effects In Bipolar Humans And In Rodents

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Electrical and magnetic field treatments are being investigated for efficacy in psychiatric disorders such as major and bipolar depression with increasing frequency. We have made the serendipitous discovery of a Low Field Magnetic Stimulation (LFMS) effect which was shown to improve mood in human subjects with bipolar disorder (BP) and in rodents in the Porsolt Forced Swim Test (FST). LFMS has characteristics similar to repetitive Transcranial Magnetic Stimulation (rTMS) except that its magnetic fields are 1/2000 weaker than rTMS, penetrate throughout the whole head, and consist of pulses delivered at the high frequency of 1 kHz. In the human LFMS study, BP subjects received a spectroscopic MRI exam with an unusual scan orientation on a 1.5T scanner over multiple visits. After several subjects finished the MR exam with obvious mood improvement, the Brief Affect Scale (BAS) was added to the study and administered immediately before and after the MR exam. Comparison groups of normal subjects who received the LFMS - MR exams and BP subjects who received a sham LFMS-MR exams were recruited. Twenty-three of 30 BP subjects reported improvement in mood of at least 1 point on the BAS scale after LFMS (mean BAS score =0.87± 0.68), compared to 3 of 10 BP subjects given sham LFMS (mean BAS score = 0.30 ±1.06), a significant difference ($z=2.63$, $p=0.009$, ordered logistic regression). In the subgroup of medication navïe BP subjects who received LFMS-MR, 11 of 11 subjects reported improvement in mood (mean BAS score = 1.18 ±0.41). In the rodent model, a tabletop LFMS system and FST was used to investigate the antidepressant effects of LFMS. Effects of the LFMS treatment were compared to those of desipramine (DMI) and fluoxetine (FLX). Immobility was affected in this test ($F(4,40)=5.0$, $p<0.01$) with LFMS ($p<0.01$) and DMI ($p<0.05$) treatments having reduced immobility, indicating antidepressant-like effects. Swimming was affected ($F(4,40)=4.24$, $p<0.01$) with LFMS ($p<0.01$) and FLX ($P<0.05$) showing increased swimming activity. Climbing was also affected ($F(4,40)$, $p<0.01$) with DMI ($p<0.01$) and LFMS ($p<0.05$) showing increased climbing activity. Considered together, the antidepressant-like effects of LFMS were qualitatively similar to, but slightly greater than, those of FLX. The observation of this effect, similar to the effects of rTMS but produced by a very different set of fields, suggests that a wide range of magnetic field strengths and waveforms may produce stimulation effects.

79. The Vasopressin V1b Receptor Antagonist, SSR149415, and the Corticotrophin-Releasing Factor1 (CRF1) Receptor Antagonist, SSR125543, Have Antidepressant-Like Effects on the DRL 72s Schedule

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Recent findings have identified neuropeptide systems as potential novel therapeutic targets for the treatment of depression and anxiety disorders. Much attention has focused on corticotrophin-releasing factor (CRF) and vasopressin, two neuroactive peptides that are known to be involved in the regulation of the hypothalamic-pituitary-adrenal stress axis. The vasopressin V1b receptor antagonist, SSR149415, and the CRF1 receptor antagonist, SSR125543, are two novel orally-active non peptide compounds which have shown anxiolytic- and antidepressant-like activities in several animal models. Here, these drugs were tested on the differential reinforcement of low rate (DRL) 72s schedule of responding, a paradigm sensitive to antidepressant drugs. The DRL 72s schedule requires rats to wait at least 72 s between lever pressing responses to earn a reinforcer. As typically observed, imipramine (10 mg/kg, i.p.) increased reinforced response frequency, shifted the frequency distribution of inter-response times (IRT) toward longer IRT durations in a coherent fashion (i.e., without disrupting the profile of the IRT distribution) and decreased bursting (IRT ≤ 6 s). These effects have been interpreted as reflecting enhanced temporal discrimination and capacity to wait for a reward, a pattern of effects typical seen with antidepressant drugs. SSR149415 (10 mg/kg i.p.) and SSR125543 (30 mg/kg, i.p.) increased reinforced response frequency and shifted the IRT frequency distribution toward longer IRT durations without changing the shape of the IRT distribution. Neither drug affected bursting. In conclusion, these results confirm further the antipressant-like potential of the vasopressin V1b receptor antagonist, SSR149415, and the CRF1 receptor antagonist, SSR125543.

80. Age and Gender Differences in Antidepressant Treatment: A Comparative Analysis of Venlafaxine and Selective Serotonin Reuptake Inhibitors

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Sponsor: Peter Roy-Byrne

Objective: Several studies have shown that gender, menopausal status, and age can influence response to antidepressants while oth-

ers have failed to show such differences. Using a large database of randomized controlled trials (RCTs) in depressed patients, we examined treatment effects with different classes of antidepressants across a variety of age and gender subgroups. **Method:** A meta-analysis was conducted using individual patient data from 31 double-blind RCTs comparing the serotonin-norepinephrine reuptake inhibitor venlafaxine/venlafaxine XR (n=3273) and selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, paroxetine, sertraline, citalopram, or fluvoxamine; n=3217) in treatment of depressed patients. Nine studies also included a placebo control group (n=932). The primary outcome measure (intent-to-treat population; last observation carried forward method) was remission, defined as a 17-item Hamilton Rating Scale for Depression (HAM-D17) score ≤7 at week 8. All tests of hypotheses were two-sided with a significance level of 0.05. Remission rates were computed separately for women and men, for older women (age >50) and younger women (age ≤50), and for older men (age >50) and younger men (age ≤50). Results from an analysis of premenopausal vs postmenopausal women (using age <40 and >55 as proxy indicators of menopausal status, respectively) also will be reported. **Results:** Women comprised 2/3 of the patient population (4889/7420; 66%). Of the total data set, 71% (5,327/7,409) were ≤50 years while 29% (2,082/7,409) were older than 50. Age and gender distributions were similar across treatment groups. Remission rates for women were: 41%, venlafaxine/venlafaxine XR; 34%, SSRIs, and 26%, placebo (P<0.0001 venlafaxine/venlafaxine XR vs SSRI and placebo; P=0.0002 SSRI vs placebo). Results were similar for men: 40%, venlafaxine/venlafaxine XR; 34%, SSRIs, and 20%, placebo (P=0.004 venlafaxine/venlafaxine XR vs SSRI; P<0.0001 venlafaxine/venlafaxine XR and SSRI vs placebo). In the subgroup of younger women, results were similar to the overall population. Remission rates: 41%, venlafaxine/venlafaxine XR; 36%, SSRIs; and 26%, placebo (P=0.002 venlafaxine/venlafaxine XR vs SSRIs; P<0.0001 venlafaxine/venlafaxine XR vs placebo; P=0.0001 SSRI vs placebo). Older women treated with venlafaxine/venlafaxine XR patients responded similarly to younger women (remission rate 41%; P=0.0001 vs SSRIs; P=0.0017 vs placebo), while the remission rate with SSRIs among older women was not significantly different from placebo (30% vs 27%, respectively; P=0.4698). In the subgroup of younger men, remission rates were 41%, venlafaxine/venlafaxine XR; 35%, SSRIs; and 25%, placebo (P=0.0124 venlafaxine/venlafaxine XR vs SSRI; P<0.0001 venlafaxine/venlafaxine XR vs placebo; P=0.0033 SSRI vs placebo). Among older men, remission rates were lower in all 3 groups: 36%, venlafaxine/venlafaxine XR; 30%, SSRIs; and 12%, placebo (P=0.1550 venlafaxine/venlafaxine XR vs SSRIs; P<0.0001 venlafaxine/venlafaxine XR vs placebo; P=0.0001 SSRI vs placebo). **Conclusion:** The efficacy of venlafaxine/venlafaxine XR was consistent across most gender and age subgroups; with the exception of older men, who responded less favorably in all 3 treatment groups relative to younger men. Consistent with previous analyses, younger women responded better to treatment with the SSRI comparators than older women. Additional analyses will explore the extent to which menopausal status and hormonal therapy modulate response to antidepressant treatment in women.

81. Botulinum Toxin Treatment of Social Anxiety Disorder with Hyperhidrosis: a Double-Blind, Placebo-Controlled Trial

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Sponsor: Jonathan Davidson

Background: Physiologic symptoms, such as excessive sweating (hyperhidrosis), are common in social anxiety disorder (SAD) and may be the primary reason for seeking treatment. Compared to symptoms of fear and avoidance in SAD, physiologic symptoms tend not to respond as well to standard treatments with SSRI's or CBT. A new treatment, botulinum toxin (Botox), may hold particular promise for hyperhidrosis in SAD. This study assesses the effects of an SSRI, paroxetine, in combination with Botox or placebo in treating SAD associated with severe hyperhidrosis. **Methods:** Forty subjects with SAD and severe axillary hyperhidrosis received 8 weeks of open-label treatment with paroxetine. Prior to beginning pharmacotherapy, subjects were randomly assigned 1:1 to receive double-blind bilateral intra-axillary interdermal injections of either Botox (50 units/axilla; N=20) or saline (50 ml/axilla; N=20). Treatment was administered according to standard protocol, with 25 2ml injections/axilla. The primary outcome was response, which was defined as a 2-point or greater reduction from baseline in the Hyperhidrosis Disorder Severity Scale (HDSS). Secondary measures included changes in the impact of hyperhidrosis, on standard measures of SAD, and in quality of life. **Results:** Response rates for Botox were 65% vs. 10% for placebo ($p < .01$). Botox produced significantly greater improvement in many daily activities which had been limited prior to treatment, as well as in work and social functioning ($p < .05$). Botox was well-tolerated. Five subjects in the Botox group withdrew during the study (side effects which appeared related to paroxetine treatment), compared to 2 dropouts in the placebo group (lack of efficacy). **Conclusion:** Botulinum toxin is effective in reducing hyperhidrosis, disability, and limitations in daily activities, when given in association with paroxetine to patients with SAD.

82. Synchronized Maternal-Infant Elevations Of Primate CSF CRF In Response To Variable Foraging Demand

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Sponsor: Bruce Lydiard

Background: The study of environment-gene interactions during neurodevelopment may facilitate our understanding of the origins of psychiatric disorders. Environmental contribution to the neurobiology of psychopathology is perhaps most relevant during infancy, where vulnerability to early life stressors is particularly evident. In the current study, we wished to examine if central CRF would provide a plausible biological vehicle for transmission of maternal affective distress to her offspring. **Methods:** 24 mother-infant bonnet macaques (Macaca Radiata) dyads, of known age and weight served as subjects. The subjects were group-housed in 4 pens of 5-7 dyads each, stabilized for several weeks prior to the study period. Although adequate food was always available, mothers faced uncertainty of food availability for 16 weeks within the first year of infant life, through a procedure dubbed "variable foraging demand" (VFD). An extensive behavioral data set and pre- and post-VFD CSF and plasma samples were obtained simultaneously on mothers and infants. **Results:** Maternal CSF CRF concentrations exhibited a significant mean elevation of 26% from pre-VFD to post-VFD; there was no effect of number of days post-partum on maternal Pre-VFD CSF CRF levels. There was a significant increase (45%) in infant CSF CRF concentrations over the 16 week period of the VFD paradigm. No infant sex differences were evident. Pre / Post - VFD differences in infant CSF CRF concentrations were positively correlated ($r = .52$; $N = 16$; $p = .0384$) with the magnitude of maternal CRF response to VFD providing evidence of synchronized CSF CRF expression by the dyad. **Conclusions:** This parallel response within the dyad suggests, as one testable hypothesis, that maternal responsivity to the stress of the VFD condition is "communicated" to her

infant via a CRF-mediated intergenerational transduction mechanism. Concordant human studies in the offspring of holocaust victims with PTSD show a similar pattern of glucocorticoid suppression as their parents. That infant CRF gene expression may model itself on magnitude of the maternal response to real-life stressor, VFD, suggests neurobiological "transmission" of affective distress from mother to infant.

83. Altered Sensitivity to the Pharmacological Effects of the GabaB Receptor Agonist Baclofen in Different Mouse Strains

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Comparison of different mouse strains can provide valuable information about the genetic control of behavioural and molecular phenotypes. Recently, interest has been increasing in the involvement of $GABA_B$ receptor in affect, as $GABA_{B(1)}$ deficient mice show anxiogenic and antidepressant-like profiles, $GABA_B$ receptor positive modulators reduce anxiety in mice and rats, and $GABA_B$ receptor antagonists induce antidepressant-like behavior in the forced swim test. The aim of current study was to determine the relative sensitivity of different mouse strains to $GABA_B$ receptor agonism, in two widely used tests of $GABA_B$ receptor function, namely hypothermia and motor incoordination. Forty mice each from 11 strains (BALB/cByJ, DBA/2, OF1, FVB/N, CD1, AJ, C3H/HeOu, 129SvPas, NMRI, C57/Bl6 and SWISS) were trained to walk on a rotarod for 300 seconds. The following day mice received 0, 3, 6 or 12 mg/kg per os of L-baclofen, the active isomer of the prototypical $GABA_B$ receptor agonist baclofen. Rectal temperature and rotarod performance up to 300 seconds were measured at 0, 1, 2 and 4 hours after drug administration. L-baclofen produced a significant hypothermia and ataxia in most, but not all, mouse strains examined. Of note, C3H/HeOu showed no hypothermic responses to L-baclofen at any dose or time in the study. BALB/cByJ and C57Bl/6 mice were affected only by the highest dose of L-baclofen used (12 mg/kg), whereas all other strains were affected also by the 6 mg/kg dose. Peak hypothermic responses to L-baclofen were reached by 1 hour post-dosing for strains DBA/2, FVB/N and NMRI, with the remainder (excepting C3H/HeOu) peaking at 2 hrs. Body temperatures had normalized in all strains within 4 hours except BALB/cByJ, DBA/2 and 129SvPas. On the rotarod, BALB/cByJ, C57Bl/6, FVB/N, OF1, CD1, SWISS and notably the C3H/HeOu strain responded ataxically to 12 mg/kg L-baclofen. DBA/2, 129SvPas and A/J mice showed ataxic responses to both 6 and 12 mg/kg. Interestingly, the NMRI strain did not show significant ataxia to L-baclofen. All mice strains had returned to baseline coordination within 4 hours after dosing. The rank order of strains from least to most sensitive for hypothermia differed from the rank order generated using ataxic sensitivity. The rank order for hypothermia from least to most sensitive was: C3H/HeOu, SWISS, NMRI, C57BL/6, CD1, A/J, OF1, BALB/c, DBA/2, FVB/N, 129SvPAS. For ataxia it was: NMRI, OF1, CD1, FVB/N, C57BL/6, A/J, SWISS, C3H/HeOu, DBA/2, 129SvPas, BALB/c.. Interestingly, some strains, such as C3H/HeOu, had markedly different ranking for hypothermic and ataxic responses, with minimal body temperature responses to L-baclofen but significant ataxia on the rotarod. FVB/N, in contrast, ranked highly sensitive in hypothermic responses, with relatively moderate levels of ataxia. These results indicates that there is differential genetic control on specific $GABA_B$ receptor populations that mediate these two responses to $GABA_B$ receptor stimulation. Further, these observations demonstrate that background strain is an important determinant of $GABA_B$ receptor mediated responses, and that hypothermic and ataxic responses may be influenced by independent genetic loci.

84. Venlafaxine XR in the Treatment of Posttraumatic Stress Disorder: A 6-Month Placebo-Controlled Study

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Objectives: While selective serotonin reuptake inhibitors (SSRIs) have shown efficacy in treating posttraumatic stress disorder (PTSD), they may not be effective for all patient types. Venlafaxine extended release (XR), a serotonin-norepinephrine reuptake inhibitor, has both antidepressant and anxiolytic effects and produces remission in patients with depression or generalized anxiety disorder. This 6-month, international, randomized, double-blind, placebo-controlled, parallel-group trial compared the efficacy of venlafaxine XR and placebo for moderate to severe PTSD. **Methods:** 329 adult outpatients (venlafaxine XR, n=161; placebo, n=168) in the ITT population were randomly assigned to treatment with flexible-dose venlafaxine XR (37.5 mg to 300 mg/d), or placebo for 24 weeks, starting with the lowest dose (37.5 mg). Patients were included if they had a primary diagnosis of DSM-IV PTSD, PTSD symptoms for ≥6 months, and 17-item Clinician-Administered PTSD scale ($CAPS\text{-}SX_{17}$) score ≥60. The primary efficacy measure was change from baseline (week 12 or time of discontinuation) in $CAPS\text{-}SX_{17}$ score. Secondary assessments included frequency of remission ($CAPS\text{-}SX_{17}$ ≤20), time to remission, PTSD symptom-free days (based on $CAPS\text{-}SX_{17}$ scores), and changes from baseline in CAPS- SX_{17} symptom cluster scores for re-experiencing, avoidance/numbing, and hyperarousal; the Stress Vulnerability Scale (SVS), Connor-Davidson Resilience Scale (CD-RISC); 17-item Hamilton Depression Rating Scale ($HAM\text{-}D_{17}$); Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF); Sheehan Disability Scale (SDS); Clinical Global Impression–Severity of Illness (CGI-S); and Global Assessment of Functioning (GAF). Between-group comparisons were made using analysis of covariance (ANCOVA), with treatment as main effect, and baseline score as covariate. LOCF analyses were used. The between-group difference in symptom-free days was compared by t-test. Remission rates were compared by Chi-square test. Time to remission was compared by Kaplan-Meier method. **Results:** 112 patients in each group completed the study. The mean maximum daily dose of venlafaxine XR was 221 mg. Mean changes from baseline in $CAPS\text{-}SX_{17}$ total scores at endpoint were -51.7 for venlafaxine XR and -43.9 for placebo (P=0.006). Mean baseline-to-endpoint improvement was significantly greater for the venlafaxine XR group than placebo in $CAPS\text{-}SX_{17}$ cluster scores for re-experiencing (P=0.008), and avoidance/numbing (P=0.006), but not for hyperarousal. Remission rates were 50.9% for venlafaxine XR and 37.5% for placebo (P=0.013). Median time to remission was 87.0 days for the venlafaxine group and 130.0 days for placebo (P=0.017). The venlafaxine XR group also showed significantly greater improvement at endpoint than placebo for symptom-free days (P=0.007), SVS score (P=0.011), CD-RISC score (P=0.002), $HAM\text{-}D_{17}$ total score (P=0.007), Q-LES-Q total score (P=0.007), SDS total score (P=0.030), CGI-S score (P=0.004), and GAF score (P=0.034). Headache and nausea were the most common TEAEs in the venlafaxine XR group. Withdrawal rates were 30.4% for venlafaxine XR and 33.3% for placebo, with no significant difference in dropouts attributable to AEs. **Conclusion:** In this study venlafaxine XR was effective and well tolerated in short-term treatment of PTSD and had beneficial effects on symptoms, functioning, quality of life, global well-being, and remission rate.

85. A Double-Blind, Placebo Controlled trial of C-1073 (Mifepristone) In the Treatment of Psychotic Major Depression

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Sponsor: Alan Schatzberg

Background: Psychotic depression is characterized by abnormalities in hypothalamic pituitary adrenal (HPA) axis activity. In a previous double-blind trial, C-1073 (mifepristone), a selective glucocorticoid receptor antagonist, had therapeutic benefits when added to standard pharmacotherapy for psychotic depression. In this trial the efficacy of C-1073 is compared with that of placebo in patients who are not on standard pharmacotherapy for the first 7 days. **Methods:** Patients who met DSM-IV criteria for PMD and were not on either antidepressants or antipsychotics were randomized in a 1:1 ratio to receive adjunctive C-1073 or placebo for 7 days in an in-patient setting. Patients were followed for 28 days. The primary endpoint was a 30% reduction in the total Brief Psychiatric Rating Scale (BPRS) at both days 7 and 28. Secondary endpoints included a 50% reduction at days 7 and 28 in (BPRS) positive symptom subscale, the Hamilton depression Rating Scale, and the Montgomery Asberg Depression Rating Scale. **Results:** 221 patients were randomized and patients in both the C-1073 and control groups improved significantly from baseline. Patients on C-1073 were significantly more likely to achieve a 30% improvement at days 7 and 28 than were placebo treated patients. In addition, C-1073 treated patients were significantly more likely to achieve a 50% reduction in days 7 and 28 on the BPRS positive symptom subscale. There were no significant benefits on the depression rating scales. C-1073 appeared well tolerated for the duration of the study with no AEs statistically more common in the C-1073 than placebo group. **Conclusion:** A 7-day course C-1073 appears significantly improve psychotic symptoms in psychotic major depression. In addition, the effects of the drug appear to be sustained for at least 3 weeks after the drug is stopped. This study provides additional evidence that the glucocorticoid receptor antagonist, C-1073, may have a role in the treatment of psychotic depression.

86. Modafinil as Augmentation Therapy for Persistent Symptoms of Excessive Sleepiness and Fatigue in Adults with Major Depressive Disorder

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Objective: Excessive sleepiness and fatigue are commonly reported symptoms of major depressive disorder (MDD) that may persist as residual symptoms despite adequate selective serotonin reuptake inhibitor (SSRI) therapy. The wake-promoting agent modafinil may prove useful as an augmentation agent in partial responders to SSRI monotherapy, particularly when excessive sleepiness and fatigue persist. We present the results of a retrospective pooled analysis of data collected from a subset of MDD patients with at least moderate levels of excessive sleepiness and fatigue who participated in 2 controlled clinical studies designed to assess the efficacy and tolerability of modafinil augmentation. **Methods:** MDD patients (18–65 years) with a partial response to adequate SSRI monotherapy for a current depressive episode participated in one of two randomized, double-blind studies. Patients received modafinil 100 to 400 mg/day or matching placebo in addition to existing SSRI antidepressant therapy for 6 or 8 weeks. Patients (N=348) selected for this retrospective pooled analysis met a common set of criteria from the 2 studies, namely an Epworth Sleepiness Scale [ESS] score of ≥10, a 17-item Hamilton Rating Scale for Depression [HAM-D-17] score between 4 and 25 [inclusive], and a Fatigue Severity Scale [FSS] score of ≥4. Efficacy measures included the Clinical Global Impression of Improvement (CGI-I: responders defined as ″very much improved″ or ″much improved″), ESS, HAM-D-17, and FSS. **Results:** At final visit, modafinil augmentation of SSRIs significantly improved overall clinical condition vs placebo (CGI-I responders [%] were 42% vs 31%, respectively; $P = .035$). Modafinil plus SSRI significantly improved wakefulness (ESS: $P = .04$ vs placebo plus SSRI at final visit). Modafinil plus SSRI also significantly improved depressive symptoms (HAM-D-17: $P = .02$ vs placebo plus SSRI at final visit). Modafinil plus SSRI reduced fatigue greater than placebo plus SSRI at final visit (FSS: -1.0 vs -0.8, respectively), but the between-group difference was not statistically significant. Three hundred (86%) patients completed and 179 (>99%) modafinil-treated patients received a ≥200-mg dose. The safety profile from the combined studies was similar to the safety profiles of the 2 individual studies. **Conclusion:** Modafinil augmentation of SSRIs in MDD patients with partial response resulted in significant improvements of overall clinical condition, wakefulness, and depressive symptoms by final visit.

87. A Double-Blind Comparison of Divalproex Versus Quetiapine for Adolescent Mania

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Controlled investigations of atypical antipsychotics suggest that they are effective and well tolerated for the treatment of mania in adults. Quetiapine has demonstrated efficacy as monotherapy for the treatment of adult mania. Moreover, the combination of quetiapine and divalproex was found to be more effective than divalproex monotherapy for the treatment of adolescent mania and quetiapine was well tolerated. However, there have been no studies directly comparing the efficacy of atypical antipsychotic monotherapy and a traditional mood stabilizer for adolescent mania. The objective of our study was to determine the comparative efficacy and tolerability of divalproex and quetiapine for the treatment of mania in adolescents with bipolar disorder. Fifty adolescents (ages 12-18 years) with a DSM-IV diagnosis of bipolar disorder, type I, manic or mixed episode, were randomized to double-blind treatment with divalproex (mean serum level 101 mg/dl) vs. quetiapine (400-600 mg/d, mean 415 mg) for 28 days. Efficacy and safety assessments were performed on Days 0, 3, 7, 14, 21, and 28, or endpoint. Primary efficacy measure was change from baseline to endpoint in Young Mania Rating Scale (YMRS). Comparative efficacy was determined by whether quetiapine was at least as effective as divalproex, defined as a change from baseline to endpoint in YMRS score in the quetiapine group at least 80% of that in the divalproex group. As secondary measures of response, group differences in Clinical Global Impression Bipolar Disorder version Improvement (CGI-I) Scale response rates (defined by <2, much or very much improved) were determined. Safety and tolerability measures included documentation of adverse events, vital signs, laboratory measures, and movement scales. Twenty-five subjects were randomized to each treatment group. The decrease from baseline to endpoint in YMRS score was 19.5 (2.4) in the divalproex group and 22.8 (2.4) in the quetiapine group. Based on the change in YMRS score in the divalproex group, we determined that the response in the quetiapine group needed to be within 4 points. The group difference in YMRS change from baseline to endpoint was 3.3 (3.4) (95% CI, -3.5, 10.1). Response rate for improvement in mania (CGI-I score <2) was greater in the quetiapine group than in the divalproex group (84% vs. 56%, P=0.03). There were no statistically significant group differences in rates of adverse events. The most common side effect in both

groups was sedation (quetiapine, N=15, 60% vs. divalproex, N=9, 36%, P=0.1). The results of this study suggest that quetiapine monotherapy is at least as efficacious as divalproex for the treatment of adolescent mania. Both quetiapine and divalproex were well tolerated.

88. Monoamine Related Genes and Association with Major Depression

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We present preliminary data from an association study of several candidate genes relevant to monoamine function and unipolar major depression. One hundred and twelve Caucasian subjects with documented history of Unipolar Major Depressive Disorder were invited to participate. Two subgroups of depressive subjects were genotyped, about half had achieved and maintained clinical remission for at least three months; the other half had well documented Treatment Resistance to at least two adequate antidepressant trials. One hundred and sixteen control subjects who denied personal history of mental illness were also genotyped. PCR based genotyping was performed at the Laboratory of Molecular Psychiatry of The University of Arizona for the following genetic polymorphisms: Serotonin Transporter Gene (Promoter region insertion/deletion polymorphism, and Intron-2 VNTR [SERT VNTR] polymorphism), Serotonin Receptor 2A (C102T), Dopamine Transporter [DAT1] (exon-15 VNTR), Catechol-O-methyl transferase gene (3'UTR dbSNP: rs165599), Serotonin Receptor 6A (C267T), Dopamine Receptor 4 gene (5'UTR insertion/deletion [DRD4 ins/del], and exon-3 VNTR), Dopamine Receptor 3 Gene (exon 1 G/A SNP), 3 Dopamine Receptor 1 SNPs at positions in relation to first nucleotide of the translational start codon +1403, -1251 and -800), Transcription factor AP2Beta gene (intron 2 VNTR), Neurotrophin BDNF (val66met). Chi-squares were utilized to test for differences in genotype frequencies between subjects within the subgroups of depressive subjects and healthy controls, in the polymorphisms described above. Whenever a dominant effect was known for the gene, genotypes were grouped accordingly for testing. Although the complete dataset will be presented, only findings with significant p values (≦.05) or trends (> .05 and <.1) are included in the abstract. There was a significant difference in genotype frequency for the SERT VNTR between depressives [10/10=17.5%, 10/12=51.8%, 12/12=30.7%] and controls [10/10=16.1%, 10/12=28.8%, 12/12=55.1](p= .008), and treatment resistant depressives and controls (p= .01), but only a trend between recovered depressives and controls (p= .077). Similarly there was a trend for significant difference in genotype frequency for the DAT1 between depressives [9/9=6.9%, 9/10=49.1%, 10/10=44%] and controls [9/9=4.1%, 9/10=36.4%, 10/10=59.5](p= .081), a significant difference between recovered depressives and controls (p= .012), and no association between treatment resistant depressives and controls. There was also a statistically significant difference for the DRD3, DRD4 VNTR, and COMT polymorphisms between recovered depressives and controls (respective p values= .046, .045, .003, .036), but not for treatment resistant depressives and controls. Furthermore, the treatment resistant depressives and the recovered depressives have statistically significant different distributions of the DRD4 VNTR genotypes (p=.003). Despite the modest sample size and preliminary nature of this report, the data suggest an association between several monoamine related genes and depressive phenotypes. The data further suggest that treatment resistant depressive subjects may differ in their genetic make up from subjects capable of standard antidepressant response, who have greater genetic association with dopamine function related genes.

89. Adjunctive Ziprasidone in Treatment-Resistant Depression: Randomized, Double-Blind, 8-Week Pilot Study

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Objective: To evaluate the efficacy of using ziprasidone as adjunctive therapy with sertraline in treatment-resistant major depression without psychotic features. **Methods:** Subjects 21 to 65 years old with a history of failure to respond to >4 weeks of adequate antidepressant therapy with ≥1 tricyclic or selective serotonin reuptake inhibitor (SSRI) entered a 6-week open trial of sertraline 100 to 200 mg/d (phase 1). Nonresponders (ie, those with ≤30% improvement on Montgomery–Asberg Depression Rating Scale [MADRS] and a Clinical Global Impression of Severity [CGI–S] score ≥4, and meeting DSM-IV major depression criteria) were randomized to 8 weeks of open-label treatment with sertraline monotherapy (100 to 200 mg/d) or combination therapy with ziprasidone 80 mg/d or 160 mg/d (phase 2). The primary efficacy measure was LS mean change from baseline (end of phase 1) to endpoint (end of phase 2) in MADRS Total. Secondary measures included Hamilton Rating Scale for Depression (Ham–D 17) and Anxiety (Ham–A), CGI–S, and CGI–Improvement (CGI–I). Protocol-defined post hoc analyses included individual MADRS item scores, as well as MADRS responder rates. Changes from baseline (end of phase 1) to endpoint (LOCF) were estimated using LS means on the basis of an ANCOVA model. **Results:** Of the 61 subjects (mean age 44.0±11.0 years) entering phase 2 of the study, 20 continued on sertraline only (mean daily dose: 176.0±28.0 mg), 22 received sertraline plus ziprasidone 80 mg/d (mean daily dose: 186.0±27.3 mg for sertraline; 72.1±12.9 mg for ziprasidone), and 19 received sertraline plus ziprasidone 160 mg/d (mean daily dose: 182.1±32.9 mg for sertraline; 115.9+35.8 mg for ziprasidone). At endpoint, LS mean change in MADRS Total score was greater in subjects receiving combination therapy with ziprasidone 80 mg/d (-6.8) or 160 mg/d (-7.9) than in those continuing on sertraline monotherapy (-4.1) (P=NS vs sertraline for both). Response rates (>50% MADRS decrease) were correspondingly higher in ziprasidone-treated than sertraline-only subjects (19%, 32%, and 10%, respectively; P=NS vs sertraline for both). Subjects receiving ziprasidone 80 mg/d demonstrated a significantly greater LS mean change in MADRS Apparent Sadness (P<0.05) and Lassitude (P<0.01) item scores, as well as in CGI–S (P<0.05) score, at endpoint than subjects receiving sertraline monotherapy. The response to combination therapy was rapid, occurring in week 1 of phase 2 in each of these categories. No specific safety concerns were observed with combination therapy, and overall there was no relation between adverse events and dosage in subjects given ziprasidone. **Conclusions:** In subjects with major depression and a history of treatment failure with SSRIs or tricyclic antidepressants, augmentation with ziprasidone was associated with greater improvement than continuation of monotherapy in nonresponders to high-dose sertraline. Differences in efficacy measures, while lacking statistical significance in part owing to the small sample size of this pilot study, were nonetheless similar in magnitude to improvements seen in augmentation studies of other atypical agents. Improvements and response rates versus sertraline were more robust in subjects given the higher (160 mg/d) dosage of ziprasidone.

90. The Prevalence and Phenomenology of Bipolar Disorder In Ottawa County Jail, Ohio

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Sponsor: Joseph Calabrese

BACKGROUND: The presence of undiagnosed and untreated severe mental illnesses, including substance use disorders, in the criminal justice system continues to present a public health dilemma,

and an urgently unmet need for the inmates, their families, and society at large. **METHODS:** At the time of booking, each inmate at the Ottawa County Jail completes the Mood Disorder Questionnaire (MDQ) and Michigan Alcohol Screening Test (MAST). Study researchers then meet with every consenting inmate in the jail to conduct a structured interview that includes obtaining basic demographic information, administering the MINI International Neuropsychiatric Interview (MINI), the alcohol and drug sections of the Structured Clinical Interview for DSM-IV (SCID), and the Addiction Severity Index (ASI). **RESULTS:** Fifty-five inmates met criteria for Bipolar Disorder (BD) of which 38 (70%) have Bipolar Type 1 disorder. As for mood state at time of booking, 30% were in mixed, 24% euthymic, 22% manic, 20% depressed, and 6% hypomanic. The prevalence of comorbid substance use disorders (SUD) in inmates with BD is 51/55 (93%). Of those meeting criteria for dual diagnosis BD, 92% were currently abusing or dependent on alcohol, 65% were cannabis, 33% cocaine, and 33% other. Sixty-five percent were using two or more substances and 42% three or more. In addition, 60% were comorbid with any anxiety disorder, 46% with Post Traumatic Stress Disorder, 27% with Generalized Anxiety Disorder, 25% with Panic Disorder, 11% with Social Anxiety Disorder, and 7% with Obsessive Compulsive Disorder. Inmates presenting in a mixed state at the time of booking had significantly higher comorbidity rates of any anxiety disorder and PTSD compared with inmates presenting depressed or euthymic. The mean delay in receiving in proper treatment since onset of symptoms of mania is 18 years although the majority (89%) had received some prior mental health treatment and/or substance use treatment. In terms of legal complications, inmates with BP had a mean of seven convictions, inmates with only SUD had a mean of 2.6, and inmates without any disorder a mean of 1.7. All the differences were statistically significant ($p = 0.004$). Inmates with BD spent a mean of 45 months incarcerated in their lifetime, compared to a mean of 16.5 months for inmates with only SUD, and a mean of 12.5 months for inmates without any disorders. The differences were also statistically significant. **CONCLUSIONS:** The majority of inmates with Bipolar Disorder have comorbid substance related disorders with more than one substance. There continues to exist a long delay in recognizing the proper diagnosis and offering appropriate treatments, although the severity burden indices are high in this population. Mental health in the criminal justice system presents a highly unmet need and requires more attention as a public health and policy issue.

91. Rates of Complete Remission of Individual Symptoms in Depressed Patients Treated with Venlafaxine, Selective Serotonin Reuptake Inhibitors, or Placebo

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Sponsor: Jan Fawcett

Background/Objectives: Treatment of depression to remission is now commonly accepted as the goal of therapeutic interventions. The purpose of this research was to compare remission of physical, emotional, and functional symptoms of depression during treatment with venlafaxine, selective serotonin reuptake inhibitors (SSRIs), or placebo. **Methods**: Original patient data from 31 randomized, double-blind studies were pooled to evaluate remission rates in 7422 depressed patients treated with venlafaxine/venlafaxine extended release (XR) (n=3273), studied SSRIs (fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine; n=3217), or placebo (n=932) for up to 8 weeks. Relative rates of complete symptom relief (17-item Hamilton Rating Scale for Depression [HAM-D_{17}] item score=0) on individual items of the HAM-D_{17} were compared. The last-observation-carried-forward method was used to handle missing data. **Results**: Results at 8 weeks revealed a significant ($P<0.05$) advantage for venlafaxine relative to studied SSRIs and placebo for individual items of depressed mood, anxiety-psychic, anxiety-somatic, somatic-gastrointestinal, somatic-general, genital, feelings of guilt, suicidal ideation, work and activities, retardation, and agitation, and relative to placebo only for hypochondriasis, weight loss, and late insomnia. Significant differences between SSRIs and placebo ($P<0.05$) were observed on the same items, with the exception of the anxiety-somatic, genital, hypochondriasis, and agitation items. **Conclusion**: These results suggest that the higher remission rates achieved with venlafaxine are due to complete symptom resolution of a broad range of physical, emotional, and functional symptoms of depression.

92. Incentive Motivation Influences Saccadic Eye Movements in Healthy, Anxious, and Depressed Adolescents

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Because the neural circuitry of saccadic eye movements is well known, behavioral analysis of saccadic eye movements provide a useful non-invasive method to probe regional brain function. Human and non-human performance on simple eye movement tasks has been found to be sensitive to psychopathology, neurodevelopment, and reward motivation (Sweeny et al., 1998; Luna et al., 2001; Lauwereyns, 2002). Herein, we evaluate the influence of incentive motivation on saccadic eye movement parameters in a sample of healthy adolescents, and adolescents diagnosed with major depression and/or an anxiety disorder. Participants were 28 healthy control adolescents (mean age 13 years; 15 females) and 23 adolescents (mean age 13.1 years; 11 female) who met DSM-IV criteria for either an anxiety or mood disorder. Of the anxiety and/or mood disorder participants, eleven met criteria for an anxiety disorder only (generalized anxiety disorder, separation anxiety disorder, and/or social phobia), while the remaining twelve met criteria for Major Depressive Disorder. Four of the adolescents with MDD also presented an anxiety disorder. The incentive motivation task was a 156 trial, computer based, monetary reward task. The task included three possible incentive conditions (monetary reward, monetary loss, and no monetary incentive) with a successful outcome (win money, avoid losing money, no incentive) being determined by making correct pro- or anti-saccadic eye movements. Data from only the anti-saccadic eye movements are presented. Overall, accuracy was similar among the healthy control and diagnosed groups. However, accuracy was sensitive to incentive condition as the number of correct anti-saccades was greater for reward and punishment trials than for no incentive trials. Additionally, a group x incentive condition interaction existed: Diagnosed participants made more correct no-incentive condition responses and less incentive (reward and punishment) condition responses compared to control participants. Diagnosed participants also tended to correct their response errors at the same rate across all incentive conditions, while the rate of correction for control participants varied as a function of condition. Latency and duration of the first anti-saccade and fixation after target onset differed between groups. This result was particularly significant when comparing differences between correct and incorrect trials. Finally, patients and controls showed different patterns of pupillary diameters as a function of accuracy. Additional exploratory analyses are conducted to examine differences anti-saccade responses between anxious and depressed adolescents. The results of this study suggest that anti-saccadic eye movement parameters are sensitive to incentive motivation in adolescent participants. Additionally, the findings from this study and further eye movement related research with incentive motivation tasks could provide valuable information on how healthy adolescents and those with a mood and/or anxiety disorder differ on reward-related functions. The use of this task paired with fMRI could help to identify the neural circuits responsible for these group differences in reward processes, and clar-

ify neural mechanisms underlying mood/anxiety disorders in children and adolescents.

93. Treatment of Patients Presenting with Unexplained Physical Symptoms in Primary Care

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In primary care, psychiatric disorders such as depression often present with multiple, unexplained physical symptoms. Primary care physicians miss a large number of psychiatric diagnoses but even when disorders are recognized, most patients with unexplained symptoms do not follow up with psychiatric referral. Because primary care is the "de facto mental health system", innovative approaches to address this problem are needed. Here, we report on the first 112 patients randomized into a controlled study comparing a CBT approach targeting physical symptoms to a control condition (Smith's consultation letter). The "manualized" intervention was administered by trained clinicians at the primary care site. Instruments included HAM-A and HAM-D, CGI anchored on somatic symptoms, and two functional measures (MOS-10 and PHQ-15). Results showed superior improvement for patients in the intervention group with statistically significant differences observed in scales measuring physical symptoms and functional status, but only borderline significance observed in depression/anxiety scales. Moreover, 65% of patients in the intervention group were rated as "much/very much improved" compared to only 28% of patients in the control group (P,0.0001, Fisher's Exact test). Results of this study indicate that patients presenting with medically unexplained symptoms can be successfully treated at a primary care site and that physical symptoms improve independent of other psychopathology.

94. Orexin Regulation of Corticopetal Cholinergic Transmission

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Sponsor: Past Travel Awardee, BMS, 2002

The basal forebrain cholinergic system is a critical component of the neurobiological substrates underlying attentional function. Orexin neurons are important for arousal and maintenance of wakefulness and are found in the area of the hypothalamus previously shown to project to the basal forebrain. We used dual-probe in vivo microdialysis in rats to test the hypothesis that orexin A (OxA) increases cortical acetylcholine (ACh) release. Intrabasalis administration of OxA (0, 0.1, 10.0 μM via reverse dialysis) dose-dependently increased ACh release within the prefrontal cortex (PFC). In a separate group of animals, local (intra-PFC) administration of OxA via reverse dialysis was found to have no significant effect on ACh release. In order to obtain anatomical corroboration of the basal forebrain as a site of orexin modulation of corticopetal cholinergic activity, we used immunohistochemistry to examine the relationship between orexin fibers and cholinergic neurons in the basal forebrain. We observed widespread distribution of orexin-immunoreactive fibers in cholinergic regions of the basal forebrain, particularly in more rostral areas where frequent instances of apparent appositional contact were observed between orexin fibers and choline acetyltransferase-positive cell bodies. Collectively, these data suggest that orexin projections to the basal forebrain form an important link between hypothalamic arousal and forebrain attentional systems.

95. Comparison of the Efficacy of Venlafaxine, Selective Serotonin Reuptake Inhibitors, and Placebo in the Treatment of Patients With Anxious Depression

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Background and Objective: Anxious depression, defined as Major Depressive Disorder (MDD) with high levels of anxiety symptoms, represents a relatively common depressive subtype, occurring in approximately 40% to 50% of patients with MDD. It is characterized by a relatively greater degree of psychiatric comorbidity and disability. The objective of this retrospective pooled analysis of individual patient data from a large database of randomized controlled trials was to evaluate the efficacy of venlafaxine, selective serotonin reuptake inhibitors (SSRIs), and placebo in the treatment of patients with anxious depression. **Method:** The analysis included individual patient data from 31 randomized, double-blind trials comparing treatment with venlafaxine/venlafaxine XR (n=3273) and studied SSRIs (fluoxetine, paroxetine, sertraline, citalopram, or fluvoxamine; n=3217) in MDD. Nine of the 31 studies also included a placebo control arm (n=932). Anxious depression was defined as patients with a score of 7 or higher on the anxiety–somatization (A/S) factor of the Hamilton Rating Scale for Depression (HAM-D). Efficacy analyses were performed on the intent-to-treat patient group, defined as all patients who received at least one dose of study medication and had at least one primary efficacy evaluation during treatment. The primary efficacy variable was the 17- item HAM-D ($HAM\text{-}D_{17}$). The primary outcome measure was remission, defined as a $HAM\text{-}D_{17}$ total score of 7 or less. An alternate outcome measure was evaluated as well, using a more stringent definition of remission ($HAM\text{-}D_{17} \leq 5$). To accommodate varying treatment durations (individual studies ranged from 4 to 24 weeks), week 8 was selected as the common endpoint for all studies. The last-observation-carried-forward method was used for statistical analysis. All tests of hypotheses were two-sided with a significance level of 0.05. **Results:** Patients classified as having the anxious depressive subtype comprised almost three quarters of the patient population (5370/7421; 72%). Compared with patients without anxious depression (ie, those with an A/S factor score <7), the anxious depressive patients had more severe illness at baseline, with a similar age and gender distribution. Remission rates ($HAM\text{-}D_{17} \geq 7$) at week 8 for patients with anxious depression were 39% for venlafaxine/venlafaxine XR, 33% for the SSRIs, and 24% for placebo ($P<0.001$ for all pairwise comparisons). Using the more stringent definition of remission ($HAM\text{-}D_{17} \leq 5$), week 8 remission rates among patients with anxious depression were 27% for venlafaxine/venlafaxine XR, 22% for the SSRIs, and 15% for placebo ($P<0.001$ for all pairwise comparisons). **Conclusion:** While treatment with venlafaxine/venlafaxine XR and with the studied SSRIs was associated with a significantly higher rate of remission at week 8 than treatment with placebo in patients with anxious depression, there was a significantly higher rate of remission at week 8 with venlafaxine/venlafaxine XR compared to SSRIs in the same subtype of depression. Results were consistent using the current standard definition of remission, attaining a $HAM\text{-}D_{17}$ score of 7 or less, as well as with a more stringent measure of treatment success, in which remission was defined as a $HAM\text{-}D_{17}$ score of 5 or less.

96. Pilot Data Analysis on the Columbia University Lithium Archive's Project

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Recent advances in neuroimaging techniques have produced data in Bipolar and Unipolar patients showing structural and neurochemical changes in the brain, including regional cell loss, decreased

volume and atrophy (Moore et al., 2000). Similarly, various treatment modalities, particularly chronic lithium, have measurable increases changes in these patients' grey matter volumes (Manji et al., 2000), most likely correlated with an increase in the cyto-protective protein -bel-2 in the CNS as seen in vivo and in cells of animal and human neuronal origin (Grey et al., 2003). These clinical and laboratory findings support the currently held hypothesis that Lithium and other psychotropic agents used in treating mood disorders may have neuroprotective and neuroregenerative properties. The following represents the beginning of our pilot data entry and analysis of this natural epidemiological experiment. **Objective:** To retrospectively review charts of patients diagnosed with Bipolar disorders that were treated with lithium to determine whether chronic lithium treatment of these patients resulted in any measurable differences in the prevalence of neurodegenerative illnesses in this unique population compared to the prevalence of these disorders in the general population. **Method:** From an archival collection of over 8000 charts taken from three Lithium clinics in New York City compiled over 40 years, an initial 444 charts were randomly selected to conduct a pilot analysis of sixteen neurodegenrative variables which were entered into a standard statistical software program. **Results:** The preliminary data analysis of this small sample of bipolar patients (N=300) was not expected to and did not reach statistical significance for all variables analyzed. However, the results did demonstrate a positive trend towards statistical significance (p-value < 0.05) for some of the variables. **Conclusion:** As our elderly population increases due to medical and sociological advances, there remain no cures in sight for neurodegenerative diseases which cost billions of dollars in healthcare worldwide. Considering the neuroprotective and neuroregenerative properties of Lithium and other psychotropic drugs, further exploration of these properties (i.e. clinical trials) should be conducted on these illnesses including Alzheimer's, Parkinson's, Multiple Infarcts, etc. Our intent is to continue entering and analyzing our unique data sample to ultimately confirm or reject the clinical and laboratory findings that chronic Lithium treatment provides neuroprotective properties in human subjects with mood disorders treated with long-term Lithium. Additionally, our goal is to establish a unique computer database of this large sample which will be made available to other researchers investigating bipolar and unipolar illnesses in the future.

97. Double-Blind Dose-finding Study of Omega-3 Fatty Acids for Postpartum Depression

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Sponsor: Alan Gelenberg

Background: Postpartum depression (PPD) is a common disorder with broad public health implications. Omega-3 fatty acids are polyunsaturated fatty acids with many associated health benefits. Epidemiological and preclinical data suggest a role for omega-3 fatty acids in PPD. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are seafood-derived omega-3 fatty acids. Three of four published placebo-controlled trials demonstrate significant benefit of EPA or EPA and DHA in major depression. Some controlled studies suggest that lower doses of omega-3 fatty acids may be more effective than higher doses. Standard antidepressants are often used for PPD, but only one placebo-controlled trial in PPD has been published. Some women are unwilling to accept antidepressant medications while breastfeeding, because long-term effects on the infant are unknown. **Methods:** Women with PPD (N=21) were recruited for an 8-week dose-finding trial of EPA and DHA. Subjects were randomly assigned to daily doses of 0.5 g, 1.4 g, or 2.8 g. Placebo capsules were provided so participants received a total of six capsules/day. Subjects were assessed at visits at baseline and weeks 1, 2, 4, 6, and 8. Serial assessments included the Edinburgh Postnatal Depression Scale (EPDS), the Hamilton Rating Scale for Depression (24-item) (HRSD), and Clinical Global Impressions Scale (CGI). Side effects were assessed at each visit. **Eligibility Criteria:** Women ages 18-45 who met criteria for a major depressive episode with postpartum onset (diagnosis verified with the Structured Clinical Interview for DSM-IV). Minimum scores of 9 on the EPDS or 15 on the HRSD were required. **Exclusion Criteria:** Previous intolerance/allergy to fish oil, current use of antidepressants, psychotic symptoms, history of mania/hypomania, and active suicidal ideation. **Results:** For all subjects who returned for at least one visit after starting omega-3 fatty acids (N=16), mean decrease in EPDS was 51.5%. Overall mean decrease in HRSD was 48.8%. 8/16 (50%) achieved EPDS < 9; 8/16 (50%) achieved HRSD < 8. For the lowest dose, 0.5 g/day (N=6), the mean decrease in EPDS was 53.7%. Mean decrease in HRSD was 48.8%. 4/6 (66.7%) had end EPDS <9; 4/6 (66.7%) had end HRSD < 8. For the intermediate dose, 1.4 g/day (N=3), the mean decrease in EPDS was 69.9%. Mean decrease in HRSD was 64.6%. 2/3 (66.7%) had end EPDS <9; 2/3 (66.7%) had end HRSD < 8. For the highest dose, 2.8 g/day (N=7), mean decrease in EPDS was 41.8%. Mean decrease in HRSD was 43.2%. 2/7 (28.6%) had end EPDS <9; 2/7 (28.6%) had end HRSD < 8. Using individual growth modeling, Level 1 analyses demonstrated that over time in the trial there was a general decline in individuals' depression scores. Level 2 analyses revealed that dose did not significantly influence differences in trajectories on either the EPDS or HRSD measures. However, the CGI did show that dose had a significant effect on trajectories. Omega-3 fatty acids were well tolerated. There were no serious adverse events. **Conclusions:** This study provides data about a novel treatment for PPD. Omega-3 fatty acids offer health benefits to the mother and to her infant if she is breastfeeding. The limitations of this pilot trial included small sample size and lack of placebo group. In this sample, depression scores decreased over time of study participation, which could have been an effect of the supplement or of time itself. The results suggest that omega-3 fatty acids might be a promising treatment for PPD.

98. Chronic Stress Decreases The Nunber Of Parvalbumin-Immunoreactive Interneurons In The Hippocampus: Prevention By Treatment With Fluoxetine

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Sponsor: Dirk Hellhammer

Previous studies have demonstrated that stress may affect the hippocampal GABAergic system. Here, we examined whether long-term psychosocial stress influenced the number of parvalbumin-containing GABAergic cells, known to provide the most powerful inhibitory input to the perisomatic region of principal cells. Adult male tree shrews were submitted to five weeks of stress, after which immunocytochemical and quantitative stereological techniques were used to estimate the total number of hippocampal parvalbumin-immunoreactive (PV-IR) neurons. Stress significantly decreased the number of PV-IR cells in the dentate gyrus (-33%), CA2 (-28%) and CA3 (-29%), whereas the CA1 was not affected. Additionally, we examined whether fluoxetine administration (15 mg/kg per day) offered protection from this stress-induced effect. Animals were subjected to a seven-day period of psychosocial stress before the onset of daily oral administration of the drug, with stress continued throughout the 28-day treatment period. Fluoxetine administration attenuated the stress-induced reduction of the number of PV-IR interneurons in the dentate gyrus, without affecting the CA2 and CA3. The effect of stress on interneuron numbers may reflect real cell loss; alternatively, parvalbumin concentration is diminished in the neurons, which might indicate a compensatory attempt. In either case, antidepressant treatment offered protection from the effect of stress and appears to modulate the hippocampal GABAergic system.

99. Presentations of Depression in Primary Care vs. Special Care Settings: Results From STAR*D

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Sponsor: Robert Golden

Objective/Background: No study has directly compared the clinical features of depression for patients entering clinical trials using identical enrollment criteria at both Primary Care (PC) and Specialty Care (SC) settings. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (www.star-d.org) provides a unique opportunity to provide such a comparison for patients with a major depressive disorder (MDD) requiring treatment. Our objective was to compare sociodemographic, course of illness, and clinical features of depression for patients concurrently enrolled in PC vs. SC settings. **Methods:** We report baseline data for the first 1500 patients enrolled in this ongoing trial. Patients were recruited from fourteen United States regional centers that were comprised of 41 clinic sites (19 PC, 22 SC). In this "hybrid" design trial, we used broadly inclusive eligibility criteria that required patients to have a DSM-IV diagnosis of nonpsychotic MDD; to not have had an unsatisfactory response to an adequate medication trial during their current episode; and to score≥ 14 on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$). Primary measures at baseline included $HRSD_{17}$; 30-item Inventory of Depressive Symptomatology ($IDS\text{-}C_{30}$); and the Cumulative Illness Rating Scale. **Results:** SC and PC patients had equivalent degrees of depressive severity ($HRSD_{17}$ = 20; $IDS\text{-}C_{30}$ = 36). SC patients were almost twice as likely to report a prior suicide attempt than PC patients (21% vs. 12%, $p<0.0001$). PC patients reported a significantly greater number and higher severity of general medical conditions. Besides suicide risk, the only distinguishing core symptom of depression was the greater likelihood of PC patients to endorse weight loss (29.7% vs. 35.3%, p=0.005 by $IDS\text{-}C_{30}$; 27.0% vs. 33.8%, p=0.001 by the $HRSD_{17}$). **Conclusion:** Depressive severity was not different, and symptomatic presentations did not differ substantially. Major depressive disorder is more similar than different among patients at SC and PC settings. Thus, similar clinical and research methods to screen for, detect, and measure the effects of treatment can be applied in both settings.

100. Nicotinic Antagonist Augmentation Of SSRI Antidepressants: Preliminary Results

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Background: There is increasing evidence that most antidepressant agents (SSRIs, tricyclics, bupropion) may exert their clinical effects, at least in part, by antagonism of central high-affinity nicotinic acetylcholine receptors (nAChRs). This is of clinical interest since nearly 50% of patients with major depression are cigarette smokers, and smoking is thought to have antidepressant effects. The present study is a "proof-of-concept" clinical trial that evaluates the potential of the high-affinity nAChR antagonist, mecamylamine hydrochloride (MEC; Inversine®), as an augmentation strategy for treatment of major depression in patients who are partial responders to serotonin-selective reuptake inhibitors (SSRIs). **Methods:** Subjects with major depression who partially responsive (based on HAM-D scores) to SSRIs (e.g., fluoxetine, sertraline, citalopram, paroxetine and fluvoxamine) are being randomized to: 1) MEC (5 mg po bid) or; 2) matching placebo (PLO; 0.0 mg/day) for a total of eight weeks. **Results:** To date, n=11 subjects (n=6 to MEC, n=5 to placebo) have completed the trial. Four out of six (67%) subjects assigned to active MEC were classified as responders at the end of the 8-week trial, as assessed by a 50% reduction in HAM-D scores, as compared to 0/5 (0.0%) subjects assigned to PLO (Pearson's c2=5.24, df=1,p=0.02). Constipation was reported as the most common adverse event (MEC group, 4/6; 67%; PLO, 2/5; 40%; c2=0.78, df=1, p=0.38). **Conclusions:** These preliminary results suggest that high-affinity nAChR antagonism may augment SSRI-treated refractory major depression. Supported in part by The Donaghue Medical Research Foundation and K02-DA-16611 to T.P.G.

101. Predictors of Smoking Cessation in Schizophrenia: Analysis of Data from Three Sequential Controlled Clinical Trials

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Our group at Yale University has conducted three sequential controlled clinical pharmacotherapy trials for smoking cessation in patients with schizophrenia and schizoaffective disorder. The purpose of the current study was to identify baseline patient characteristics that predict smoking cessation treatment outcome among the 120 patients who have completed these trials to date. The three individual trials were of 10 weeks duration, and the behavioral platform included weekly group therapy emphasizing motivational enhancement, cognitive-behavioral therapy, social skills training and psychoeducation. These behavioral interventions were augmented by pharmacological treatments including: Study #1, Open-label transdermal nicotine patch (TNP, 21 mg/24h; n=45, George, T.P. et al., 2000. Am. J. Psychiatry. 157: 1835-1842); Study #2, Sustained-release bupropion (BUP) vs. placebo (PLO) (n=32; George, T.P. et al., 2002. Biol. Psychiatry. 52: 53-61); Study #3, the combination of TNP (21 mg/24h) with either BUP or PLO (n=42 with enrollment target of n=100). Overall cessation rates in the three studies were 35.6%, 31.3% and 20.0% respectively (Chi square=NS). Logistic regression analysis was used to predict 7-day point prevalence smoking abstinence at the end-of-trial (EOT) from the following variables: age, race, gender, baseline cigarettes per day, depressive symptoms, negative symptoms, degree of nicotine dependence, class of antipsychotic medication, psychiatric diagnosis, TNP treatment and BUP treatment. Controlling for differences among studies in EOT cessation rates, the strongest predictors of abstinence were lower levels of nicotine dependence, and treatment with bupropion and atypical antipsychotic medication. Our findings suggest that atypical antipsychotic treatment could serve as the focus for tailored interventions for the treatment of nicotine dependence in this vulnerable subpopulation of psychiatric smokers. Supported by NIDA grants K02-DA-16611, R01-DA-13672 and R01-DA-14039 (to T.P.G.), NARSAD (to T.P.G.), the VISN 1 MIRECC, and the Yale (P50-DA-13334) and Brown (P50-CA-84719) Transdisciplinary Tobacco Use Research Centers (TTURCs).

102. The "Sweet Spot" For The Plasma Dim Light Melatonin Onset For Winter Depressives Treated With Low-dose Daytime Melantonin: Support For The Phase Shift Hypothesis (PSH)

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SAD patients took capsules containing either placebo or melatonin (0.225-0.3 mg in 3-4 divided doses) every two hours beginning at waketime [zeitgeber time (ZT) 0]. Each year from 1998 to 2001, patients were placed into one of three cohorts, the first beginning in

early January and the last beginning at the end of January. Each cohort was divided into 3 groups. The AM melatonin group (n=33) took melatonin no later than ZT 6 (and took placebo thereafter) and the PM melatonin group (n=33) took melatonin no earlier than ZT 6 (and took placebo beforehand). The placebo group (n=34) took only placebo. Patients could not tell what was in the capsules. For one baseline and 3 treatment (Tx) weeks, patients were asked to maintain consistent sleep times (according to individual weekday habits). The ZT when the dim light melatonin onset crossed the 10 pg/ml threshold (DLMO10) was calculated by subtracting the average clock time of awakening for the prior week (recorded by the activity monitors) from the clock time of the DLMO10. Patients from 1998 were eliminated from these analyses because activity monitors were not yet available to accurately assess waketime. Patients from the third cohort were also excluded from these analyses, because of differences between this cohort and the other two cohorts studied earlier in the winter. Hypothesizing that optimum mood would occur when DLMO ZT=14 hours (the average of historical controls), our findings uniformly and consistently support the original PSH, which states that phase-delayed SAD patients (ZT≥14) should respond to a corrective phase advance and phase-advanced patients (ZT<14) should respond to a corrective phase delay. Polynomial curves fit to pre- and post-Tx SIGH-SAD scores vs. DLMO ZTs were statistically significant (pre-Tx $R2 = 0.23$, $df = 44$, $p = 0.003$; post-Tx $R2 = 0.26$, $df = 43$, $p = 0.002$): patients whose DLMO ZTs were closer to 14 had lower depression ratings than those further away. Percent change in SIGH-SAD and change in absolute deviation from DLMO ZT 14 correlated significantly ($r = -0.34$, $df = 44$, $p = 0.02$): the closer patients' DLMO ZTs moved towards DLMO ZT 14, the more depression ratings decreased. Post-Tx and change results became more robust with removal of the placebo group (post-Tx $R2 = 0.34$, $df = 27$, $p = 0.003$; pre to post-Tx change $r = -0.49$, $df = 27$, $p = 0.01$). These findings support the PSH: SAD patients whose DLMO ZTs were phase advanced (n=14) or delayed (n=33) with respect to waketime respond to a corrective phase shift toward DLMO ZT 14. A phase-delayed DLMO ZT suggests a subsensitivity to light or long intrinsic circadian period, and a phase-advanced DLMO ZT suggests a hypersensitivity to light or short intrinsic circadian period; both light sensitivity and intrinsic period are likely under genetic control. It would be of interest to re-analyze the data from previous studies using the DLMO ZT 14 standard; however, the substantial placebo component of light may obscure treatment findings. Our data provide continuing support for phase typing (advanced or delayed) and the recommendation to avoid overly phase-shifting SAD patients, since symptoms worsen if patients are phase-shifted beyond DLMO ZT 14. To the best of our knowledge, this may be the first psychiatric disorder for which a physiological marker has been identified that correlates with symptomology before, after, and in response to treatment.

103. Haloperidol Ameliorates the Reductions in Sensorimotor Gating and Camp Levels Seen in Mice Overexpressing the G-Protein Subunit G Alpha S

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Dysfunction of the cAMP/PKA pathway along with changes in G-protein signaling have been noted in patients with schizophrenia. Our laboratory has developed transgenic mice in which the G-protein subunit Gαs is overexpressed to test the hypothesis that altered G-protein signaling contributes to specific endophenotypes associated with schizophrenia, such as sensorimotor gating deficits. Previously, experiments were conducted with Gαs* transgenic mice that overexpress a constitutively active isoform of Gαs driven postnatally in forebrain neurons by the CaMKIIα-promoter. Gαs* transgenic mice were shown to exhibit elevated adenylyl cyclase activity (Wand et al., J. Neurosci, 2001, v21, p5297) as well as several behavioral endophenotypes of schizophrenia, including decreased prepulse inhibition of the acoustic startle (PPI; Gould et al., Neuropsychopharm, 2004, v29, p494). Despite exhibiting increased adenylyl cyclase activity, Gαs* transgenic mice show decreased cAMP levels in hippocampus and cortex, possibly due to a compensatory increase in phosphodiesterase activity. The current experiment was undertaken to test the hypothesis that antipsychotic treatment would ameliorate the reductions in PPI and cAMP seen in the Gαs* transgenic mice. Administration of 0.1 mg/kg haldoperidol selectively improved PPI in the Gαs* transgenic mice. Further, in cortex, 0.1 mg/kg haloperidol only increased cAMP levels in Gαs* transgenic mice. Additional experiments were conducted with C57BL/6J mice to determine if pharmacological disruption of PPI by amphetamine would also be associated with decreases in cAMP levels. Administration of 10 mg/kg DL-amphetamine lowered cAMP levels in hippocampus, cortex, and cerebellum; however, 10 mg/kg D-amphetamine only lowered cAMP levels in cortex. These experiments suggest that cAMP levels in cortex may play a key role in sensorimotor gating. Given the limitations of studying constitutive transgene expression, we developed a line of transgenic mice in which the wildtype isoform of Gαs is overexpressed under the control of a tetracycline-responsive promoter (tetO-Gαs). Expression of tetO-Gαs only occurs in animals that also express the tetracycline-responsive transactivator (tTA) under the control of the CaMKIIα promoter. This bigenic promoter system restricts expression to postnatal forebrain neurons, and transgene expression can be suppressed at any time by administering doxycycline to these animals, thus allowing for the differentiation between acute and chronic effects of the transgene of interest. Like Gαs* transgenic mice, tTA/tetO-Gαs transgenic mice exhibit several behavioral endophenotypes of schizophrenia, including decreased PPI. Importantly, reductions in PPI were reversed in the tTA/tetO-Gαs transgenic mice by administration of either doxycycline (200 mg/kg) or 1.0 mg/kg haloperidol. Future experiments will determine if tTA/tetO-Gαs transgenic mice also demonstrate reduced levels of cAMP, if haloperidol reverses amphetamine-induced decreases in cAMP, and if the decreases in cAMP in Gαs* mice are due to increased phosphodiesterase activity. In summary, we have demonstrated that both genetic and pharmacological disruption of PPI correlate with decreased cAMP levels in cortex, which, at least in the case of the genetic disruption, can be reversed by antipsychotic treatment. Supported by: NIMH Conte Center (R. Gur, PI). The authors affirm that this work has been carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals and was fully approved by the IACUC of the University of Pennsylvania.

104. Safety and Tolerability of Antipsychotics in Children and Adolescents

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BACKGROUND: Antipsychotics prescriptions have increased markedly in recent years. This applies not only to adult population, but also to children and adolescents, a particularly vulnerable group in which the safety and tolerability of these drugs have scarcely been assessed. We hypothesized that side effects in this group of patients will be more pronounced than those seen in adults. **METHODS:** We are conducting a one-year longitudinal, naturalistic study of 125 children and adolescents treated with antipsychotics, regardless of diagnosis. The study is being conducted in a catchment area that includes two inpatient units, three outpatient units and one day hospital. Clinical and sociodemographic data have been collected at baseline. The information gathered at each visit (baseline, 6 months and 1 year) includes an electrocardiogram, blood test (CBC; biochemistry, including prolactin, thyroid hormones and glycosilated haemoglobin lev-

els), height and weight, and extrapyramidal side effects (EPS), which are being evaluated with the Involuntary Movements Scale (IMS). The person that evaluates EPS has been specifically trained in the use of the IMS, with periodical interrater and intrarater reliability assessments (ICC from 0.8 to 1.0 for the different scale items). **RESULTS:** At present, we have been able to evaluated 80 children, 21 of whom were drug-naive at baseline. 24 of them have completed the six-months' follow-up. The mean age of our sample is 14.8 years (SD = 2.47). 58.8% (n=47) of our patients are male. Forty-four percent have a psychotic disorder, 15% have an eating disorder, 8% non-specific conduct disorders, and 5% affective disorders. Other less frequent diagnoses are autism and other general pervasive developmental disorders, mental retardation, tic disorders, attention deficit and hyperactivity disorders. At baseline, 10% (8) of our patients have only been only on first 1st generation antipsychotics, 36.25% (29) only on 2nd second generation antipsychotics only; and 12.5% have taken a combination of both. The mean number of antipsychotics for a given patient was 1.86 (SD = 1.28). Only 11.3% (9) were taking stimulants at baseline. 8.8% (7) had previous history of dystonic reactions. The most frequently endorsed side effects were sleepiness (47.5%), increased (18.8%) and decreased (17.5%) salivation, rhinitis (18.8%), increased appetite (16.3%) and headache (15%). In the drug-naive group (n= 21), at baseline, we found prevalence rates of 22.3% for mild dyskinetic movements, and 5.6% for mild parkinsonian signs. Among patients that were already taking antipsychotics (n= 59), 32.2% showed mild dyskinetic movements, and 19.4% mild parkinsonian signs. Differences between these two groups were statistically significant ($p<0.01$). We have not found significant changes in blood tests, at baseline nor at the six months visit, except for hyperprolactinaemia in 81.8% of patients at baseline. Comparing baseline and six-months follow-up results, there is a significant increase in global dyskinesia ratings ($p<0.05$), but not in parkinsonism or akathisia. There is a significant increase in weight ($p<0.01$), and a significant decrease of prolactin levels from baseline to the second visit ($p<0.03$). **CONCLUSIONS:** Side-effects of antipsychotic drugs should be carefully monitored in children and adolescents. Further investigation in this area is required.

105. Neurobiological Consequences of Early Developmental Exposure to Methylphenidate in Rats

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Evidence from laboratory animals indicates that repeated exposure to psychostimulant drugs produces sensitization to their rewarding effects, a process that in humans would be expected to increase vulnerability to substance abuse. However, therapeutic administration of psychostimulants such as methylphenidate (MPH; Ritalin) in children with attention deficit-hyperactivity disorder (ADHD) reportedly reduces the risk of substance abuse. Here we examined in rats some of the consequences of exposure to stimulant drugs during a period of early development. We exposed rats to MPH (2.0 mg/kg) twice daily during early adolescence (postnatal days [P]20-35) and then conducted a battery of tests designed to explore if this early treatment would cause behavioral or molecular alterations during adulthood (P60). In place conditioning studies, early developmental exposure to MPH caused dramatic alterations in sensitivity to cocaine: intermediate doses of cocaine that had no effects in control rats caused conditioned place aversions, whereas higher doses of cocaine that caused conditioned place preferences in control rats had no effect. These data suggest that exposure to MPH during this developmental period may promote dysphoria-like or anhedonia-like signs in rats. Similar exposure to cocaine (15 mg/kg) during the same developmental period produces the same effects in this assay. To confirm these results in another assay, we tested rats exposed to MPH using intracranial self-stimulation (ICSS), a complex operant procedure that is highly sensitive to the function of brain reward systems. Early MPH exposure reduced the ability of cocaine to potentiate the rewarding effects of medial forebrain bundle (MFB) stimulation. These data again suggest that early exposure to psychostimulant drugs promotes anhedonia-like responses, particularly when sensitivity to cocaine is used to quantify reward. However, MPH exposure did not alter sensitivity to the rewarding effects of electrical stimulation of the MFB itself under our test conditions. To examine if early exposure to MPH causes the emergence of other depressive-like behaviors in rats during adulthood, we also studied behavioral patterns in the forced swim test (FST). Rats exposed to MPH became immobile faster and spent more time in immobility postures in the FST, suggesting an increased tendency toward despair-like behaviors. Molecular studies conducted in parallel revealed that the behavioral adaptations caused by early developmental exposure to MPH are accompanied by persistent increases in the expression of CREB (cAMP response element binding protein) within the nucleus accumbens shell (NASh). Interestingly, increases in CREB activity within this region have been previously associated with the development and expression of depressive-like signs in rats. In summary, exposure to MPH during a period of early adolescence in rats (P20-35) promotes anhedonia-like, dysphoria-like, and despair-like signs during adulthood (P60), and these signs are accompanied by long-lasting alterations in levels of CREB within the NASh. Considering that the role of the NASh in reward-related behaviors is well established, these adaptations may indicate collectively that early developmental exposure to psychostimulants causes a general dysfunction of brain reward systems during adulthood. Indeed, other groups have shown that this treatment also reduces sensitivity to natural rewards such as sucrose, novelty, and sexual behavior. These studies highlight the need for a more thorough understanding of the long-term consequences of early developmental exposure to psychotropic drugs.

106. Psychological Stress or CRF Causes a Delayed Disruption of Prepulse Inhibition in Rats

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Sponsor: Past Travel Awardee, BMS, 1998

Prepulse inhibition (PPI), an operational measure of sensorimotor gating, refers to the phenomenon in which a weak stimulus presented immediately before an intense startling stimulus inhibits the magnitude of the subsequent startle response. PPI is deficient in a number of psychiatric illnesses including schizophrenia that involve a putative breakdown in sensorimotor gating. Stressful events can exacerbate schizophrenic symptomatology, yet the effects of stress on PPI have been relatively understudied. This study compared the effects of a purely psychological stressor (predator exposure) to those of a noiciceptive physical stressor (footshock) on PPI and baseline startle responses in rats over an extended period of time following stressor presentation. Male Sprague-Dawley rats were exposed (within a protective cage that prevented physical contact) to ferrets for 5 min or left in their homecage and then tested for PPI immediately, 24 hours, 48 hours, and 9 days after the exposure in a session consisting of 120-dB pulses and prepulse + pulse trials with prepulses that were 3, 6, or 12 dB above background. The effects of footshock (3, 1-sec, 1.5-mA presentations, 20 sec apart) were evaluated in a separate set of rats. Finally, the profile of effects seen with stressor presentation was compared to that elicited by the stress hormone corticotropin-releasing factor (CRF, 3ug/5ul given intracerebroventricularly). PPI was unaltered immediately after ferret exposure, but was significantly disrupted 24 hours later. This disruption normalized by 48 h, and at the 9-day time point, there was a trend towards increased PPI in ferret-exposed rats compared to controls. There was no effect of predator stress on baseline startle re-

sponses. In contrast, footshock failed to affect PPI, but did elevate baseline startle responses immediately after stressor presentation. CRF mimicked elements of both stressors: PPI was disrupted 24h but not immediately after CRF administration (as with predator stress), and baseline startle responses were increased immediately after CRF administration (as with footshock). These results indicate that 1) a purely psychological stressor produces a delayed disruption of PPI that is independent of changes in baseline startle reactivity, 2) different types of stressors have distinct effects on startle plasticity, 3) stimulation of CRF receptors recapitulate stress effects on PPI and startle magnitude.

107. Overall Treatment Effectiveness as Measured by Time Continuing on Antipsychotic Therapy

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Background: Continuation of antipsychotic medication is a strong negative predictor of relapse. Indeed, antipsychotic discontinuation is associated with diminished treatment effectiveness and increased risk of illness relapse (Herz et al., 1991). Discontinuation may occur due to patient or physician decisions encompassing lack of efficacy, adverse events, and other factors. All-cause treatment discontinuation captures all of these reasons and has been identified as an important long-term clinical endpoint (Stroup et al., 2003). In this post-hoc analysis, we examined continuation on antipsychotic therapy in head-to-head clinical studies of olanzapine versus other antipsychotics (typical and atypical). **Methods:** Studies were included in this meta-analysis if they met the following criteria: duration of >12 weeks, double-blind randomized treatment assignment, at least 20 patients per treatment arm, no protocol-specified definition for mandatory discontinuation prior to 12 weeks, and if there were at least 2 studies for each antipsychotic comparator. Through a PubMed literature search, we identified 13 available studies that met the inclusion criteria. Patients′ diagnoses included (DSM-IV-TR) schizophrenia, schizophreniform disorder, and schizoaffective disorder. One of the olanzapine-ziprasidone comparator studies has not been included in the analysis at this time because the data required for the analysis is not available. Based on the continuation time in the studies, weighted mean hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated; in addition, reasons for discontinuation were analyzed. The numbers of comparative studies included in this meta-analysis, along with the combined number of patients, were as follows: 5, olanzapine (n=421) versus risperidone (n=426); 2, olanzapine (n=550) versus ziprasidone (n=525); 5, olanzapine (n=537) versus haloperidol (n=439); 3, olanzapine (n=201) versus clozapine (n=202). There were 4 antipsychotics that did not meet the criteria of at least two published studies for each comparator: quetiapine n=175, amisulpride n=70, fluphenazine n=30, and perphenazine n=23. However, for thoroughness, reasons for discontinuation will be presented from these studies. **Results:** Compared with olanzapine, the HRs (CIs) were as follows: haloperidol, 1.4 (1.2, 1.7; $p < 0.0001$); clozapine, 1.2 (0.9, 1.6; $p = 0.312$); risperidone=1.3 (1.1, 1.6; $p = 0.0047$); and ziprasidone=1.6 (1.4, 2.0; $p < 0.0001$). The heterogeneity tests for all treatment comparisons were not significant indicating no significant interaction between treatment effect (as measured by HRs) and the respective study. Approximately 54% of olanzapine-treated patients continued through the end of the studies, compared with 46% of risperidone-, 45% of ziprasidone-, 35% of haloperidol-, and 55% of clozapine-treated patients. We will present survival curves with log-rank test statistics for each study along with formal meta-analyses. **Conclusions:** Olanzapine appears to be associated with significantly longer continuation of treatment relative to haloperidol, risperidone and ziprasidone, but not clozapine.

108. Homocysteine Reducing Strategies Improve Symptoms in Chronic Schizophrenic Patients with Hyperhomocysteinemia

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Elevated homocysteine levels are a risk factor for Alzheimer's disease as well as cerebrovascular disease 1. Homocysteine is neurotoxic in vitro 2. Recently, markedly elevated homocysteine levels were reported in young male schizophrenia patients 3. Since folic acid, B-12 and pyridoxine have marked homocysteine-reducing properties 4, we conducted a study of these vitamins in chronic schizophrenia patients selected for elevated plasma homocysteine levels. Chronic schizophrenia patients with levels over 15mM were accepted for study after written informed consent. The design was a double-blind crossover with one tablet a day containing 2mg folic acid, 25 mg pyridoxine and 400 mg B-12. After 3 months patients were crossed over from active vitamin to placebo or vice versa. Thirty seven patients entered the study, thirty six males and one female. All patients entering the study were symptomatic but had shown no major clinical changes for at least one month. Clinical ratings were made monthly using the Positive and Negative Syndrome Scale (PANSS) and Abnormal Involuntary Movement Scale (AIMS). Plasma was taken for homocysteine monthly. Neuropsychological tests were administered by the research physician, blind to patient condition (placebo/vitamin), in the following standardized sequence: Diget Span, Rey Auditory Verbal Learning Test (RAVLT); Wisconsin Card Sort 64 card version (WCST); Complex Figure Drawing. Homocysteine levels declined markedly on vitamin treatment within one month from a mean of 25mM to a mean of 10mM. Patients improved 5.7 PANNS points more on three months of vitamin treatment than on three months of placebo (1.9 points more on the positive symptoms subscale; 1.9 points more on the negative symptoms subscale; 1.9 points more on the general psychopathology subscale). Contrast analysis (with planned comparison between the two periods of treatment) showed significant effect of vitamin treatment for group that starts with vitamins, $F = 10.21$; $df = 1,34$; $p < 0.003$ and for group that starts with placebo, $F = 8.02$; $df = 1,34$; $p < 0.007$). In neuropsychological testing in the first phase of the study, the group receiving vitamins differed significantly from the placebo group in improvement in both measures of the WCST: improvement in categories completed ($p = 0.027$) and a reduction in perseverative errors ($p = 0.037$). The present study suggests that specific vitamins in a specific clinical population defined by hyperhomocysteinemia may yield measurable clinical benefit.

109. Alterations in the Expression of Proteins Associated with AMPA Receptor Trafficking in the Prefrontal Cortex in Schizophrenia

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Sponsor: James Meador-Woodruff

Evidence of abnormalities of glutamatergic neurotransmission have been found in the prefrontal cortex (PFC) in schizophrenia. Clinical studies have suggested that ampakines, positive modulators of AMPA receptors, improve cognitive function in schizophrenic patients, while enhancement of AMPA receptor-mediated currents by these compounds may potentiate the activity of antipsychotics.

AMPA receptor trafficking is a critical aspect in the regulation of synaptic efficacy at the glutamatergic synapse. Localization, cell surface expression, and activity-dependent regulation of AMPA receptors are modulated and maintained by a complex network of protein-protein interactions associated with targeting, anchoring, and spatially organizing synaptic proteins at the cell membrane. These proteins alter receptor sensitivity to glutamate and modulate signaling cascades associated with synaptic transmission by linking AMPA receptors to critical intracellular effector molecules. It has been suggested that the protein NSF (N-ethylmaleimide-sensitive fusion protein), that interacts with the C-terminus of GluR2, regulates the "constitutive pool" for recycling of AMPA synaptic receptors independently of NMDA activation. The GluR2 and GluR3 AMPA subunits interact with at least three PSD proteins: GRIP1 (glutamate receptor-interacting protein 1), ABP (AMPA receptor-binding protein), and PICK1 (protein interacting with C- kinase 1). These proteins are linked to vesicular trafficking in the "regulated pool" of AMPA receptors, and are dependent on NMDA activation, regulating the intracellular "storage" of AMPA receptors. SAP97, on the other hand, trafficks GluR1 containing newly synthesized AMPA receptors. Stargazin is a novel protein that binds to all four AMPA subunits, and has been identified as a mediator of AMPA receptor function in a two-step trafficking model, in which it first conveys AMPA receptors to the neuronal surface and then sweeps them laterally into postsynaptic sites. In previous studies from this lab, we found no changes in the expression of AMPA receptors and associated subunits in schizophrenic brain. In contrast, expression of some of these intracellular trafficking proteins might be altered in schizophrenia, resulting in an apparent abnormality of AMPA receptor function despite normal apparent levels of total cellular AMPA receptors and AMPA receptor subunits. In situ hybridization and western-blot experiments in postmortem samples of PFC in schizophrenia indicate that there is increased expression of the proteins related to the "regulated pool" that immobilize AMPA receptor containing vesicles in an intracellular pool, including GRIP1, while there is no change in the expression of NSF, a protein mediator of the "constitutive" NMDA-independent recycling of AMPA receptors. These data indicate that in the PFC in schizophrenia, AMPA receptors may be assayed to be normal in total number, but are functionally deficient due to abnormalities in trafficking and subsequent availability for signal transduction by incorporation in the postsynaptic cell membrane. These results suggest that assay of receptor expression in brain may be an inadequate measure of the overall state of a given receptor subtype given emerging findings on the complexities of the cell biology of receptor regulation.

110. Chronic Disruption of GABAergic Transmission within the Medial Prefrontal Cortex Affects Amygdalar Intrinsic Circuits

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Sponsor: Anantha Shekhar

Massive reciprocal connections link the amygdala to the medial prefrontal cortex. Such connections are thought to be involved in a number of physiological functions related to the processing and expression of emotions. Not surprisingly, disruption of these circuits has been postulated to occur in several major psychiatric disorders, such as schizophrenia, bipolar disorder, major depression and post-traumatic stress disorder. We tested the hypothesis that a disruption of GABAergic transmission within the medial prefrontal cortex, thought to occur in many of these diseases, may affect specific amygdalar intrinsic circuits. Abnormalities thus induced in the amygdala may in turn account for several symptoms characteristic of major psychiatric disorders. In a previous set of experiments, acute local infusion of the GABA-A receptor antagonist picrotoxin within the infralimbic (IL) cortex (ventral portion of the medial prefrontal cortex) was used to investigate patterns of neuronal activation within the intercalated cell masses of the amygdala (ICM). Induction of the immediate early gene protein product Fos was found to be significantly increased in the ICM, both ipsi- and contra-laterally to the injection side. Analysis of GABA immunocytochemistry also suggested that the IL cortex may increase GABA concentration in ICM. Overall, these results raise the possibility that inputs from the IL cortex directly activate the ICM. Such activation is likely to result in prolonged effects, involving changes in gene expression, protein synthesis and GABA release, that could modify the responsiveness of the ICM to inputs from the basolateral nucleus of the amygdala. A chronic paradigm was used for the present experiments in order to more closely mimic the chronic course of major psychiatric disorders. Adult male rats were implanted with a cannula aimed at layer 2 of the IL cortex and connected through a catheter to an osmotic pump inserted subcutaneously. Picrotoxin (150 uM) or vehicle (artificial cerebrospinal fluid) were continuously infused (0.2 ul/hr) over 8 days. Rats were sacrificed, perfused with fixative and the brains removed and sliced on a freezing microtome. Serial sections throughout the amygdala were processed for immunocytochemistry using antisera raised against GABA, parvalbumin (PVB), calretinin (CR) and neuropeptide Y (NPY). In rats infused with picrotoxin, the optical density of GABA immunoreactivity within the ICM, in particular within the main cell island, was significantly increased ($p = 0.01$). Numerical densities and total numbers of neurons expressing PVB, CR and NPY were measured over all amygdalar subregions. PVB- and NPY-positive neurons were found to be significantly decreased in the basomedial nucleus ($p = 0.03$ and $p = 0.04$, respectively). No significant changes were detected in the remaining amygdalar nuclei (lateral, basal, cortical, central, medial nuclei and their subregions). Numerical densities of CR-positive neurons were not affected by picrotoxin infusion in the IL cortex. Taken together, the present results indicate that chronic GABA blockade within the IL cortex affects specific neuronal populations within the amygdala. These effects appear to be focused on a restricted region including the basomedial nucleus and the adjacent main ICM, which in turn give origin to inputs to the medial prefrontal cortex and to the centro-medial complex of the amygdala, respectively. These results support the hypothesis that a disruption of GABAergic transmission in the IL cortex, such as it is postulated to occur in schizophrenia, may profoundly alter amygdalar intrinsic circuits.

111. The Selective Inhibitor of the Glycine Transporter-1 SSR504734: A Potential New Type of Antipsychotic

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Phencyclidine-like compounds that act as non-competitive antagonists at the NMDA receptor induce schizophrenic-like symptoms in humans, presumably by impairing glutamatergic transmission. Hence, a compound that potentiates this neurotransmission, i.e., by increasing extracellular levels of glycine (a requisite co-agonist of glutamate at the NMDA receptor) might possess antipsychotic activity. Blockade of the glycine transporter 1 (GlyT1), that controls extracellular levels of glycine should increase availability of glycine in the vicinity of NMDA receptors and, thereby, potentiate glutamatergic neurotransmission. SSR504734 (2-chloro-N-[(S)-phenyl[(2S)-piperidin-2-yl]methyl]-3-trifluoromethyl benzamide, monohydrochloride) is a selective and reversible inhibitor of native human, rat and mice GlyT1 (IC50 = 18, 15 and 53 nM, respectively). In ex vivo studies, it reversibly blocked glycine uptake in mouse cortical

homogenates (ED50: 6.4 mg/kg i.p.), with a rapid onset and long duration of action. In vivo, an i.p dose of 10 mg/kg increased extracellular levels of glycine in dialysate obtained from the rat prefrontal cortex (PFC). This increase in glycine levels had functional impacts on glutamate neurotransmission, as SSR504734 potentiated NMDA-mediated EPSC′s in rat hippocampal slices (MEC: 0.5 μM) and mouse rotational behavior induced by intrastriatal injection of glycine (MED: 1 mg/kg i.p.). It also normalized activity in two models of hippocampal and PFC hypofunction (both induced by activation of pre-synaptic CB1 receptors): it reversed the decrease in electrically-evoked [3H]ACh release in rat hippocampal slices (MEC: 10-7 μM) and the reduction of spontaneous firing of rat PFC neurons (1 mg/kg i.v.). SSR504734 increased extracellular levels of dopamine in the PFC of rats, prevented ketamine-induced metabolic activation in limbic areas of mice, reversed the hyperactivity and the increase in the EEG spectral energy induced by MK-801 in mice and rats, respectively, and normalized a spontaneous deficit of prepulse inhibition in DBA/2 mice. Across these measures, the MED ranged from 10-30 mg/kg, i.p. Lower doses of SSR504734 (MED: 1 - 3 mg/kg i.p.) reversed selective attention deficit and hypersensitivity to the locomotor effects of d-amphetamine in adult rats treated neonatally with high doses of PCP. While these data indicate a potential of SSR504734 for the treatment of schizophrenia, this compound was also active in models of depression and anxiety, such as the chronic mild stress procedure in mice (10 mg/kg i.p.) and the ultrasonic distress calls in rat pups separated from their mother (MED: 1 mg/kg sc). Moreover, it increased (30 mg/kg i.p.) the latency time to onset of paradoxical sleep in rats, an effect shared by many antidepressants. In conclusion, SSR504734 is a potent, selective and orally active GlyT1 inhibitor, exhibiting activity in animal models of schizophrenia, anxiety and depression. Its mechanism of action targets one of the primary causes of schizophrenia, namely an hypoglutamatergic state. As such, it may be more efficacious than current antipsychotics by alleviating not only positive symptoms but, also, negative symptoms and co-morbid depression and anxiety states. Note: All experiments were carried out in accordance with the ″Guide for the Care and Use of Laboratory Animals″ adopted and promulgated by the NIH.

112. Prediction of Real World Functional Skills Deficits in Schizophrenia: Performance Based Measures of Function Skills vs. Neuropsychological Performance

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Sponsor: Philip Harvey

Background: Functional impairments in schizophrenia are a major source of disability and are a new target for pharmacological treatment, through attempts at cognitive enhancement. The nature of the relationship between functional skills measured in a real world setting and performance-based functional skills assessment is not clear and it is further unclear as to which of these measures would be most related to Neuropsychological (NP) performance. **Method:** Baseline data from a longitudinal study of the course of NP and functional status of older (age 50-85) schizophrenia patients (N=69) were examined. A composite score was created from a battery of NP tests. Symptoms were rated with the PANSS. Functional status was examined with a performance-based measure (University of California performance Based Skills Assessment: UPSA) as well as ratings from real-world caretakers (Specific Levels of Functioning: SLOF). The UPSA assesses the ability to plan activities, manage finances, effectively communicate, and use public transportation. The SLOF consists of caretaker ratings of physical functioning, personal care skills, interpersonal relationships, social acceptability, activities, and work skills. **Results:** The two functional variables were highly correlated with each other ($r = .63$ $p<.01$) and the NP composite score was slightly, but nonsignificantly ($p=.33$), more highly correlated with performance-based functional skills scores($r = .66$, $p<.01$) than with real world functioning ($r = .54$, $p <.01$). When the relationship between the SLOF and NP performance was examined for direct vs indirect (mediated by UPSA performance) influences, it was found that the entire relationship between NP performance and real-world functional status was mediated by UPSA scores, which accounted for 40% of the variance in the SLOF. It was found that PANSS general symptoms predicted an additional 7% of the variance in SLOF scores above and beyond UPSA performance. **Conclusions:** Similar to previous research, NP performance was a significant correlate of real-world functional skills performance, but this relationship did not account for any unique variance when performance-based measures of functional skills were considered. These data suggest that valid performance-based measures of functional skills may be suitable outcome measures in clinical treatment trials that attempt to improve functional outcome in schizophrenia. These findings are remarkably consistent with recent studies of patients with HIV, where NP performance was correlated with performance-based and real-world measures of functional skills, but where those performance-based measures and the severity of depression accounted for all of the reliable variance in real-world outcome.

113. Divergence Of PPI and P50 Suppression Deficits in Schizophrenia Patients

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Objectives: Schizophrenia patients have both automatic (involuntary) and controlled (voluntary) deficits in information processing. Two major automatic inhibitory information processing deficits that have been repeatedly observed in schizophrenia patients are deficient prepulse inhibition (PPI) of the startle response, and deficient suppression of P50 event-related potentials (ERPs). This study tested two hypotheses: 1) in the same large cohort of schizophrenia patients, both PPI and P50 suppression deficits would be observed; 2) PPI and P50 suppression deficits in the same schizophrenia patients would be independent of each other. **Methods:** A large sample ($n = 93$) of schizophrenia patients and normal control subjects was screened and diagnosed using the SCID (or SCID-NP) structured interviews and toxicological tests. Prepulse inhibition of the startle response was assessed according to standard methods, using 70 dB background noise, 86 dB SPL discrete prestimuli preceeding 114 dB startle stimuli by 30, 60 and 120 msec. P50 ERPs were assessed using 1-msec 89 dB click pairs, separated by 500 msec. The S1 and S2 responses to the clicks yielded a percent suppression score. Comparisons between the patient and normal control subjects were conducted by ANOVA. Simple regression analyses were used to examine whether PPI and P50 suppression deficits were significantly associated with each other. Subjects were excluded for low startle magnitude (< 10 units), or S1 amplitude (< 1 microvolt), or impaired hearing (threshold > 40 dB at 1000 Hz). For all comparisons, an alpha of $p<0.05$ was used. **Results:** ANOVA of PPI revealed a significant interaction of diagnosis x prepulse interval ($p<0.005$), reflecting significantly reduced PPI in schizophrenia patients compared to controls at the 60 msec prepulse interval ($p<0.05$). Schizophrenia patients also exhibited deficient P50 suppression compared to controls ($p<0.05$). This deficit in P50 suppression reflected a significant reduction in P50 amplitude in response to S1 in schizophrenia patients ($p<0.001$), with no group difference in P50 amplitude in response to S2 ($F<1$). Regression analyses revealed no significant correlation between PPI (across all intervals, or limited ot 60 msec intervals) and P50 suppression in schizophrenia patients or control subjects (all correlations approximately equal to zero). **Conclusions:** While this cohort of schizophrenia patients had both PPI and P50 suppression deficits (confirming

our first hypothesis), these deficits did not correlate with each other (confirming our second hypothesis). It appears that these two very commonly reported automatic processing inhibitory deficits in schizophrenia patients are independent and dissociable from each other. Thus, these two measures of inhibition that are used in assessing information processing deficits in schizophrenia patients probably have separable neural substrates, genetic architecture, and may have differential responses to established and new treatment compounds. Supported by MH42228 and MH65571.

114. Long-term Weight Change with Quetiapine Treatment in Schizophrenia: A Comprehensive Data Review

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Sponsor: Stephen Zukin

Introduction: Atypical antipsychotics have become established as first-line treatments for schizophrenia. While the atypical antipsychotics offer benefits in terms of improved efficacy and tolerability compared with conventional antipsychotics, they each have different tolerability profiles and some are associated with adverse effects that can significantly impact on patients' quality of life, particularly given the long-term nature of schizophrenia treatment. Weight gain is associated with different atypical antipsychotics to varying extents, most notably with olanzapine and clozapine (Meyer JM. J Clin Psych 2001; 62 (Suppl 27): 27-34), and may have a number of serious consequences. Besides the potential effect on patients' self-esteem, which can affect adherence and, ultimately, clinical outcomes, in the longer-term substantial weight gain can have possible safety implications such as increased risk of cardiovascular disease and type 2 diabetes. **Objective:** To determine the magnitude and pattern of weight change in patients with schizophrenia treated with long-term (≥26 weeks) quetiapine ('Seroquel') monotherapy. **Methods:** A retrospective analysis of data from quetiapine-treated patients with schizophrenia was conducted. Data from all patients in the AstraZeneca clinical trials program who received quetiapine monotherapy for ≥26 weeks, had baseline weight and height measurements, and weight and dose information from a visit at Week 26 or later were analyzed. Descriptive statistics are presented for change in weight (kg) from baseline to final observation, stratified by baseline body mass index (BMI; kg/m^2) category and modal dose of quetiapine. Confidence intervals (95% CI) were calculated for the mean change in weight from baseline to last observation. **Results:** This analysis includes a total of 661 patients (69% male, 31% female) with diagnoses of schizophrenia who had been treated with quetiapine monotherapy for ≥26 weeks. The mean duration of quetiapine treatment was 17.8 months and the mean modal dose was 467 mg/day. Mean weight change in these patients was +2.3 kg (95% CI 1.6, 3.0) and the median weight change was +1.5 kg. Analysis of mean weight change stratified by baseline BMI category showed that the greatest weight gain (+4.0 kg; 95% CI 1.4, 6.7) occurred in patients who were underweight at baseline (BMI ⟨18.5; n=26). Patients with a normal baseline BMI in the range 18.5 to ⟨25 (n=325) had a mean weight change of +3.3 kg (95% CI 2.4, 4.2) and those in the BMI 25 to ⟨30 group (n=189) had a mean change of +1.6 kg (95% CI 0.4, 2.9). In contrast, in patients with a baseline BMI ≥30 (n=121), the mean weight gain of +0.4 kg was not statistically significant (95% CI −1.6, 2.4). Weight change was also analyzed according to patients' modal daily dose of quetiapine. This analysis showed no relationship between quetiapine dose and weight change: at doses ≤300 mg/day (n=218), mean weight gain was 2.1 kg (95% CI 1.1, 3.2); at ⟩300 to 500 mg/day (n=172), it was 2.7 kg (95% CI 1.4, 4.1); and at ⟩500 mg/day (n=271), it was 2.2 kg (95% CI 1.0, 3.3). **Conclusions:** Mean weight change during long-term (≥26 weeks) quetiapine treatment of patients with schizophrenia was +2.3 kg. There was no apparent association between weight change and dose of quetiapine.

115. Genome-Wide Association Study for Olanzapine Treatment-Emergent Weight Gain

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Treatment-emergent weight gain observed with atypical antipsychotic therapy continues to be a clinical concern with genetic factors likely playing a role. The genetic contribution to weight gain has been investigated using a candidate gene approach (reviewed by Muller et al 2004). Although significant associations with candidate genes such as the Serotonin 5-HT2c Receptor Gene (Reynolds et al 2002) and CYP2D6 (Ellingrod et al 2002) have been reported, negative results have also been described (Muller et al 2004, Hong et al 2001). The lack of consistent findings has led to uncertainty as to the significance of reported associations. Therefore, we undertook a large-scale effort to investigate many genes across the genome in a large cohort of patients for treatment-emergent weight gain. Using a cohort of adult patients diagnosed with schizophrenia, schizoaffective, or schizophreniform disorder who had taken oral olanzapine for a minimum of six months, case-control populations were chosen from the tails of the weight-gain distribution. The cases (n=255) represented the 20% extreme weight gainers, and the controls (n=258) consisted of the 20% of the individuals who gained the least weight (non-gainers), both measured by change in body mass index. Mean (±SD) body mass index for the weight gainers was 33.2±4.4 kg/m2 and for the nongainers, 28.3±5.9 kg/m2. A regression model with age, gender, and ethnicity as covariates was used to define the weight-gain distribution balancing the weight gainers and nongainers for these factors. Phase I of the analyses involved pooling of the DNA for each group, weight gainers and nongainers. Each pool of DNA was genotyped for ~1.6 million single nucleotide polymorphisms (SNPs) using the Perlegen Sciences platform. The allele frequency difference between the weight gainers′ and nongainers′ pools was calculated from three replicate determinations on each pool, for each of the SNPs genotyped. A total of 30,000 SNPs were then carried forward to phase II, in which all 513 individuals were individually genotyped. The 30,000 SNPs genotyped on each individual were chosen based on three criteria: 1) SNPs with the largest estimated allele frequency differences between the two pools (≥0.084) (n=23,281 SNPs); 2) SNPs with estimated allele frequency differences of ≥0.065 between pools but where the pooled data from multiple SNPs matched the expected correlational structure based on haplotypes as defined in Perlegen′s haplotype map (n=5,000 SNPs); and 3) 1,719 SNPs from 47 candidate genes. Association analyses between the 30,000 SNPs and weight-gain phenotype were completed using Fisher′s exact test. Three hundred eleven SNPs were identified as significantly different ($p<0.001$, uncorrected for multiple testing) between weight gainers and nongainers. Bioinformatics tools, additional scoring algorithms, and statistical analyses were used to narrow the list to the most interesting SNPs and gene regions. Methodology, additional interesting findings, and biologic correlates will be presented.

116. Maternal Exposure to Toxoplasmosis and Risk of Schizophrenia in Adult Offspring

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Sponsor: Jean Endicott

Objective: We aimed to examine the relationship between maternal antibody to toxoplasmosis and risk of schizophrenia and other schizophrenia spectrum disorders in the offspring. Toxoplasmosis is known to adversely affect fetal brain development. **Method:** In a nested case-control design of a large birth cohort, born from 1959-1967, we conducted serologic assays for toxoplasma antibody on ma-

ternal serum specimens from pregnancies giving rise to cases of schizophrenia and other schizophrenia spectrum disorders (N= 63) and matched controls (N=123). Toxoplasma IgG antibody was quantified using the Sabin-Feldman dye test. The IgG titers were classified into three groups: negative (<1:16) (reference), moderate (1:16-1:64), and high (>1:128). **Results:** The adjusted odds ratio (95% CI) of schizophrenia/schizophrenia spectrum disorders for subjects with high maternal toxoplasma IgG antibody titers was 2.61 (1.00, 6.82), p=.051. There was no association between moderate IgG antibody titers and risk of schizophrenia/spectrum disorders. **Conclusions:** These findings suggest that maternal exposure to toxoplasmosis may be a risk factor for schizophrenia. The findings may be explained by re-activated infection, or an effect of toxoplasma IgG antibody on the developing fetus. Given that toxoplasmosis is a preventable infection, the findings, if replicated, may have implications for reducing the incidence of schizophrenia.

117. The Effect of Galantamine on Sensory Gating Abnormalities in Patients with Schizophrenia

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Patients with schizophrenia are characterized by sensory gating impairments, which can be assessed with P50 event-related potentials obtained during a paired-click paradigm. P50 is under the regulation of multiple neurotransmitters, including acetylcholine. Acetylcholine is thought to induce sensory gating through its effect on the alpha-7 nicotinic receptor and the inhibition of the response to the second auditory stimulus. Nicotine has been previously shown to normalize P50 in patients with schizophrenia. We have previously shown that the acetylcholinesterase inhibitor, donepezil, also improves P50 in patients with schizophrenia. Of particular interest was the observation that donepezil, similar to acetylcholine and nicotine, exerted its effect through diminishing the response to the second or test auditory stimulus, an effect thought to reflect normalization of the gating process. In the context of a double-blind, placebo-controlled, parallel group clinical trial, we are examining the effect of galantamine, an acetylcholinesterase inhibitor and allosteric modulator of the alpha-7 nicotinic receptor, on P50. Thirty-two subjects have completed baseline and end-of-study P50 assessments. The effect of galantamine on P50 S2/S1 ratio, S1 and S2 amplitude and latency will be presented. We hypothesize that galantamine, because of its mechanism of action, will have a beneficial effect on sensory gating in these patients.

118. Diabetes And Antipsychotic Medications....Are We Ready?

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Sponsor: Timothy Crow

There is an intense scientific interest and growing public concern regarding the risk of developing weight gain, diabetes mellitus, and related metabolic disturbances during treatment with anitpsychotic medications. Hyperglycemia, hypertriglyceridemia, new onset diabetes and even diabetic ketoacidosis have been reported (through case reports and series, pharmacovigilance and various pharmacoepidemiologic studies) in patients receiving antipyschotic medications. This emergent information has recenlty prompted the Food and Drug Administration to request changes in the labeling of such medications. Additionally, several expert groups and consensus panels have provided guidance on this issue. Various approaches have been promulgated to inform the detection, monitoring, and management of weight gain and metabolic disturbances during antipsychotic therapy. To address this burgeoning interest in a manner complementary to current information and guidelines, we sampled the perceptions and clinical 'readiness' to detect and manage these adverse effects among general and specialist psychiatrists in 3 U.S. states. Clinicians indicated that some assessment measures (eg. personal and family history, height and weight) were readily attainable and routinely evaluated, while others (fasting blood glucose, fasting lipid profile) were more difficult to obtain; the latter were evaluated on a more inconsistent basis across the psychiatrists sampled. Clinicians expressed concern over weight gain and metabolic effects, with some indicating that these considerations have now altered the way they prescribe second generation anitpsychotic medications. This presentation will share details on clinician's perceptions of an evolving standard of care and the current extent to which actual practice reflects recently developed guidelines.

119. Is Glutamatergic Therapy Efficacious in Schizophrenia?

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The hypoglutamatergic hypothesis of schizophrenia pathophysiology is critically important, in part because of its special relevance to negative symptom psychopathology and cognitive impairments. These illness domains account for much of the long-term morbidity and poor functional outcomes in schizophrenia, and are unmet therapeutic needs. Small N studies suggest that glycine, d-cycloserine, d-serine, and sarcosine improve negative symptoms with weaker evidence suggesting an effect for enhancing cognition. However, some glycine and d-cycloserine studies fail to support efficacy. A definitive answer is crucial in evaluating the promise of this therapeutic pathway. Four centers, supported by four collaborative RO1s, have completed a clinical trial testing four hypotheses: 1] glycine is superior to placebo for negative symptoms; 2] d-cycloserine is superior to placebo for negative symptoms; 3] glycine is superior to placebo for cognition; and 4] d-cycloserine is superior to placebo for cognition. The study design and assessment measures use the model now being accepted to avoid the pseudospecificity problem. The design is a RCT with co-administration of experimental drug or placebo with previously prescribed antipsychotic for 16 weeks in patients who have low to moderate psychosis, EPS, and depression that remain stable throughout the study. In July 2004, the last of 171 randomized subjects completed the trial. The data are in the final stage of cleaning, and the code has not been broken and no results are available. This presentation will include complete data for intent to treat primary analyses of the four hypotheses using mixed model analysis of variance for repeated measures. This is proposed as a "hot topic", because it represents a definitive study of the hypoglutamatergic hypothesis, which is unlikely to be repeated, and because of the importance of drug discovery for unmet needs in schizophrenia. The design and analytic strategy was peer reviewed, and no data from this study will be reported prior to the ACNP meeting.

120. Aging and Visual Motion Discrimination in Normal Adults and Schizophrenia Patients

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Background: Motion perception is impaired in many neuropathological conditions, including schizophrenia. Motion perception also declines in the course of normal aging. Whether aging plays a role in deficient motion processing of schizophrenia remains unclear. This question is important because normal aging is accompanied by a neurodegenerative process that may be implicated in the

pathophysiology of schizophrenia. In this study, we addressed the question by assessing whether aging is an additive factor in motion discrimination deficits of schizophrenia patients. **Methods:** We examined motion perception in schizophrenia patients (n=44) and normal adults (n=40) whose ages range from 18 to 55. We employed two visual tasks 1) velocity discrimination, a motion perception task, and 2) contrast detection, a baseline visual task. In the velocity discrimination task, subjects were asked to identify which of two targets in a trial moved faster. In the contrast detection task, subjects were asked to identify which of two intervals in a trial contained a moving target. The thresholds for the two tasks were determined for each subject using psychophysical methods. **Results:** Schizophrenia patients showed significantly increased thresholds (degraded performance) in velocity discrimination in comparison with normal adults. The degraded performance in schizophrenia patients was not related to age, in the range tested (18 to 55 years old). In contrast, velocity discrimination in normal adults was affected by age, as indicated by significantly increased thresholds beginning by age 45. In the same age range, contrast detection was not significantly affected in either group. **Conclusions:** Aging degrades velocity discrimination in normal adults even in its early stages (by 45 to 55 years old). Aging, however, does not introduce additional impairment to motion discrimination deficits in schizophrenia patients through age 55. Inasmuch as faulty GABAergic modulation is implicated in both the aging visual system and schizophrenia, similar motion discrimination deficits in schizophrenia patients and aging adults suggest that the neural mechanisms underlying motion processing in schizophrenia and aging are associated.

121. Ziprasidone versus Haloperidol for the Treatment of Agitation

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Sponsor: Albert Weissman

Objective: To compare the efficacy of sequential IM/oral ziprasidone vs IM/oral haloperidol in the treatment of agitation in patients with an acute psychotic disorder. **Methods:** Post hoc analyses of pooled data from 2 studies comparing mean reductions in BPRS agitation factor (sum of items 2, 6, 10, and 17), activation/aggression factor (sum of items 6, 7, 17), anxiety/depression factor (sum of items 1,2,5,9), positive factor (sum of items 4, 8, 12, 15), and negative factor (sum of items 3,13,16,18) scores over the first 3 and 7 days among patients with an acute psychotic disorder. In the first study (a 7-day study of subjects with an acute non-organic psychosis), 90 patients received <3 days IM ziprasidone, then oral ziprasidone (80-200 mg/d, mean 90.5 +/- 44.9 mg/d) and 42 patients received IM haloperidol, then oral haloperidol (10-80 mg/d, mean 14.0 +/- 10.1 mg/d). In the second study (a 6-week study of subjects with an acute exacerbation of schizophrenia or schizoaffective disorder), 417 patients received IM ziprasidone, then oral ziprasidone (80-160 mg/d, mean 116 +/- 30.4 mg/d) and 133 patients received IM haloperidol, then oral haloperidol (5-20 mg/d, mean 11.5 +/- 3.6 mg/d). Effect was assessed by Hierarchical Linear Model analysis - repeated assessments of a BPRS factor over time served as the dependent variable. The two independent variables were 'treatment group' (between subject factor) and 'time' (within subject factor). Interaction between treatment group and time was included in the model. **Results:** In the first three days of treatment ziprasidone was superior to haloperidol on the agitation (p=0.0013), activation/aggression (p=0.0276), and anxiety/depression factors (p=0.0256), but no differences were seen on the positive (p=0.3129) or negative factors (p=0.1235). The differences observed might be attributable to a slight initial worsening of symptoms for the subjects receiving haloperidol in one of the two studies from which the data was drawn. After three days efficacy measures for each of the two treatments converged and further improvement was likely due to a time effect. **Conclusions:** Post hoc analyses indicate possible efficacy advantages of ziprasidone over haloperidol for the treatment of agitation. Given the tolerability advantages of ziprasidone over haloperidol, overall effectiveness would be expected to be greater for ziprasidone. Appropriately designed clinical efficacy trials will need to be done to confirm these preliminary findings.

122. Viral Detection Arrays: Proof of Concept

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Sponsor: Terry Goldberg

Microarray technology has become an increasingly important tool in psychiatric research. A unique array based pathogen chip has been developed in our laboratory for the detection of viral RNA expression levels or DNA prevalence from test samples. A set of long oligonucleotides (60-mer) was designed based on highly conserved regions within viral families, as well as heterogenic regions characterized by individual subfamilies. In addition, genes reflecting different stages of pathogen infection were also included in the oligonucleotide set to enable the chip to potentially define the stage of the viral infection. A total of 1600 oligonucleotides representing approximately 100 pathogens were immobilized on a glass surface for pathogen detection. To validate the viral microarray chip, we first analyzed the sensitivity and reproducibility of the microarray platform. Then, we applied the chip to virally infected cell cultures to detect diverse viruses and their infectious stages. Total RNA from viral cell lines was linearly amplified using in vitro transcription in combination with a template switch technique. Samples were examined by cohybridization of a viral cell line aRNA, labeled with Cy5 (red), and a reference aRNA, labeled with Cy3 (green), to the pathogen microarray chip. Log_2 ratios of normalized intensity were used for comparative measures of a cell line against the reference. Microarray reproducibility was established from duplicate hybridizations of the self-comparison replicate microarrays of the viral cell lines MMLV and SV40. Mean, median and std. Dev of log_2 ratios were calculated for all the genes. For the MMLV cell line mean log_2 ratios = –0.0065, median = 0.0122 and std. Dev = 0.2872. For the SV40 cell line mean log_2 ratios = –0.0047, median = 0.0088 and std. Dev = 0.2741. Data distribution for the microarray platform shows a normal distribution with 95.5% of replicate measures falling within a log_2 ratio of 0.56 of the mean when probes were filtered for reliable spot measures. To asses microarray sensitivity, studies were performed to examine the distribution of log_2 ratio scores for the comparisons between a cell line and the reference. Probes reported good correlation in replicate experiments when all 1,442 probes with signals >300 were analyzed ($R^2 = 0.72$) for the comparison MMLV-reference and $R^2 = 0.82$ for the AC37-reference comparison. Thus, the microarray platform provides a good sensitivity and reproducibility. Virally infected cell lines were used to detect transcripts of viruses infecting those cell lines and their infectious stage. These studies detected transcripts from retroviruses HERV-K and MMLV, herpesviruses (HSV-1, HSV-2, EBV and HCMV) and SV40 virus. We also performed viral serial dilution experiments (cell cultures mock infected or infected with different titers of HSV-1 or HCMV viruses) to establish microarray viral detection sensitivity. These findings suggest that this array based platform is able to detect a broad spectrum of viruses in a single assay while simultaneously discriminating among different stages of the viral infection. This method may be used to provide evidence of viral infection in postmortem tissue from psychiatric patients as well as a wide range of other diagnostic categories.

123. Metabolic Risk With Second-Generation Antipsychotic Treatment: A Double-Blind Randomized 8-week Trial of Risperidone and Olanzapine

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Since the introduction of the first antipsychotic medication in the 1950s, clinicians have been challenged with side effects of conventional antipsychotic treatment including extrapyramidal side effects (EPS) and tardive dyskinesia (TD). Now, psychiatric clinicians are once again faced with serious medical co-morbidity associated with antipsychotic treatment. Risperidone and olanzapine are the two most widely prescribed of the new antipsychotic medications. Both have recently come under scrutiny for potential weight and metabolic consequences. This is a report of an 8-week multicenter, randomized, double-blind, parallel-group comparison of risperidone (2-6 mg/day) and olanzapine (5-20 mg/day) for people with schizophrenia or schizoaffective disorder (N=377). At week 8, the mean BMI increase was 1.3 kg/m2 (0.13) in the olanzapine group versus 0.7 kg/m2 (0.13) in the risperidone group ($p<0.001$). There was virtually no change in the HgbA1C for the olanzapine-treated subjects (+0.01%) while there was a significant decrease in risperidone-treated subjects (-0.20%) ($p=0.05$). Significant mean increases in total cholesterol, LDL and triglycerides also occurred during 8 weeks of olanzapine and significant decreases were seen in the group receiving risperidone monotherapy. Baseline values and prior therapy did not contribute to the significant differences observed, however, increases in weight and metabolic parameters were linked to a higher study discontinuation regardless of drug. The fact that clinically and statistically significant changes occurred (both positive and negative) in eight weeks in this double-blind study is a critical point. Thus, in contrast to recent treatment recommendations, monitoring for laboratory changes should occur within eight weeks of medication initiation in order to rapidly understand and work with the metabolic changes associated with these medications.

124. Small Myelin-Associaed Glycoprotein (S-Mag) Gene Expression during Normal Human Development and in Elderly Schizophrenics

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Sponsor: Rachel Yehuda

Neuroimaging and neuropathological studies have demonstrated white matter alterations in schizophrenia (SZ) patients. Oligodendrocytes are evidently affected, and the downregulation of some myelin-related genes in the frontal cortex has been demonstrated by microarray studies and further validated by single-gene analyses in middle-aged and elderly SZ patients. We previously reported that both isoforms of myelin-associated glycoprotein (large, L- and small, S- MAG) have reduced expression in dorsolateral prefrontal (DLPFC) and anterior cingulate cortex (AC) - but not inferior parietal (IP), superior temporal (ST), or occipital cortices (OC) - of SZ patients relative to normal (NL) controls. While surprisingly few studies have concentrated on the potential functional differences of the two MAG isoforms, evidence indicates that they perform distinct functions and should be examined independently. The two alternatively spliced isoforms of MAG are developmentally regulated in rodents (L-MAG is expressed early and S-MAG predominates in adults), however humans exhibit a different pattern of expression since L-MAG is the primary isoform in adult brain. In order to better understand the role of S-MAG during cortical development and throughout life, the current study determines the developmental expression profile of S-MAG in a normal human series of DLPFC postmortem tissue ranging in age from infant to 100 years. In addition, we explored the relative abundance of S-MAG mRNA in different cortical regions of elderly SZ and NL control subjects. METHODS: Postmortem samples from gray and white matter dissections of DLPFC during normal human postnatal growth (5 weeks-1 year, n=13), maturation (14-24 years, n=14) and aging (31-98 years, n=44) were assessed for S-MAG gene expression via real-time RT-PCR. For a separate analysis, a cohort consisting of antemortem assessed and research diagnosed elderly SZ patients (n=32), Alzheimer Disease (AD) patients (n=12), and age matched normal controls (n=22) were analyzed for S-MAG expression from homogenates of frozen tissue dissected from the DLPFC, AC, IP, ST, and OC. RESULTS: In the normal developmental cohort, S-MAG expression from gray and white matter DLPFC dissections followed the same pattern of expression, with mRNA levels significantly increasing from infancy to young adulthood (S-MAGg, $p<.01$; S-MAGw, $p<.04$), declining during middle age and maintaining such expression into the 10th decade of life. Regional analysis in diseased relative to normal brains demonstrated that S-MAG expression in the DLPFC was 4 times higher than the next highest expressing region, the ST, in NL controls ($p=0.00003$) and 7.7 times higher in the SZ group ($p=0.00003$). CONCLUSIONS: While white matter expansion has been observed from infancy to adulthood, these results empirically document an increase in S-MAG mRNA and demonstrate that after a peak during adolescence, adult expression levels are maintained throughout life. In our cohort of elderly SZ and NL control subjects, regional analyses indicate that S-MAG expression is much greater in the DLPFC relative to other cortical regions, an increase that is inflated in SZ patients. This raises the possibility that despite the generally depressed levels of S-MAG expression in the SZ subjects relative to NL controls, compensatory mechanisms may be engaged in the DLPFC to overcome the S-MAG deficits.

125. Are Anti-depressants a Possible Treatment for the Schizophrenia Prodrome?

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Sponsor: Sam Siris

The Recognition and Prevention (RAP) program of Zucker Hillside Hospital in New York focuses on adolescents between the ages of 12-18 who are considered to be in the prodromal phase of schizophrenia. Throughout the first five years of the RAP research program, treatment has followed a naturalistic strategy in order to build an hypothesis-generating evidence base. RAP clinicians, who have been independent of the research team, have provided treatment according to best practice standards. This observational approach has now provided considerable information about the response of prodromal symptoms to the types of treatments typically used in a real world situation. As of 7/1/04, 152 patients have completed the basic RAP research protocol. Out of the total sample, 39 subjects were selected for this report because they me the following three criteria: 1) were narrowly defined as being prodromal, based on attenuated positive symptoms only; 2) were treated with either an anti-depressants (ADP, n=13), a second generation anti-psychotic (SGAP, n=9), or a combination of both (n=17); and 3) had been clinically followed for a minimum of two years after intake. Subjects receiving a combination of ADPs and SGAPs were similar on all dimensions measured to adolescents receiving SGAPs only. Although the treatment groups did not differ in overall positive or negative symptoms at baseline, those patients prescribed ADPs had significantly higher ($p=.02$) baseline anxiety

(but not depression) and those treated with SGAPs had significantly higher disorganized thought (p=.02). Two dimensions were of interest at follow-up: 1) functional outcome, as measured by social isolation and school failure and 2) conversion to psychosis. Adolescents in all three treatment groups showed substantial improvement on all measures of school and social functioning, with no differences emerging among them. This suggested that ADPs were as effective as SGAPs in improving school and social problems in prodromal youngsters. A third of this sample converted to psychosis over the follow-up period, with a significantly higher (p<.001) number of converted subjects treated with SGAPs (all 13 conversions had been prescribed SGAPs, no patients taking ADPs have converted). However, this difference appears, to some extent, to be related to non-adherence. Non-adherence to treatment appears to be a major risk factor for conversion to psychosis and to be considerably higher in adolescents taking SGAPs than ADPs. Risk for psychosis was found to be increased tenfold for those adolescents non-adherent with prescribed treatment (i.e. 92% of conversions to psychosis were non-adherent with SGAP medication). In general, adolescents appear more cooperative with ADP treatment: regardless of outcome, 21% of adolescents were non-adherent with ADPs compared with 60% of those medicated with SGAPs. It is thus suggested that since functional outcome is about the same, conversion rates lower and adolescents more cooperative with treatment, ADPs appear to offer a reasonable alternative to anti-psychotics for the early treatment of at least some adolescents in the prodromal phase of schizophrenia. It should be noted that, at present, these findings remain subject to challenge because they are based on an open-label study. We are therefore in the process of comparing a frequently used ADP (sertraline) with a frequently used SGAP (risperidone) in a randomized, double-blind, double-dummy clinical trial currently underway in the RAP program.

126. Understanding and Predicting SGA Associated Weight Gain

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In a set of guidelines written by an American Diabetic Association panel,[, 2004 #1] we recommended periodical weighing of patients on second-generation antipsychotic medications (SGAs) in order to predict which patients will experience significant weight gain, so that weight management can be instituted in a timely fashion. Unfortunately, there is very limited data on how to predict long-term weight gain from initial weight gain. It is necessary to have long-term data; otherwise inferences are made based on assumptions about what happens on a long-term basis made in the absence of any empirical data. Most controlled studies are short, 4-10 weeks. To fill this gap, we present empirical data useful in such predictions and better describe the weight gain associated with SGAs. We obtained from Lilly the raw data of 6 long-term, double-blind, randomized, controlled studies comparing olanzapine against other medications of multi-episode schizophrenia as defined by 18 weeks or more of treatment. We evaluated weight gain in completers, in observed case analysis at each time point, and last-observation-carried-forward (LOCF). We used as our index of weight gain percent weight gain. We will present the time course of weight gain for all five drugs. We evaluated the predictors of weight gain from initial weight gain at week 1 to 6 weeks, gender, ethnicity, baseline BMI (Body Mass Index), age, exposure to previous antipsychotic drugs, and smoking status. In the international trial of olanzapine and haloperidol, we examined whether or not the percent weight gain plateaued over time in just patients who completed the entire 52-week study. The rate of weight gain was greatest in the first week, and was clearly significantly decreased by week 6 and some months later decreased to zero. We also explored the artifact in weight gain produced by early dropout carried forward (LOCF). There were almost no dropouts for excessive weight gained. There was no correlation between dropping out because of poor efficacy or other side effects and weight gained at end point. Weight gain at 6-weeks predicted final weight gain for all drugs studied. At 6-weeks, the correlation approached 0.70. Baseline BMI and age were inversely correlated with weight gain to a modest degree (r = about 0.2). African-Americans gained more weight than Caucasian or other ethnic groups, but this difference was small. Gender failed to influence percent weight gain. Patients who had been previously treated with second-generation antipsychotics (SGAs) gained less weight than those on FGAs. Smokers gained less weight than non-smokers in the studies where smoking was measured i.e., the international comparison of olanzapine and haloperidol and this occurred to a proportionally equal degree with both drugs. There were variation in weight gain between SGAs. Since olanzapine was used in all studies, one could examine the percent weight gain in different studies of the same drug. Percent weight gain differed quite substantially (20-fold) from study to study and depending on time period chosen or design. Our data supports the usefulness of weight gain in the first 6 weeks as a predictor of weight gain after the weight has plateaued. We will present prediction equations.

127. Reversal Of Dopamine Depletion-Induced Dendritic Spine Loss In Prefrontal Cortical Pyramidal Cells By Olanzapine

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Post-mortem analyses and in vivo imaging studies of schizophrenia have consistently revealed a decrease in the volume of the prefrontal cortex (PFC). However, this does not appear to be attributable to an overall decrease in cell number. Studies have consistently revealed changes in presynaptic markers in the PFC in schizophrenia, including a decrease in dopaminergic axons in the PFC. Similarly, a decrease in dendritic length and dendritic spine density has been reported by several groups. It is possible that a loss of dopamine results in dendritic remodeling of pyramidal cells in the PFC. We examined this possibility in the adult rat, using 6-hydroxydopamine (6-OHDA) injections into the midbrain ventral tegmental area (VTA) to lesion the dopamine (DA) innervation of the PFC. We initially examined dendritic spine density in layer V pyramidal cells of the PFC in adult rats subjected to VTA lesions and sacrificed three weeks later. The lesions markedly (~75%) decreased PFC DA concentrations, but did not significantly decrease (~15%) PFC norepinephrine concentrations. Analysis of Golgi-impregnated cells revealed that basilar dendritic spine density was significantly decreased (~19%) in layer V pyramidal cells. We then subjected another group of adult rats to VTA 6-OHDA or sham lesions, and three weeks later animals in all three groups were started on olanzapine (7.5 mg/kg po, haloperidol 1.5 mg/kg, or 0.75% sucrose in water vehicle). After three weeks of drug treatment animals were sacrificed. The decrease in dendritic spine density in layer III and V pyramidal cells was present in lesioned animals that received vehicle starting three weeks post-operatively, but in olanzapine-treated animals we observed a near-complete recovery of dendritic spine density in both layer III and V pyramidal cells. Analysis of dendritic spine density distributions revealed that there was a recovery of all but the most densely spinous (>10 spines/10 micrometer dendritic length) dendrites. Data from the haloperidol-treated animals are now being analyzed. The current data offer a mechanism to account for the dendritic remodeling observed in the prefrontal cortex and the ability of an atypical antipsychotic drug to slow the progressive loss of PFC volume in first-episode schizophrenic subjects treated with olanzapine.

128. Adjuvant Therapeutic Effects of Galantamine on Negative Symptoms and Apathy in Inpatients with Chronic Schizophrenia: An Open Label Prospective Study

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A regionally selective deficiency of the expression of the alpha7 nicotinic acetylcholine receptor (nAChR) has been reported in schizophrenia. This selective impairment of acetylcholine receptor-mediated neurotransmission explains, at least in part, some of the disturbances in pathophysiology (e.g., impaired sensory inhibition and impaired voluntary smooth pursuit eye movement performance) and psychopathology (e.g., inability to sustain attention and loosening of associations). Further, impaired sensory inhibition occurs in unaffected first-degree biological relatives of index patients with schizophrenia, is inherited in an autosomal dominant manner, and serves as an endophenotype for genetic studies. Galantamine is a positive allosteric effector of nACRs, in addition to inhibiting acetylcholinesterase activity. In view of galantamine's allosteric potentiating effects and the deficit in nAChR-mediated neurotransmission, we studied its adjuvant therapeutic properties in inpatients with chronic schizophrenia using an open-label design. Galantamine was added to stable regimens of antipsychotic medications and titrated to the maintenance dose of 24 mg/day over a 3 week period; thereafter, patients were maintained on this dose for two-months. Eleven patients have been enrolled and seven have received study medication. Formal ratings were obtained on baseline, at the end of titration, and after one and two months on the maintenance dose (24 mg/day). Rating instruments included the BPRS, SANS, and the Marin Apathy Evaluation Scale, among other instruments. Adjuvant galantamine has been well-tolerated and no subjects were withdrawn due to intolerable side effects nor was worsening of either extrapyramidal side effects or mood observed. Data will be presented on the effects of adjuvant galantamine administration on negative symptoms and mood in this sample of hospitalized inpatients with schizophrenia. Importantly, several patients have requested to remain on galantamine after their completion of the protocol.

129. Evidence for Developmentally Mediated Alterations in the Balance of Gray and White Brain Volume in Young First-Degree Relatives of Schizophrenia Patients

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Sponsor: Past Travel Awardee, BMS, 2003

Background: Normal brain development occurs along a systematic schedule dictated by a complex combination of genetic and environmental interactions. Several systematic changes in the structural and functional organization of the brain, particularly into adolescence and young adulthood have been documented. Structural development includes progressive changes in the balance of gray and white matter, as a result of concurrent processes of programmed synaptic loss and white matter expansion during adolescence. The dynamic nature of these processes is thought to stabilize by young adulthood. *In vivo* MRI-measured volumes of gray and white matter are sensitive to developmentally mediated processes such as programmed synaptic loss and white matter expansion. The ratio of these volumes (GM/WM) can provide useful information about the structural integrity of the entire brain. Given that schizophrenia has a basis in abnormal neurodevelopment, such an analysis in young individuals with schizophrenia, and young individuals at risk for schizophrenia may prove informative. **Methods:** We analyzed *in vivo* structural MRIs of healthy controls (HC; n=79), offspring of schizophrenia patients who are at high risk for the illness (HR; n=40), and first-break schizophrenia patients (FB; n=61) (all subjects aged 8-25). Our aim was to assess a) differences between the groups in GM/WM and b) the relationship between age and GM/WM in each of these populations separately. **Results:** Preliminary analyses of variance revealed a significant reduction in GM/WM in FB subjects compared to HR or HC, $F_{2,177}=10.26$, $p<.0001$. Simple linear regressions revealed significant negative correlations between GM/WM and age in all three study groups (Fs > 14, $p<.001$). Exploratory forecast modeling using exponential smoothing was used to approximate subtle trend characteristics beyond the linear order. The results suggested a decrease in GM/WM in HC in childhood and adolescence, followed by a plateauing in young adulthood. Similar analyses in HR indicated a decreasing trend continuing beyond adolescence into young adulthood. An articulated developmental trend was absent in FB. **Discussion:** The results suggest schizophrenia is marked by a significant reduction in GM/WM, consistent with documented reductions in heteromodal GM in the illness. The trend analyses suggested that HR might be associated with progressive imbalances in GM/WM beyond adolescence and into the typical age of onset of the illness. The results are consistent with the neurodevelopmental model of schizophrenia and suggest that genetic vulnerability for the illness may be expressed by developmentally mediated alterations in the balance of gray and white matter in the brain.

130. Rapid Genomic Array Analysis of Copy Number Abnormalities in a Patient with Psychosis and der(18)t(18;?)(p12;?)

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Sponsor: David J. Kupfer

Array-based copy number analysis has recently emerged as a rapid and efficient means of mapping complex chromosomal abnormalities. We have compared two such techniques, using bacterial artificial chromosome (BAC) and single nucleotide polymorphism (SNP) arrays in the evaluation of a 45 year-old female with dysmorphic features, mental retardation, psychosis, and an unbalanced, derivative chromosome 18, (46, XX, der(18)t(18;?)(p12;?). Both array-based methods demonstrated that the additional material on chromosome 18 was of 5p origin. The 5p duplication mapped telomeric to 25.320 Mb (BAC array) and 25.607 Mb (SNP array), corresponding to the band 5p14.1. Both BAC and SNP arrays also showed a deletion involving chromosome 18p extending telomeric from 8.437 Mb (BAC array) and 8.352 Mb (SNP array), corresponding to band 18p11.23. Molecular cytogenetic mapping using fluorescence in situ hybridization (FISH) supported the array findings and further refined the breakpoint regions, confirming that the BAC and SNP chips were equally useful in this regard. Both case reports and linkage analyses have implicated these chromosomal intervals in psychosis. The array-based experiments were completed over the course of several days. While these methods do not eliminate traditional fine-mapping if the precise location of breakpoints is of interest, they provide a very rapid and efficient means of identifying the origin and general extent of deleted and duplicated chromosomal material in complex rearrangements.

131. Surgically Implantable Long-Term Antipsychotic Delivery System Produces Progressive Reversal of PPI Deficits in Brattleboro Rats

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Deficits in prepulse inhibition (PPI) of the startle reflex analogous to those seen in schizophrenia are the basis for a number of ani-

mal models with predictive validity for antipsychotic efficacy. Recently our laboratory has been studying the Brattleboro (BB) rat as a potential animal model of schizophrenia-like PPI deficits. The BB rat differs from Long Evans (LE) rats by a single base-pair mutation coding for the neurohormone vasopressin. Similar to patients with schizophrenia, BB rats exhibit naturally reduced PPI (face validity) and increased striatal D2 receptor levels (construct validity) compared to LE rats. In addition, we have shown that the reversal of PPI deficits in BB rats by established and putative antipsychotics with a time-course that models the time-course of their therapeutic effects in humans (predictive validity). A useful animal model should be able to evaluate novel putative methods of treatment. In this study we tested the effects of a surgically-implantable formulation of haloperidol that has been created using biodegradable polymers. These implants have demonstrated steady release of drug for 5 months. We subcutaneously implanted pellets that contained either haloperidol or placebo in LE and BB rats. Haloperidol implants, but not placebo implants, progressively increased PPI in BB rats but not LE rats. By the end of three weeks the PPI deficit in BB rats relative to LE rats was eliminated. These findings are consistent with the effects of daily subcutaneous haloperidol injections in BB rats that we previously reported and so support the ability of this surgically-implantable system to provide efficacious long-term delivery of antipsychotic medications to patients with psychotic disorders. The results also further demonstrate the usefulness of the BB rat as a model with good predictive validity and strong utility for evaluating novel antipsychotic treatments.

132. Pharmacological and Molecular Characterisation of a Positive Allosteric Modulator Selective for the Muscarinic M4 Receptor Being Developed for the Treatment of Psychosis

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The five muscarinic acetylcholine receptor subtypes (M1-M5) share highly conserved protein sequences providing moderate pharmacological differentiation with existing small molecule ligands. Allosteric modulators, targeted to sites outside the acetylcholine-binding domain, may allow for greater receptor subtype selectivity and provide for activity-regulated drug action. Here, we report the identification of a novel selective allosteric potentiator for the M4 receptor using both functional and radioligand binding assays. This molecule displays no activity at M1, M3 or M5 receptors in both assays, but weak and low affinity partial agonistic activity at both M2 and M4 receptors. A modest allosteric action can be observed at M2 receptors when this molecule is applied at high concentrations (at least 100-fold of that required for M4). The cooperativity factor (a) of this molecule with Acetylcholine (ACh) binding at M4 receptors is estimated to be at least 20 and appears to be even greater for enhancing functional responses. The mechanism of action appears to be independent of receptor states or G-protein coupling, but is primarily due to its enhancing the affinity of ACh for M4 receptors. Site-directed mutagenesis studies reveal that residues on the third extracellular loop play a critical role in the allosteric potentiation effect of this molecule. In vivo, the compound potentiates the anti-dopaminergic effects of oxotremorine and donepezil in the rat conditioned avoidance assay, suggesting potential therapeutic utility in the treatment of psychosis. The unique combination of highly selective and cooperative properties of this novel allosteric enhancer provides a novel pharmacological tool to study allosterism of class A G protein-coupled receptors and probe the physiologic role of M4 receptors in vitro and in vivo.

133. Multiple Dopamine Receptors in the Prefrontal Cortex of the Rat Regulate Set Shifting

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It is well established that mesocortical dopamine (DA) activity acting on D1 receptors plays an essential role in mediating working memory functions regulated by the prefrontal cortex (PFC). In comparison, relatively less is known about the importance of PFC DA receptors for executive functions such as behavioral flexibility. A previous study (Ragozzino, 2002) reported that blockade of D1 receptors in the medial PFC of rats caused a selective impairment in behavioural flexibility on a cross maze task when rats were required to shift from a response to a visual-cue strategy, and vice versa. However, the roles that PFC D2 and D4-like receptors play in attentional set-shifting remains to be elucidated. In the present study, rats were subjected to two days of testing on a cross maze. On the first day, rats learned a response discrimination, requiring them to always turn in the same direction (left/right) in order to receive food reward. On the second day, rats had to suppress the use of the previously learned strategy and use a novel visual discrimination rule to locate food, requiring them to enter the arm that contained a visual cue. Intra-PFC infusions of the D2 receptor antagonist eticlopride (1 ug) prior to testing on the second day impaired behavioral flexibility; rats took more training trials to learn the new strategy (~100 trials) compared to saline treated animals (~65 trials). Analysis of the errors revealed that the deficit was due to perseveration on the previously learned strategy. In contrast blockade of PFC D4 receptors with L-745,870 (10 ug) actually improved attentional set-shifting, whereas similar infusions with the D4 agonist PD 168,077 (1 ug)impaired performance. Collectively, these data suggest that multiple receptors in the PFC are essential for attentional set-shifting and that the mechanisms by which mesocortical DA mediates behavioral flexibility may be different than those which underlie working memory, and may have important implications for developing novel treatment strategies for cognitive deficits observed in diseases such as schizophrenia.

134. When What You Hear Is Not What You Say: Gamma-Coherence to Distorted Speech Is Reduced in Healthy Comparison Subjects but not in Patients With Schizophrenia

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Communication between frontal lobes, where speech is generated, and temporal lobes, where it is perceived may occur through the action of an efference copy/corollary discharge mechanism that prepares the temporal lobes for the expected sound. Gamma-band synchrony between these regions may reflect a "binding of expectation with experience". We tested the hypothesis that there would be reduction in gamma-band coherence when what is heard is not what was said. We also tested the hypothesis that patients with schizophrenia would show deficits in this gamma-band reflection of the efference copy/corollary discharge mechanism. EEG was recorded from 21 healthy adult subjects and 21 patients with schizophrenia (DSM-IV) as they uttered the sound [a:] (Talking condition) and as the sounds were played back (Listening condition). As they spoke, real-time feedback was (1) pitch-shifted down 1 semi-tone, (2) pitch-shifted down .5 semi-tone, or (3) not pitch-shifted. Event-related gamma (38-42 Hz) coherence between frontal and temporal sites was calculated relative to the onset of the sound. In healthy controls, but not in patients, frontal-temporal gamma-band coherence was greater during Talking than Listening. In healthy controls, but not in patients, gamma-band coherence was reduced when speech was distorted one semi-tone. Gamma-band synchrony may reflect a "binding of expectation with experience". Disruption in this synchrony may signal

speech production circuits to implement adaptation routines to adjust speech. A failure in this mechanism could have far-reaching effects, spanning difficulties from language learning to motor awkwardness.

135. Occupancy of Dopamine D2 Receptors by Aripiprazole at Steady State Dosing in Schizophrenia Measured with [18F]Fallypride PET

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Sponsor: Anissa Abi-Dargham

This study examined dopamine D2 receptor occupancy by the antipsychotic medication aripiprazole across the clinical dose range in individuals with schizophrenia. Seven subjects with schizophrenia (age 32 ± 8.4 years, gender 6M/1F) and six healthy controls (age 28 ± 6.7 years, gender 4M/2F) participated in this study. Subjects were taking daily aripiprazole doses of 5 mg, 7.5 mg, 10 mg, 40 mg (n = 1) and 15 mg (n = 3) for an average of 8.4 ± 8 weeks (min 3 weeks). PET scans were performed on the ECAT EXACT HR+ PET camera after injection with the radiotracer [18F]fallypride. Regions of interest (ROIs) were drawn on each individual's co-registered MRI. The specific-to-nonspecific distribution coefficient, V3", was determined using the simplified reference tissue model, with the cerebellum serving as the region of reference. D2 occupancy by aripiprazole was calculated as (V3" CTR - V3" SCH)/ V3" CTR * 100. At the time of scanning, the plasma levels of aripiprazole ranged from 102 ng/mL (5 mg dose) to 324 ng/mL (40 mg dose). In all regions, at every dose, aripiprazole achieved near complete occupancy at the D2 receptors, with an average occupancy across regions of 89% ±12% (n = 126, 18 regions per subject). Despite the near complete occupancy of D2 receptors, all subjects had normal prolactin levels (range 1.0 - 8.9 ng/mL) and displayed low to no EPS (AIMS 2.3 ± 3.8, Barnes Akathisia 1.2 ± 1.6, Simpson-Angus 12.3 ± 1.5). This is the first study documenting the D2 receptor occupancy of aripiprazole in subjects with schizophrenia at clinically effective dosages. Consistent with previously published data in healthy controls (1), aripiprazole achieved near complete occupancy of D2 receptors without inducing prolactin elevation or EPS. D2 receptor occupancy of more than 80% by full antagonists is associated with high incidence of EPS (2). The absence of EPS or prolactin elevation under near complete occupancy of D2 receptors observed in this study supports that aripiprazole acts as a partial agonist in the living human brain. This study was supported by a grant from Bristol-Myers Squibb. References: 1. Yokoi F, Ph DM, Grunder G, Biziere K, Stephane M, Dogan AS, Dannals RF, Ravert H, Suri A, Bramer S, Wong DF: Dopamine D(2) and D(3) Receptor Occupancy in Normal Humans Treated with the Antipsychotic Drug Aripiprazole (OPC 14597). A Study Using Positron Emission Tomography and [11C]Raclopride. Neuropsychopharmacology 2002; 27(2):248-59; 2. Farde L, Nordstrom AL, Wiesel FA, Pauli S, Halldin C, Sedvall G: Positron emission tomography analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Arch. Gen. Psychiatry 1992; 49:538-544

136. Brain Metabolite Abnormalities in the White Matter of Elderly Schizophrenic Subjects: A 4 Tesla MRS Study

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Sponsor: Jack Gorman

Introduction: Emerging evidence suggests that abnormalities in oligodendroglia or myelination may lead to white matter pathology that may contribute to the disease processes of schizophrenia (1). However, only few recent studies have evaluated the white matter in the brains of schizophrenic patients. Moreover, the interaction effects between the pathophysiological processes of schizophrenia and the normal degenerative process of aging may produce white matter changes which could contribute to the progressive deterioration in cognitive and functional abilities observed in some elderly schizophrenics. Since neurochemical changes have been documented with normal aging and in patients with schizophrenia, this study used proton proton magnetic resonance spectroscopy (1H MRS) to assess white matter abnormalities of the brains of elderly schizophrenic patients. **Methods:** All subjects were over the age of 60 and were evaluated with a diagnostic interview, assessments of symptomatology and an extensive neuropsychological battery. In addition, screening laboratory studies were performed (including complete blood count, routine chemistry, liver enzymes, and thyroid function tests) and urine toxicology screen. MRI and localized 1H MRS were performed on a Varian 4 Tesla scanner in 22 elderly patients with schizophrenia (mean age 66, sd=7.5 years) and 17 elderly control subjects (mean age 70.2, sd=5.9 years). MRS data were acquired using an optimized double sin echo sequence (PRESS) {Ernst, 1996 #419}, with TE=30 ms, TR=3000 ms, 64 averages, and 2 kHz bandwidth. In each subject, 6 MRS voxels were planned: 1) right and left dorsolateral frontal white matter; 2) right and left medial temporal white matter; 3) right and left occipital white matter. Typical voxel sizes ranged between 3-5 mL, depending on the individual's anatomy and location of the voxels; placement of the voxels depended on standard landmarks and care were taken to avoid inclusion of significant amounts of gray matter. To avoid the ambiguities caused by metabolite ratios, metabolite concentrations of NA, CR, CHO, MI, and GLX were determined using the LC Model Program {Provencher, 1993 #1550}. **Results:** Compared to the healthy elderly subjects, the schizophrenia subjects as a group showed decreased NA in the dorsolateral frontal white matter and the medial temporal white matter regions bilaterally. However, no significant decreases in the neuronal marker N-acetylaspartate (NA) were observed in the occipital brain regions. The schizophrenic subjects also had decreased glial marker myoinositol (MI) and elevated glutamate+gluatmine (GLX) in most of the brain regions. In contrast, soluble choline compounds (CHO) were elevated in the dorsolateral prefrontal brain regions. Lastly, age-associated decline in total creatine and in CHO in the frontal white matter were observed only in the elderly schizophrenics but not in comparison subjects. **Conclusions:** Collectively, these findings suggest significant losses of metabolites that are associated with neurons and glial cells in the white matter of elderly schizophrenics. Some of these changes appear to worsen with age. Furthermore, elevated GLX suggests increased extracellular glutamate which might contribute to excitotoxicity to neurons and glial cells. Future studies with a novel MRS sequence will allow delineation of the changes in glutamate in the brains of schizophrenic subjects.

137. Shifts in Myelin Integrity Uncovered by Diffusion Tensor Imaging (DTI) During Psychosis Exacerbation and Remission in Good-Responding Schizophrenia

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Evidence of altered connectivity (the correlation between neuronal activity at remote sites) has been reported in some patients with schizophrenia. Such altered connectivity suggests a failure of functional wiring between information processing centers in brain. Further support of altered connectivity has come from diffusion tensor imaging and anisotropy, which indicates impaired directionality of myelinated fiber tracts in some schizophrenics. Previous studies have also indicated evidence of immune activation within the CNS of some schizophrenics during

psychosis exacerbation. We re-investigated such central immune activation together with white matter diffusivity (Dm) using Diffusion Tensor Imaging (DTI) in schizophrenics subsequently found to be good responders (GR) and poor responders (PR) during 28 days of antipsychotic drug treatment. GR patients evidenced elevation of the pro-inflammatory cytokine interleukin-6 (IL-6) in the CSF ($p < 0.05$) at neuroleptic-free baseline and demonstrated increased Dm of central white matter ($p = 0.008$) during psychotic exacerbation. Increased Dm is consistent with extracellular edema. The pathological Dm was reduced ($p < 0.03$) following reduction of psychotic symptoms by 84% during treatment with antipsychotic drugs. PR patients had neither abnormal Dm at baseline nor significant Dm change during the course of antipsychotic drug treatment. GR patients manifest an episodic functional-disconnect- syndrome (FDS) during psychosis exacerbation which is associated with inflammatory cytokine elevation, disruption of white matter integrity, and of information processing. Remission of psychosis is associated with partial recovery of white matter integrity.

138. A Pilot Study Assessing the Effects Of Dar-0100 (A Dopamine D1 Full Agonist) on Regional Brain Activity and Task-Specific Activation in Patients with Schizophrenia

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Background: Studies in non-human primates have shown that dopamine D1 receptors play an important role in memory and cognition. There are several studies providing evidence that supports the hypothesis that dopamine D1 agonists can reverse performance deficits in either aged non-human primates, or in primates with lesions to dopamine systems. Unfortunately, no centrally-active selective D1 agonists have been available to test such ideas. This study utilizes the first full D1 agonist, dihydrexidine (DAR-0100). DAR-0100 has somewhat higher D1 affinity, and greater D1 selectivity, than ABT-431, the only other D1 agonist to be given to humans. Availability of this drug has permitted us to conduct an initial pilot study assessing the safety and efficacy of low doses of DAR-0100 on prefrontal cortical blood flow and cognitive function in patients with schizophrenia. **Methods:** The effects of DAR-0100 on resting blood flow in the prefrontal cortex and neural activity in regions involved in working memory are being evaluated. A within subject cross-over design is being used in 20 adults (18-65 yrs of age) with SCID diagnosed schizophrenia. Subjects are outpatients whose stable doses of selected antipsychotic medications still leave a moderate level of remaining negative symptoms. Following a screening visit, subjects are admitted for a 48 hour inpatient hospitalization. Each morning at 8 am they are scanned on a 3T MRI scanner for resting perfusion, followed by a BOLD fMRI scan during the n-back working memory task. They then receive 20 mg of DAR-0100 (or placebo) sc over 15 minutes. Over the next 45 minutes they have intermittent MRI scans of perfusion and BOLD activity during the working memory task. Response data and serum levels are collected. A repeat MRI scan is done at 6 pm, without any infusions. The following morning they have a repeat of the Day 1 schedule, and receive either DAR-0100 or placebo (whichever was not given on Day 1). Within day, as well as between day, comparisons will be made to test for potentially increased rCBF with DAR-0100. **Results and Conclusions:** Data collection is underway at the time of submission. This first proof-of-concept study has important implications for the treatment of cognitive and memory deficits in schizophrenia and other CNS disorders. Study Funded by the Stanley Medical Research Institute. DAR-0100 was generously provided by DarPharma, Inc., Chapel Hill NC.

139. Optimization of Long-acting Risperidone for Maintenance Therapy in Schizophrenia

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Sponsor: George M. Simpson

Objective: Continuous therapy with antipsychotics is essential to achieving remission and an optimal outcome in patients with schizophrenia. The objective of this study was to examine long-term clinical outcomes and dosing in patients with psychotic disorders who were transitioned from oral antipsychotics to long-acting injectable risperidone. **Method:** Patients with psychotic disorders were randomized to long-acting risperidone 25 or 50 mg every 2 weeks in a 52-week, prospective, randomized, double-blind, multicenter study. Prior antipsychotic dose was considered in the randomization process. Patients in the study were symptomatically stable, with no signs of relapse in the 4 months prior to baseline, and taking stable doses of oral antipsychotic medication for 4 weeks prior to baseline; stratification by average or higher-than-average risperidone equivalents was conducted to provide information regarding optimal long-term dosing. Efficacy measures include the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions of Severity (CGI-S) scale. Safety assessments include reporting of treatment-emergent adverse events, the Extrapyramidal Symptom Rating Scale (ESRS) and the Abnormal Involuntary Movement Scale (AIMS). **Results:** Results are reported here for the 6-month, blinded interim endpoint of the ongoing trial. The study includes 324 stable patients (62.3% male, mean age, 40.9±11.9 years). Previous treatment of monotherapy or combination therapy included fifty-seven patients (17.7%) taking conventional antipsychotics prior to the study, and 312 patients (96.3%) taking atypical antipsychotics: aripriprazole, 18 (5.6%) patients; olanzapine, 95 (29.3%) patients; quetiapine, 38 (11.7%) patients, risperidone, 145 (44.8%) patients; and ziprasidone, 16 (4.9%) patients. There was a significant reduction in mean±SD total PANSS score from 66.5±16.4 at baseline to 60.2±15.8 ($P<0.001$). There was an increase in the percentage of patients rated on the CGI-S as not ill to mildly ill, from 45.5% at baseline to 62.3% at endpoint. There was an improvement in mean±SD CGI-S score from 3.50±0.9 to 3.2±1.0 ($P<0.001$). The most common treatment-emergent adverse events (≥10%) were insomnia (23%), headache (14%), anxiety (11%), and schizophrenia not otherwise specified (11%). The ESRS subjective score (mean±SD) decreased from 2.0±2.9 to 1.7±2.4 ($P<0.05$). The physician's rating of parkinsonism (mean±SD) decreased from 4.6±6.8 to 3.5±5.3 ($P<0.001$), and the physician's rating of dyskinesia (mean±SD decreased from 1.5±3.4 to 1.1±2.8 ($P<0.05$). Scores for physician's ratings of dystonia and akathisia were very low at baseline and throughout the first 6 months of the study. The AIMS score (mean±SD) for items 1–7 improved significantly, from 1.6±3.0 to 1.3±2.6 ($P<0.05$). **Conclusions:** Interim data suggest that maintenance therapy with long-acting risperidone provides further symptomatic improvements, is well tolerated, and decreases movement disorder severity in stable patients with schizophrenia or schizoaffective disorder. Supported by Janssen Medical Affairs, L.L.C.

140. Assessment of Antipsychotic-Related Diabetes Mellitus in a Medicaid Population: Sensitivity to Study Design

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Sponsor: Alexander Glassman

Objective: Retrospective studies using large patient databases have reported conflicting findings regarding diabetes risks associated with antipsychotics. Sensitivity of findings to study design was assessed within a

Medicaid psychosis population. **Methods:** Administrative data were analyzed for more than 100,000 Ohio Medicaid patients with claims for psychoses both treated and untreated with antipsychotics. Screening for preexisting diabetes, identification of diabetes with prescription claims only, and antipsychotic monotherapy provide better control for confounding influences and represent a stronger study design. Diabetes odds ratios for patients treated with clozapine, olanzapine, quetiapine, risperidone, ziprasidone, or conventional antipsychotics versus untreated patients were estimated varying the above criteria. Patients untreated with antipsychotics included those who were not treated with antipsychotics for extended periods of time and had at least 2 claims for schizophrenia, bipolar disorder, or major depressive disorder. Logistic regression controlled for patient age, sex, type of psychosis, length of observation/treatment, antipsychotic dosage, preexisting excess weight or dyslipidemia, and use of other drugs with potential diabetogenic effects. Selection bias was also assessed for risperidone, olanzapine, and quetiapine. **Results:** Under the weakest study design (no prescreening, use of medical or prescription claims, and no monotherapy requirement), all of the antipsychotics were associated with statistically significant ($P<0.05$) higher odds of diabetes relative to untreated patients with psychoses. Estimated odds ratios were: clozapine 1.468 (95% CI: 1.333-1.617), olanzapine 1.108 (95% CI: 1.050-1.170), quetiapine 1.270 (95% CI: 1.197-1.348), risperidone 1.232 (95% CI: 1.169-1.299), ziprasidone 1.226 (95% CI: 1.100-1.367), and conventionals 1.159 (95% CI: 1.098-1.224). Under the strongest study design (screening for preexisting diabetes 8 months prior to observation, use of prescription claims only, antipsychotic monotherapy), odds ratios relative to patients untreated with antipsychotics were significant for clozapine (1.484, 95% CI: 1.138-1.934) and olanzapine (1.149, 95% CI: 1.001-1.319), while those for quetiapine (0.998, 95% CI: 0.834-1.195), risperidone (1.124, 95% CI: 0.983-1.284), ziprasidone (0.717, 95% CI: 0.415-1.239), and conventionals (1.025, 95% CI: 0.885-1.187) were nonsignificant. Based on comparison of antipsychotics with respect to trends in diabetes frequency, antipsychotic dosage, and proportion of patients with preexisting diabetes, it appears that risperidone in particular and quetiapine were adversely affected by selection bias, which favored olanzapine. Evidence from case reports, chart reviews, and clinical trials do suggest differential risks of excessive weight gain and diabetes/hyperglycemia among the atypical antipsychotics and may have contributed to selection bias by affecting practitioner prescribing behavior. **Conclusions:** In large database studies, estimated risks of diabetes among antipsychotics are affected by study design. When a more rigorous design was employed, clozapine and olanzapine alone among the atypical antipsychotics were associated with diabetes risk that was significantly greater than that in untreated patients with psychoses. These findings were made despite evidence indicating selection bias favoring olanzapine and disfavoring risperidone and quetiapine.

141. Does Industry Sponsorship Influence The Results of Antipsychotic Trials?

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Introduction: More than at any other time in history, the pharmaceutical industry is being closely scrutinized and even sued. Many are concerned that the industry may subtly influence the outcome of random-assignment double-blind studies to favor their product. It is noteworthy that sponsors report their drug as being superior (at least in certain parameters) to their competitors. There is a small literature showing that more favorable results are reported by pharmacologically-sponsored than non-sponsored studies. This effect may be partly accounted for by a bias to only report studies which favor a company's product (i.e., publication bias) -particularly in studies which are not well-controlled. **Methods:** We examined whether pharmaceutical company sponsorship influenced the relative efficacy of the second-generation antipsychotics in all controlled, randomized, blinded studies. One hundred twenty-four studies comparing a second-generation antipsychotic (SGA) to a first-generation antipsychotic (FGA) were identified and independently evaluated for efficacy (using a previously reported methodology). Since sponsorship information was not available for many of the studies, we contacted the author(s) of all of the studies. Further, if they failed to respond, we made repeated efforts (such as contacting individuals at international meetings to inquire personally as to sponsorship as well as contacting other members of their department, etc. We obtained an almost 100% response. As there are data to suggest that some SGAs (but not all) may have superior efficacy compared to FGAs, we evaluated sponsorship for each drug separately and pooled these results over all drugs. In other words, we compared the effect of sponsorship on the efficacy of the SGAS to the FGAS. **Results:** We were unable to find any effect of sponsorship on differential efficacy. **Conclusions:** Since we were not able to find an effect of sponsorship it may be that random-assignment and double-blinding removed bias. We will also report on other variables which potentially might influence the result of randomized blinded trials. For example, since patients are increasingly becoming treatment resistant, does this fact make it more difficult to show that a SGA is better than a FGA? These results will be examined in the perspective of the literature on the influence of sponsorship and other variables on the outcome of meta-analysis.

142. Update On Psychopharmacology Curriculums: Is There Any Relationship Of Teaching To Clinical Practice?

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Objective: Globally there is a widely shared perception that the teaching of psychopharmacology has not kept pace with scientific advances in neuroscience and with controlled outcome data. As a result, clinical practice leaves much to be desired. In part to meet this need, there has been one ACNP model psychopharmacology curriculum (1987) as well as three subsequent versions produced by the ASCP (1997, 2001, 2003). Over half of major residency programs in the US are using the curriculum. But, there remain major obstacles to widespread implementation. This poster reviews some of the problems and suggests steps to meet this challenge. **Method:** Based on two follow up studies (of users of the curriculum) and meetings with residency training directors, obstacles and problems have been identified. **Results:** Six key problems in implementation and their potential solutions are described. As such, a third edition features revision and updating of the "how, when, why, and with which evaluative tools" to teach psychopharmacology in a psychiatric residency program. All lectures and appendices have been updated. Ten new lectures have been added including five from the recently developed ACNP geriatric psychopharmacology curriculum. Lectures now have multiple-choice questions and are in PowerPoint. **Conclusions:** Collaboration between psychiatric educators and psychopharmacology teachers is necessary to improve both the teaching and the clinical practice of psychopharmacology. Having a structured curriculum may be mandatory to improve resident competence. Of most interest to teachers of psychopharmacology, is that we already are working on the next edition which will include, among other advances, active collaboration with AADPRT to improve pedagogy, neuroscience and competency components.

143. Asssoication of a CRH Gene Haplotype with HPA Axis Activity in Rhesus Macaques

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Sponsor: Travel Awardee, BMS, 2004

Corticotropin-releasing hormone (CRH) is the primary neuropeptide responsible for activation of the hypothalamic-pituitary-

adrenal (HPA) axis, and perturbations of these systems are associated with stress-related and alcohol use disorders. As such, the *CRH* gene may be a good candidate for investigating genetic variation as it relates to vulnerability to anxiety and mood disorders, neuroendocrine stress axis dysregulation, and alcoholism. We have identified a number of polymorphisms within the 5′–flanking and coding regions for the *CRH* gene in rhesus macaques (rh*CRH*). One haplotype cluster (rh*CRH-A2*) is present in 15% of the animals in our colony. *In vitro* studies using a pDsRed expression system demonstrated higher basal- and forskolin-stimulated promoter activity in the rh*CRH-A2* construct compared to the nonvariant rh*CRH-A1* construct. We wanted to determine whether the rh*CRH-A2* haplotype cluster would be associated with increased HPA axis activity at baseline, following a psychosocial stressor and in response to alcohol. At 6 months of age, rhesus infants (N=232) were subjected to 96h of social separation stress, and adrenocorticotropin (ACTH) and cortisol levels were determined at baseline and at 1, 2 and 96 h of separation stress. At approximately 4 y of age, a subset of animals (N=90) received an intravenous infusion of alcohol (2-2.2 g/kg), and ACTH and cortisol levels were determined at baseline and following alcohol infusion. Effects of rh*CRH* gene variation on HPA axis output were analyzed using repeated measures ANOVA. Among infants, rh*CRH-A2* was associated with increased ACTH levels at baseline. The rh*CRH-A2* haplotype cluster was also associated with increased ACTH and cortisol levels following alcohol. These data demonstrate that rh*CRH* gene variation is associated with increased HPA activity both at baseline and in response to alcohol in rhesus macaques and may suggest a role for human *CRH* gene variation in the susceptibility to stress- and alcohol-related disorders.

144. sNPS On Chips: COMT SNP Association With Expression? A Word Of Caution!

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Gene expression microarray analysis in psychiatric research typically compares the expression of tens of thousands of genes in postmorten brain tissue between affecteds and matched controls. In contrast, genetic studies identify SNPs associated with these disorders in genomic DNA. Often, SNPs found associated with psychiatric disorders are postulated to affecte gene expression. We determined both gene expression and SNP genotype in >60 brain samples from subjects affected with depression, bipolar disorder or schizophrenia and controls. We genotyped >40 SNPs in a variety of candidate genes previously postulated to be involved in psychiatric disorders. One common SNP, the Val(108/158)Met coding variant in the catechol-O-methyltransferase (COMT) gene, was found highly significantly associated with expression level, as determined by RMA analyses on Affymetrix arrays (Irizarry et al. 2003). This association was reproducible across several brain regions and across hybridization performed in several laboratories. The Met allele has lower enzymatic activity, and showed an apparent increase in expression by about 20-30% per allele, with heterozygotes, as expected, intermediate in expression. It thus appeared that expression compensated for activity differences. However, a second probe set for COMT on the same array did not show this asso-ciation. To investigate this discrepancy, we investigated the expression difference at the probe level of the array. We found that a single oligonucleotide on the Affymetrix array showed a twofold difference in expression, whereas other oligos for COMT showed only non-specific differences in expression. This one oligonucleotide had the polymorphic Met allele in the center of its sequence, thus effectively creating a mismatch probe for the Val allele. We conclude that the apparent expression difference was an artifact due to the presence of the SNP on the oligo. This result was unexpected since typically hybridization of more than 10 oligonucleotides is averaged before analysis, and RMA downweighs results from atypically hybridizating oligos. However, while the larger twofold difference was reduced to only a 20% difference, it remained significant and showed the misleading expression difference. The artifact observed is likely to be quite common. A screen of Affymetrix oligos of the 133AB Plus Chip against dbSNP identified more than 30,000 SNPs that are present with one allele on that chip. It remains to be seen how often these cause a significant effect. Because of linkage disequilibrium between SNPs such artifacts can also be observed when the genotyped SNP is not present on the cDNA. Presence of common SNPs need to be taken into account when interpreting oligonucleotide microarray expression data.

145. Central Oxytocin and Vasopressin in Aggression

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Objective: Animal studies suggest a role for central oxytocin (OXY) and vasopressin (VASO) in the regulation of aggression. In this study we examined the relationship between CSF OXY and CSF VASO and aggression in adult personality disordered subjects. **Methods:** Lumbar CSF for morning basal levels of oxytocin and vasopressin were obtained from 36 subjects with DSM-IV personality disorder between the ages of 20 and 50. Aggression was assessed dimensionally through the use of the Life History of Aggression (LHA) assessment; general personality traits were assessed using the Eysenck Personality Questionnaire. Unless otherwise noted, Spearman correlations are reported. **Results:** CSF OXY correlated inversely with LHA Aggression ($r = -.35$, $p = .034$) and directly with CSF VASO (Spearman $r = .33$, $p = .051$). The relationship between CSF OXY and VASO was inverse and moderate in magnitude ($r = -.45$, $p = .007$). Removal of one multivariate outlier improved the correlations with LHA Aggression (OXY: $r = -.45$, $p = .007$; VASO: $r = .38$, $p = .023$). Subsequent multiple regression analysis without this subject revealed a significant relationship between CSF OXY, but not CSF VASO, and LHA Aggression (OXY: part $r = -.36$, $p = .029$; VASO: part $r = .20$, $p = .263$). CSF OXY did not correlate with other general personality variables such as Eysenck Neuroticism ($r = -.08$), Psychoticism ($r = .08$), or Extraversion ($r = .00$). **Conclusions:** This first report of a relationship between CSF OXY and aggression in the human literature is consistent with data from animal studies. While CSF VASO also demonstrates a correlation with aggression, this relationship may be mediated through a shared relationship with CSF OXY. Lack of correlation with general personality variables suggest that this relationship may be more specific to aggression.

146. Medial Prefrontal Cortex is Essential for Conditioned Aversion to Sex Behavior in the Male Rat

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Sponsor: Gary Gudelsky

Several components of the limbic system are activated during male rat sexual behavior, as reflected by increased expression of the immediate early gene c-fos. In particular, studies from our lab demonstrated that mating or mating-associated environmental cues induce Fos in the infralimbic and prelimbic regions of the medial prefrontal cortex (mPFC). However, data from our lab also demonstrated that the mPFC is not necessary for the expression of sexual motivation or performance. In particular, lesions of the infralimbic and prelimbic regions of the mPFC or lesions of all regions of the mPFC did not affect any component of male sexual behavior. Instead we hypothesized that the mPFC is necessary for the formation of conditioned aversion associated with male sexual behavior. The current study investigated the hypothesis that the mPFC is necessary for the acquisition of copulation contingent aversive conditioning to lithium chloride (LiCL). Ibotenic acid was used to lesion both

the prelimbic and infralimbic components of the mPFC in sexually experienced males. Lesioned and sham (mPFC vehicle injected) animals were then subjected to 10 consecutive conditioning sessions during which 0.15M LiCL (20ml/kg) was paired with ejaculation by systemic i.p. injection, while control animals were injected with saline. This dose of LiCL is sufficient to produce visceral illness and the paradigm has previously been shown to cause inhibition of sexual behavior. Indeed, sexual behavior in LiCl treated sham animals was significantly reduced by session 6 as compared to saline treated sham males. However, LiCl treated mPFC lesioned males continued to copulate throughout the entire experiment. These data suggest that the mPFC is essential for establishment of associations between sexual reward and malaise and the subsequent inhibition of sexual motivation. Hence, these results support a role for mPFC in the control of impulsive behaviors, specifically related to sex behavior. Supported by NIHDK59803 (JFD), and MH60781, DA14591 (LMC).

147. Different Approaches to Dose Finding: The Duloxetine Example

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Sponsor: Smiriti Iyengar

Introduction: Dose-response relationships in drug development are typically assessed by means of multiple arm studies with fixed doses of the test drug. Khan et al., 2003 showed that this approach did not reveal efficacy dose relationships for most antidepressants. Some of the issues associated with dose finding are the range of doses tested and the effect sizes (measure of the change in performance of a drug-treated group over and above that of a placebo-treated group, when controlling for variability). **Method:** Two approaches that were utilized are discussed here. One involved pooling results across multiple studies in major depressive disorder (MDD) and this was contrasted with the study of duloxetine for diabetic neuropathic pain (DNP) that utilized a single study with multiple fixed doses. Six MDD studies, virtually identical, were designed with varying but overlapping doses. Duloxetine was tested at doses of 40mg/d, 60 mg/d, 80 mg/d and 120 mg/d. The single study in DNP utilized fixed doses of 20, 60 and 120 mg/d of duloxetine. **Results:** Meaningful differences between doses in tolerability and efficacy were identifiable from the pooled MDD data. The influence on outcome variance across studies was addressed using statistical methods including effects size, relative risk, and odds ratios. Meaningful differences were also seen in tolerability and efficacy in the DNP data. It is noteworthy that a six-fold range of doses was studied in DNP, but only a three-fold range in MDD, and that the effect sizes for key variables were greater in DNP. **Conclusions:** During development of a drug, different approaches can be used to find the minimum effective dose. These can include making inferences across multiple protocols, or using a single study with multiple doses. However, during dose-finding, it is important to have a range of effect size that is wide enough among the doses to use any approach. These strategies have broad implications for pharmacology research and careful design is required to maximize validity of either method.

148. The Role of the Vagus Nerve in the Behavioral, Neurochemical and Neuroendocrine Responses to Interleukin-1 and Endotoxin in Mice

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Sponsor: Adrian Dunn

The vagus nerve is known to be an important route for signalling from the periphery to the brain. in the present experiments we examined the effects of subdiaphragmatic vagotomy on the responses of mice to interleukin-1β (IL-1β) and endotoxin (LPS). Subdiaphragmatic vagotomy did not alter the consumption of food pellets or sweetened milk, nor did it alter the reductions in the consumption induced by IL-1β and LPS. However, while vagotomy did not alter basal plasma concentrations of ACTH and corticosterone, it attenuated the increases that followed IL-1β or LPS treatment. Also, whereas basal concentrations of brain norepinephrine (NE) and serotonin (5-HT) were not altered, the increases in NE and 5-HT metabolism and the increases in brain tryptophan that follow IL-1β or LPS were attenuated. These results suggest that the hypophagic responses are not directly related to the changes in hypothalamo-pituitary-adrenal (HPA) axis activity, nor the changes in catecholamines and indoleamines. These results resemble those we obtained previously in rats, although in that species, vagotomy almost completely prevented the noradrenergic response assessed by microdialysis. Thus although the vagus may be involved in the endocrine, the catecholamine, and the indoleamine responses to IL-1 and LPS, it seems unlikely that the neurochemical or endocrine changes are directly responsible for the anorexia induced by IL-1β or LPS. Supported by NINDS.

149. Interferon Effects on Behavior, Corticosterone, Catecholamines and Indoleamines in Mice and Rats

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Interferon-α (IFN-α) therapy induces depressive symptoms in patients. We have studied the effects of various forms of IFN-α on behavioral tests that respond to depressing and antidepressant treatments, while also assessing body temperature, plasma hormones, and the metabolism of catecholamines and indoleamines in mice and rats. Administration of mouse IFN-α and human IFN-α either peripherally (ip 20-50,000 U) or intracerebroventricularly (icv 5,000 U) did not significantly alter their core temperature compared to vehicle injected animals. Mice were tested in the tail-suspension test, the Porsolt forced swim test, and in the open field after peripheral (ip) or intracerebroventricular (icv) injections. Desmethylimipramine and imipramine both reduced immobility in the tail suspension test and in the forced swim test. There were no significant alterations in the behavior of mice in the open field following icv injections of mIFN-α (5000 U) or hIFN-α. In the tail suspension test, mIFN-α increased immobility, suggesting some depression-like activity, whereas hIFN-α (10,000 U) tended to decrease immobility or had no effect. In the forced swim test, mIFN-α had variable effects, often increasing immobility, but sometimes decreasing it. hIFNa tended to decrease immobility, but often had no effect. In rats, icv rIFN-α (1500 U) increased immobility (floating) in the forced swim test, but had no effect in the open field. In several experiments in both mice and rats, icv IFN-α induced modest increases in the metabolism of norepinephrine (NE - assessed by MHPG), and serotonin (assessed by 5-HIAA), as well as in tryptophan in various brain regions, but these effects were not particularly consistent. Likewise, IFN-α administration by either route induced modest increases in plasma corticosterone. These results are largely consistent with those we had observed previously in mice. Overall, it appears that homologous IFN-α had depression-like effects in the tail suspension test in mice, and in the forced swim test in rats. hIFN-α did not produce consistent effects. There were no changes in body temperature following IFN-α in mice. The changes in brain catecholamines and indoleamines were not consistent, and there were only modest increases in plasma glucocorticoids. These results are in contrast to the marked fever and the activation of the HPA axis observed in many patients when IFN-α is administered to humans.

150. Differential Effects of d-Amphetamine, Adderall® and Other Amphetamine Isomers on Dopamine Neurotransmission in the Striatum and Nucleus Accumbens Core

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Sponsor: Greg Gerhardt

Adderall® and dextroamphetamine (Dexedrine®), first line stimulant medications used in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD), differ only in the presence of 25% levoamphetamine (the stereoisomer of dextroamphetamine in Adderall). Our hypothesis is that the observed differential clinical effects of these stimulants can be explained by the effects of l-amphetamine on d-amphetamine-evoked dopamine (DA) and norepinephrine (NE) release in critical brain regions. High-speed chronoamperometric recordings using Nafion-coated carbon fiber microelectrodes and microdialysis were used to measure Adderall vs. d-amphetamine induced release of DA and NE in the striatum and nucleus accumbens (core) of both anesthetized and freely moving Fischer 344 rats (3-6 months old). Significant differences were found between Adderall and d-amphetamine, as well as racemic amphetamine and straight l-amphetamine, in the kinetics of DA release in the striatum and nucleus accumbens core using voltammetry. Applications of equal volumes of Adderall (1.35mM) produced a significantly greater amplitude of DA release compared to d-amphetamine (1mM) and d,l-amphetamine (2mM). Resulting average peak amplitudes were (mean SEM) $0.63 \pm 0.10, 0.31 \pm 0.03, 0.35 \pm 0.03$ μM DA ($p<0.001$, $p<0.01$)($n=12,20,15$ signals respectively). The rise time (seconds) of DA release was significantly longer between Adderall (148 ± 32)and d-amphetamine(73 ± 16)($p<0.05$), but not with d,l-amphetamine (82 ± 17). The amplitude of DA changes was not significantly different using reverse microdialysis in the anesthetized rat despite the presence of additional l-amphetamine in Adderall as compared to d-amphetamine in the striatum and nucleus accumbens core. These data were replicated in the freely moving animal with ip injections of the amphetamine isomers at concentrations similar to those administered in the treatment of ADHD. These data support the hypothesis that Adderall may produce its different clinical effects as compared to d-amphetamine in part through alterations in the dynamics of DA release in the striatum and nucleus accumbens. Further studies in the prefrontal cortex will be needed to assess the role of norepinephrine in the differential response to amphetamine isomers. Supported by USPHS grants MH70840, MH01245, DA14944, and NS39787.

151. Hyperphagia Induced by GABAA Receptor-Mediated Inhibition of the Nucleus Accumbens Shell: Dependence Upon Intact Neural Output from The Central Amygdaloid Region

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Sponsor: Ann Kelley

A double-cannulation study was carried out in rats to investigate the effects of inactivating sites within the basolateral amygdaloid complex (BLA) or central amygdaloid region (CeA) upon feeding responses elicited by GABAA receptor stimulation within the nucleus accumbens (Acb) shell. As previously shown, infusions of the GABAA receptor agonist, muscimol (0, 25 ng), directly into the Acb shell acutely increased chow intake in ad-libitum-fed rats. This effect was not altered by co-infusions of muscimol (0, 20 ng) into the BLA. In contrast, muscimol infusions (0, 5, 20 ng) into the CeA dose-dependently reduced feeding elicited either by intra-Acb shell GABAA receptor stimulation or by food deprivation, and produced a dose-dependent syndrome of stereotyped forepaw treading. Further analyses revealed that intra-CeA infusion of the low muscimol dose diminished average feeding bout duration without altering the number of feeding bouts initiated, while the high dose completely abolished feeding. Intra-CeA tetrodotoxin (50 pg) pretreatment blocked feeding elicited from the Acb shell but prevented neither the reduction of feeding nor the elicitation of forepaw treading induced by intra-CeA muscimol, verifying that the muscimol effects resulted from inhibition of CeA output neurons, rather than the putative disinhibition of output associated with muscimol-induced suppression of local inhibitory intra-CeA circuits. Hence, feeding elicited by intra-Acb shell GABAA receptor stimulation requires intact information processing and output from the CeA, but not the BLA. Moreover, reductions in feeding produced by intra-CeA muscimol are associated with the dose-dependent recruitment of a competing behavior, forepaw treading.

152. Tolerance to Somnolence: Preclinical Mechanisms and Clinical Evidence With Quetiapine

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Sponsor: Philip Seeman

Objective: Somnolence is a common side effect of agents that block histamine (H_1) receptors and with first-generation antihistamines, rapid tolerance to somnolence often occurs. Somnolence is also frequently reported in patients receiving atypical antipsychotics and may be a result of the affinity of this class of drugs for the H_1 receptor. However, each atypical antipsychotic has a distinct receptor-binding profile and differing affinity for the H_1 receptor. Quetiapine has a high H_1-receptor affinity and high ratio of H_1 to dopamine (D_2) receptor binding. Thus, it is conceivable that the H_1 receptor is completely blocked at considerably lower doses of quetiapine than are required for D_2 receptor blockade. As a consequence of the complete blockade of H_1 receptors, tolerance to the antihistaminergic effects of quetiapine may develop. The objective of this analysis was to determine whether tolerance to somnolence occurs with quetiapine by analyzing the incidence, severity, and duration of somnolence in patients treated with quetiapine, and examining the relationship, if any, between somnolence and dosage. **Methods:** A retrospective analysis of the quetiapine safety database consisting of data from 77 clinical studies (8 placebo-controlled) was conducted. In addition, a subanalysis of the double-blind placebo-controlled studies in the database was also conducted. Descriptive statistics are presented for somnolence reported as an adverse event, including data on time of first onset, severity, and resultant withdrawals. **Results:** A total of 7894 quetiapine-treated patients (median age 39 y, range 12—98 y) were included. These patients had diagnoses of schizophrenia (82.2%), bipolar disorder (8.6%), dementia (5.7%), other (1.6%), or were healthy volunteers in phase I trials (2.0%). The subanalysis assessed 1291 patients treated with quetiapine and 612 patients treated with placebo. Of the 7894 patients who received quetiapine, 2013 (25.5%) reported somnolence at least once. In the placebo-controlled subanalysis, 330/1291 (25.6%) quetiapine-treated patients reported somnolence compared with 57/612 (9.3%) placebo-treated patients. Severity of somnolence was reported to be of mild intensity in the majority of patients receiving quetiapine (71.2%) and placebo (80.7%). First onset of somnolence in quetiapine- and placebo-treated patients was most common in the first week of treatment, with <1% of patients reporting somnolence after the fourth week of treatment. The median duration of somnolence was 8 days for all quetiapine-treated patients. Median durations in the placebo-controlled subanalysis were 5 days and 4 days for quetiapine- and placebo-treated patients, respectively. Sixty-two percent of patients who reported somnolence experienced resolution by the end of treat-

ment. Of the patients who reported somnolence while taking quetiapine, only 38% reported somnolence on the last day of treatment. Only 1.3% (99/7894) of patients treated with quetiapine withdrew from treatment as a result of somnolence. No association was found between the incidence of somnolence and quetiapine dose or diagnosis. **Conclusions:** Analysis of the quetiapine database has shown that somnolence events were generally mild, observed early in treatment, and subsequently disappeared with prolonged treatment. The most plausible explanation for the transient nature of these effects is the development of tolerance to somnolence with quetiapine treatment. The lack of dose-relatedness further supports the hypothesis that the H_1 receptor is completely blocked at low doses of quetiapine.

153. D1 And D2 Dependent Limbic and Cortical Inputs into the Nucleus Accumbens Selectively Mediate Different Aspects of Goal-Directed Behavior

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Sponsor: Anthony Grace

The nucleus accumbens (NAcc) receives synaptic inputs from the hippocampus (HPC) and the prefrontal cortex (PFC), believed to mediate context and motor information integration and output selection for goal-directed behavior. In our previous study, we showed that tonic and phasic dopamine (DA) release selectively modulates HPC and PFC inputs into the NAcc via D1 and D2 receptors, respectively. In this study, we investigated behavioral significance of this mechanism using plus maze with asymmetrical infusion procedure. In the tasks, animals made turns based on a visual cue in the maze (visual cue task) or response direction (response direction task; animals always had to turn to the same direction regardless of a visual cue) to obtain rewards. After reaching response criterion in either one of the tasks, the task was switched to the other and continued until criterion performance lever was reached. One group of rats received inactivation of the HPC with lidocaine infusion (20 ug/0.5 ul saline) combined with either saline (0.5 ul, HPC-sal, n=6), D1 antagonist (SCH23390, 1.0 ug/0.5 ul, HPC-D1, n=3), or D2 agonist (quinpirole, 10 ug/0.5 ul, HPC-D2, n=3) injection into the NAcc of the opposite hemisphere 5 minutes before session started. Anther group of rats received lidocaine inactivation of the PFC with either saline (PFC-sal, n=6), D1 antagonist (PFC-D1, n=3), or D2 agonist (PFC-D2, n=3) injection into the NAcc. For control rats (PFC-sal and HPC-sal), it took 50.3 +/- 5.3 trials in visual cue task and 70.8 +/- 10.7 trials in the response direction task to reach criterion. Perseverative errors made at task switching were 6.5 +/- 2.2 trials. HPC-D1, but not HPC-D2, rats required a significantly larger number of trials to reach criterion in both visual cue and response direction tasks compared to control animals (HPC-D1, 74.7 +/- 10.6 trials in visual cue task, 88.3 +/- 8.5 trials in response direction task; HPC-D2, 45.7 +/- 4.7 trials in visual cue task, 65.3 +/- 8.4 trials in response direction task). However, perseverative errors in both HPC-D1 and HPC-D2 rats were not different from control rats (HPC-D1, 6.0 +/- 1.0 trials; HPC-D2, 5.3 +/- 2.3 trials). On the other hand, PFC-D2, but not PFC-D1 rats, showed a distinct increase in perseverative errors at task switching (PFC-D1, 4.3 +/- 0.6 trials; PFC-D2, 11.7 +/- 2.1 trials), although the number of trials that both PFC-D1 and PFC-D2 rats took to reach criterion for the task before switching did not differ from control rats. These results suggest that D1-mediated HPC-NAcc information processing may be crucial for learning a response strategy, which may be related to D1 receptor activation upon phasic DA release evoked by reward presentation. On the other hand, D2 mediated PFC-NAcc information processing is crucial for switching to a new strategy for achieving a goal, which may be related to decreased D2 receptor stimulation upon suppression of tonic DA release caused by absence of expected rewards.

154. A Multicenter Investigation of Fixed-Dose Nalmefene in the Treatment of Pathological Gambling

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Sponsor: Past Travel Awardee, BMS, 2003

Context: Pathological gambling is a disabling disorder that affects approximately 2% of the general population. Although relatively common, there exists only limited information regarding the effectiveness of pharmacotherapy for this illness. **Objective:** To compare the efficacy of nalmefene, an opioid antagonist, with placebo in adults with pathological gambling. **Design:** Sixteen-week, randomized, fixed-dose, double-blind trial. **Setting:** Fifteen centers across the United States. **Participants:** Between March, 2002 and September, 2002, 207 persons meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for pathological gambling were randomized to treatment. **Intervention:** Subjects were randomized to either one of three fixed doses of nalmefene (25mg/d, 50mg/d or 100mg/d) or placebo. All subjects randomized to medication were begun at 25mg/d for one week and then either continued at 25mg/d or increased to 50mg/d or 100mg/d beginning at week 2. **Main Outcome Measures:** Mean change from baseline on the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS) assessing gambling thoughts/urges and gambling behavior. **Results:** Nalmefene (25mg/d) was significantly (p=0.009) superior to placebo on the PG-YBOCS total score (mean baseline-to-end-point decrease from 22.8 to 11.1 compared to mean decrease from 23.5 to 15.8 for placebo). Nalmefene (25mg/d) was also significantly (p=0.002) superior to placebo in reducing gambling behavior and was significantly (p=0.004) superior to placebo in reducing gambling thoughts/urges. Although efficacy looked similar in the 50mg/d and 100mg/d compared to the 25mg/d group, the data for the higher dose groups are compromised by greater and earlier discontinuation rates. Although many subjects (65.7%) discontinued treatment, the probability of discontinuing the study for those assigned to 25mg/d was not statistically different from those assigned to placebo. Incidents of adverse events were higher with increasing dosage (nalmefene 50mg/d, 100mg/d). **Conclusions:** Nalmefene was associated with a statistically significant reduction in pathological gambling severity, including gambling behavior and gambling thoughts/urges.

155. Effects of NMDA Receptor Glycine Site Agonists Upon Parkinsonian Symptoms and Tardive Dyskinesia

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Sponsor: Daniel C. Javitt

Dysfunction of NMDA receptor mediated neurotransmission may represent a cardinal component of schizophrenia pathophysiology. Clinical trials with medications that act as full (glycine (GLY), D-serine (DSR)) or partial (D-cycloserine (DCS)) agonists at the NMDA-receptor associated GLY site have demonstrated that treatment with each of these compounds may result in significant symptom reductions when used in conjunction with conventional neuroleptics or newer atypical antipsychotics. The most significant glycine site agonists-induced improvements were registered in negative symptoms, with positive, cognitive, and depressive symptoms affected to a lesser extent. However, accumulating data indicate that glycine site agonists may also beneficially affect parkinsonian symptoms and tardive dyskinesia (TD). Both clinical and basic science findings support this hypothesis. In two recent double-blind, placebo-controlled, 6-week crossover studies, the efficacy and safety of GLY (0.8 g/kg/day) and DSR (30 mg/day) used as adjuvants to

risperidone and olanzapine were examined in treatment-resistant schizophrenia patients for which, in contrast to previous studies, paucity of drug-induced parkinsonian and TD symptoms, did not represent a compulsory inclusion criteria. GLY treatment (n=17) resulted in a mean 42.6% ±52.5% (p=0.009) reduction in extrapyramidal symptoms, as measured by the Simpson-Angus Scale for Extrapyramidal Symptoms (SAS), and a mean 57.3% ±70% (p=0.012) reduction in TD scores, as measured by the Abnormal Involuntary Movement Scale (AIMS). DSR treatment (n=39) resulted in mean 31.7% ±33% (p<0.0001) and 38.7% ±56% (p<0.0001) reductions in SAS and AIMS scores respectively. Neither SAS nor AIMS scores changed significantly during treatment with placebo and the GLY- and DSR-induced reductions in parkinsonian and TD symptoms remained significant even after the improvements in Positive and Negative Symptom Scale (PANSS) symptom clusters were taken into account. Recently, a beneficial effect of GLY-site agonists against drug-induced dyskinesias has also been demonstrated using the putative TD analogue vacuous chewing movements (VCM) rat model. Following 24 weeks of treatment with haloperidol decanoate (0.38 mg/kg/4 weeks) rats (N=40) were randomized to receive one intraperitoneal injection with 1.6 g/kg GLY, 10 mg/kg ("low-dose") DCS; 100 mg/kg ("high dose") DCS or saline ("placebo"), respectively. Behavior was videotaped at intervals during the experiment and all VCM, rearing, grooming, and immobility episodes were analyzed and scored. Haloperidol administration decreased motor activity and significantly induced VCM. High dose DCS significantly reduced VCM without affecting other motor parameters. GLY treatment resulted in significantly less VCM but also reduced rearing, grooming, and mobility. In contrast, low dose DCS and placebo did not significantly alter any of these parameters. These findings indicate that the use of GLY and DCS results in attenuation of VCM in rats and may have an effect on TD in humans. Taken together, the accumulating body of evidence indicating possible effects of GLY-site agonists upon motor symptoms suggests that this type of compound: 1) may represent an efficacious treatment against antipsychotic drug-induced side effects, 2) should be assessed as an innovative treatment strategy in neurodegenerative disorders characterized by prominent motor symptoms. In this context, preliminary data from a pilot study examining DSR (30 mg/kg/day) efficacy and safety as adjuvant treatment in Parkinson's disease will also be presented.

156. The Effects of the COMT-inhibitor Tolcapone on Cognition in Healthy Human Subjects: Modulation by the COMT Val$^{108/158}$Met Polymorphism

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Sponsor: ACNP Secretariat

Important aspects of cognitive function in healthy human subjects are mediated by catecholaminergic systems. One source of individual variation is the COMT gene, which contains a common functional polymorphism (Val108/158/Met) that produces a significant change in enzyme activity. The val allele produces the high activity enzyme, which breaks down dopamine more rapidly than the low activity enzyme of the met allele. In normal human subjects, the val allele has been associated with poorer prefrontal cortical function than the met allele due to the presumably reduced dopaminergic activity. We predicted that a COMT inhibitor that crosses the blood brain barrier, tolcapone, would improve working memory in normal controls and in particular those homozygous for the val allele, whereas it would slightly impair performance for those homozygous for the met allele. Interestingly, this drug has not hitherto been studied in healthy individuals as a cognitive enhancing agent. In a double blind, placebo-controlled crossover study, 42 normal controls (14 val/val, 21 val/met and 7 met/met) were given 200mg of tolcapone three times a day for seven days during the tolcapone arm and a placebo three times a day for seven days during the placebo arm. Each participant was given vitamin B2 as a masking agent to hide urine discoloration produced by the tolcapone. Each participant was given a neuropsychological battery of tests consisting of prefrontally mediated measures of working memory, executive function, and attention. Results generally supported our hypothesis. Significant (p<.05) and near significant (p<.10) drug effects (reaction time in two working memory tasks, Trails B and the N-Back) and drug by genotype effects (in an episodic memory paradigm as well the attention set shifting stage of the CANTAB) were found. In these drug by genotype interactions, individuals homozygous for the val allele generally improved in performance, whereas those homozygous for the met allele generally worsened. Several other tests thought to engage prefrontal circuitry did not demonstrate these effects: the Wisconsin Card Sorting Task, the letter-number span, and verbal fluency. These results indicate that the COMT val/met polymorphism may predictive of normal human cognitive response to COMT inhibitors. Tolcapone in particular may prove to be a valuable tool for improving prefrontal function in val/val individuals.

157. Duloxetine in the Treatment of Fibromyalgia in Women Results from Two Clinical Trials

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Sponsor: David Wong

Objective: To assess the efficacy of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine, on the reduction of pain severity in female subjects with primary fibromyalgia, with or without current major depressive disorder MDD. The results of two studies of duloxetine in female subjects with fibromyalgia are presented. **Method:** All subjects met American College of Rheumatology criteria for primary fibromyalgia and both studies were 12 week randomized, double blind, placebo controlled trials that compared duloxetine with placebo for efficacy and safety in treating subjects with fibromyalgia. Study 1 compared duloxetine 60 mg twice daily DLX60BID N92 with placebo PBO N92 and Study 2 compared duloxetine 60 mg once daily DLX60QD N118 and DLX 60 BID N116 with PBO N120. Fibromyalgia Impact Questionnaire FIQ and Brief Pain Inventory BPI were assessed in both studies with the FIQ total and pain scores indicated as co-primary endpoints in Study 1 and the BPI average pain severity score indicated as the primary endpoint in Study 2. Other secondary outcome measures for both studies included mean tender point pain threshold, tender point number, FIQ fatigue, rest, and stiffness scores, Clinical Global Impression of Severity CGI, Patient Global Impression of Improvement PGI, and other BPI severity and interference scores. Mood improvement was evaluated using the Beck Depression and Anxiety Inventories Study 1 and the 17 item Hamilton Rating Scale for Depression Study 2. Health outcome measures were also assessed. Treatment group differences in change from baseline to endpoint were evaluated using an ANCOVA model. **Results:** In Study 1, duloxetine treated subjects improved significantly more than placebo treated subjects on the FIQ total score p 0.029, and on the FIQ pain score p 0.035. Duloxetine-treated subjects demonstrated significantly greater improvement on most efficacy measures compared with placebo treated subjects. In Study 2, duloxetine treated subjects improved significantly compared with placebo treated subjects, on the BPI 24 hour average pain score p<0.001, each dose vs. PBO DLX60QD vs. PBO: difference -1.23 95% CI 1.82, 0.64 DLX 60 BID vs. PBO difference -1.24 95% CI 1.83, 0.65. In study 2, significant improvement was observed with duloxetine compared with placebo on the FIQ total and pain score p<.001. In both studies, DLX60BID showed superiority over placebo in improvement in mean tender point threshold p<0.01 and reduction in number of tender points p<0.05. In both studies, duloxetine doses significantly improved the CGI p<0.05 and PGI p<0.05 scores, and several BPI pain severity and interference scores compared with placebo, with no significant differences between the duloxetine doses.

Duloxetine treatment groups were statistically superior to placebo on most health outcome measures including three out of ten variables obtained from the Medical Outcomes Study Short Form 36 SF36. In both studies, duloxetine treatment improved fibromyalgia symptoms and pain severity regardless of baseline MDD status. The treatment effect on significant pain reduction was independent of the effect on mood or anxiety symptoms. Significantly more duloxetine treated subjects reported treatment emergent adverse events Study 1 PBO 74.8%, DLX 90.4% Study 2 PBO 79.2%, DLX60QD 92.4%, DLX60BID 90.5%. The rates of serious adverse events were similar between duloxetine and placebo treated subjects in both studies. **Conclusion:** Duloxetine is an efficacious and safe treatment for fibromyalgia symptoms in female subjects with or without MDD.

158. Algorithmically Designed Allosteric Peptides Ameliorate Behavioral Defects in Animal Model of ADHD

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Sponsor: Past Travel Awardee, BMS, 2001

The behavioral effects of active (in vitro and in vivo; centrally and parenterally), de novo D2 dopamine receptor targeted, D-amino acid peptides were systematically evaluated. These peptides were designed using patented methods. Pilot data suggests that "hydrophobic eigenmode matched" D2 dopamine receptor targeted, D-amino acid, retro-inverso (reversed amino acid order) peptides may "repair" many of the aberrant behavioral characteristics in the rat model of ADHD, the spontaneously hypertensive rat (SHR). Peptide effects include: (1) Reversing the SHR's deficiency in sensory motor gating (prepulse inhibition, PPI); (2) Reducing the exaggerated nonselective attention (rearing) behavior of the SHRs; (3) Reducing the exaggerated "open field" (time in center) exploratory behavior of the SHRs; and (4) Reducing the exaggerated total motoric behavior (total timed distance moved) of the SHRs. Animals of the SHR's progenitor species, the Wistar-Kyoto (WKY) normotensive rats, served as controls. WKY rats do not demonstrate these ADHD-like defects. The peptides expressed as all D-amino acid retro-inverso congeners, resist proteolytic digestion and have been shown to act for hours when given parenterally. In addition to systematic dose-response, behavioral screening of 5 additional peptides that have already demonstrated significant effects on the D2 dopamine system, an additional 15mer peptides from the existing template, as constrained and guided by the results of the behavioral testing of the existing peptides were designed. This work offers an alternative mechanistic approach to the common psychopharmacological stimulants used in ADHD. In vitro work suggests that these behaviorally active algorithmically designed peptides work by a positive modulatory (allosteric) action on the D2 receptor, allowing the endogenous levels of dopamine to act more efficiently. The efficacy of the oral administration of these algorithmic peptides in the animal model will be examined. (This work was supported by MH-58026)

159. A Bi-directional Pharmacokinetic Interaction Study of Lamotrigine and The Combined Oral Contraceptive Pill in Healthy Subjects

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Sponsor: Joseph DeVeaugh-Geiss

Introduction: This study was designed to investigate the effects of Microgynon 30 [combined oral contraceptive (COC) 30 mcg ethinylestradiol+150 mcg levonorgestrel] on the pharmacokinetics (PK) of lamotrigine (LTG) and the effects of lamotrigine on the PK of the COC. **Methods:** This was an open-label study of 22 healthy young females. In accordance with the standard prescribing instructions, subjects took the COC for 21 days, followed by a 7 day pill-free interval. On Day 21, PK profiling for the COC components was conducted. Subjects restarted COC on Day 29 and LTG titration was begun (starting dose 25mg/day, titrated to a maximum of 300mg/day, according to standard prescribing instructions). On Day 105, when subjects had received 300mg/day of LTG for 35 days and were on Day 21 of the COC cycle, PK profiling for the COC components and LTG was performed. The COC was discontinued on Day 105 and LTG was continued for an additional 3 weeks. On Day 126, PK profiling for LTG was performed. Additional single blood samples to determine serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and sex hormone binding globulin (SHBG) were taken on Days 5-7 and 89-91, and to determine serum progesterone on Days 20-22 and Days 104-106. **Results:** Sixteen patients completed the study and provided evaluable PK parameters. The COC had a clinically relevant effect on the PK of LTG (on average, the AUC(0-24) decreased 52% and the Cmax decreased by 39% in the presence of the COC). LTG had a minimal effect on the PK of the ethinylestradiol component of the COC (on average, the AUC(0-24) decreased 7% and the Cmax increased by 2% in the presence of the lamotrigine), but had a modest effect on the levonorgestrel component of the COC (on average, the AUC(0-24) decreased 19% and the Cmax decreased by 12% in the presence of the lamotrigine). Furthermore, changes in serum FSH, LH, and estradiol were observed on Days 89-91 compared to Days 5-7. A slight reduction in serum progesterone levels was observed on Days 104-106 compared to Days 20-22. In general, LTG was well-tolerated in healthy young females when co-administered with COC at doses of up to 300mg/day. **Conclusions:** The COC has a clinically relevant effect on the pharmacokinetics of lamotrigine; on average, systemic exposure to lamotrigine in the presence of the COC was found to be approximately 50% of the exposure in the absence of the COC.

160. An Analysis of Baseline Functional Disability in a Cohort of Employed Adult Patients with Attention-Deficit/Hyperactivity Disorder

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Sponsor: Gary Tollefson

Objective. Functional impairment in the workplace is an important yet understudied component of Attention-Deficit/Hyperactivity Disorder (ADHD) in adulthood. Baseline data is presented on work productivity in a sample of employed adults with ADHD entering a long-term pharmacotherapy study. These data are discussed in the context of work productivity seen in a community sample, as well as a depressed sample. **Methods.** The present sample consisted of 264 adult patients (ages 18 to 49) employed for pay at least 20 hours per week and meeting DSM-IV-TR criteria for both a current diagnosis of adult ADHD and a historical diagnosis of childhood ADHD as assessed by the Conners Adult ADHD Diagnostic Interview for DSM-IV, with a CGI-Severity-ADHD score ≥4. Assessment measures included but were not limited to the Endicott Work Productivity Scale (EWPS)[1], Global Assessment of Functioning (GAF), the SF-36, and the investigator-rated version of the Conners Adult ADHD Rating Scales (CAARS). **Results.** This cohort of working ADHD adult patients stated that their expected weekly working hours were 40.5 (SD 10.5, n=261), and their actual weekly working hours were 38.5 (SD 13.8, n=263). Mean EWPS total score was 49.7

(SD 16.6, n=262), indicating work impairment greater than that seen in not only a community sample (mean=22.3, SD 12.9, n=66)[1], but also a sample of patients with Major Depressive Disorder (mean=39.4, SD=17.6, n=35).[1] Items endorsed as occurring most frequently included: difficulty concentrating on the task at hand, becoming bored, difficulty with organization and prioritization, daydreaming/worrying/staring into space, and wasting time looking for misplaced items. Patients were moderately to severely symptomatic (mean CGI-S= 4.6, SD 0.7; mean CAARS-Investigator rated= 35.2, SD 7.7), with moderate to severe functional impairment (mean GAF= 56.5, SD 6.4). The sample was similar to that seen in 2 large clinical trials in terms of ADHD symptomatology.[2] **Conclusion.** Results indicate a high degree of work impairment in a cohort of ADHD adults who are working nearly full time, which is as severe as, if not more severe, than that seen in a sample of patients with major depression.[1] These data add validity to the occupational impairments associated with ADHD in adults[3] and suggest the need for further attention to this area of study. The EWPS appears to be a measure that is sensitive enough to assess functional work impairment in a sample of adult ADHD patients. 1 Endicott J, Nee J. Endicott Work Productivity Scale (EWPS): a new measure to assess treatment effects. Psychopharm Bull 1997;33:13-16. 2 Michelson D, Adler L, Spencer T, Reimherr FW, West SA, Allen AJ, Kelsey D, Wernicke J, Dietrich A, Milton D (2003): Atomoxetine in Adults with ADHD: Two Randomized, Placebo-Controlled Studies. Biol Psychiatry 53(2): 112-20. 3 Faraone SV, Biederman J, Spencer T et al. Attention deficit-hyperactivity disorder in adults: an overview. Biol Psychiatry 2000; 48:9-20.

161. Electrophysiological Properties Of Genetically-defined Striatal Neurons

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There has been considerable effort to differentiate the function of subpopulations of striatal medium-sized spiny neurons (MSSNs) that contain the different subtypes of dopamine (DA) receptors. In addition, subpopulations of MSSNs differ in their projection targets, in peptide content, and in the expression of several receptor subtypes. Recently, mice that express enhanced green fluorescent protein (EGFP) reporter genes coupled to specific DA and acetylcholine receptor subtypes in MSSNs have been generated with the aid of modified bacterial artificial chromosomes (Gong et al., Nature 425: 917-925, 2003). We have compared some of the electrophysiological properties of EGFP-positive MSSNs that express DA D1 or muscarinic M4 (direct pathway) and DA D2 receptor subtypes (indirect pathway). EGFP-positive cells were visualized in slices or after acute enzymatic dissociation. Whole-cell patch clamp recordings in slices revealed that the basic membrane properties were similar in D1/M4- and D2-positive cells. All MSSNs recorded in current clamp mode displayed hyperpolarized resting membrane potentials. However, the threshold for firing action potentials was more depolarized in D1/M4- than in D2-positive neurons. Spontaneous synaptic activity was similar in D1/M4- and D2-positive cells, but large-amplitude inward currents were only observed in D2-positive cells. After blockade of GABAA receptors, only D2-positive cells displayed large, long-lasting spontaneous membrane depolarizations. In dissociated MSSNs inward currents evoked by N-methyl-D-aspartate (NMDA) were similar in both populations. NMDA currents were enhanced by a D1 receptor agonist. The percent increase was greater in D1/M4- than in D2-positive MSSNs. In contrast, a D2 receptor agonist, reduced the amplitude of NMDA currents in all cells. These data demonstrate differences in electrophysiological properties of subpopulations of MSSNs defined by selective expression of D1/M4 and D2 receptors and could explain the selective vulnerability of subgroups of MSSNs in specific neurodegenerative diseases. Supported by NIH Grant NS33538 and GENSAT.

162. Prevalence of Metabolic Disturbances in Patients Using Atypical Antipsychotic Medications: Analysis of Cross-sectional Data at a Los Angeles County Mental Health Clinic

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Sponsor: Past Travel Awardee PMRTP, 2002

OBJECTIVE: Accumulating evidence over the past few years has shown that metabolic disturbances associated with the use of atypical antipsychotic medications are common. Many studies involved predominantly male Caucasian patients; therefore, little is actually known about the prevalence and the management of metabolic disturbances in ethnic minorities who are on atypical antipsychotic medications. This study aims to determine the prevalence of diabetes and dyslipidemia in a multi-ethnic group of patients exposed to different types of atypical antipsychotic medications at a Los Angeles County Mental Health Clinic. **RESEARCH DESIGN AND METHODS:** A target number of 150 patients, male or female are recruited from an outpatient clinic who have been on one or more atypical antipsychotic medication for at least one month. Patients who are not already on glucose control medications are recruited to undergo the 2-hour oral glucose tolerance test. Information on demographics and history of medications are obtained from patients, as well as information on dietary habits and activity level. Physical measurements of weight, height, hip, waist circumferences, and laborary data on lipids, fasting glucose, and hemoglobin A1C are also collected. **RESULTS:** Cross-sectional analysis of collected data will help to determine the prevalence of metabolic disturbances and to determine the extent to which these patients are treated and well-controlled for these metabolic disturbances. **CONCLUSIONS:** The demograhpic, psychosocial, physical, and pharmacologic attributes that may play a role in the development of metabolic disturbances will be examined for the purpose of generating future studies to help better understand and manage the problem of metabolic disturbances with the use of atypical antipsychotic medications.

163. Analysis of Adult Neurogenesis in Serotonin Transporter Knockout Mice

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Sponsor: Travel Awardee, Memorial, 2004

Background: In addition to its role as a neurotransmitter, serotonin (5HT) is an important regulator of morphogenetic activities during early brain development as well as during adult neurogenesis and plasticity. 5HT system homeostasis is particularly critical to the genesis, differentiation, and maturation of neuronal cells and networks in brain regions controlling sensory inputs, stimulus processing, and motor output. With respect to cortical development, 5HT is an important differentiation signal and the period for 5HT action corresponds to the period when incoming axons begin to establish synaptic interactions with target neurons and to elaborate a profuse branching pattern. Targeted inactivation of components of serotonergic signaling such as the 5HT transporter generate animal models that facilitate the dissection of the roles of 5HT in the formation and plasticity of neocortical and subcortical structures. **Methods:** We therefore investigated hippocampal neurogenesis in 5HT transporter

deficient mice by BrdU injection and immunohistochemistry, as well as establishing primary cultures from adult mouse hippocampi. **Results:** Proliferation in 5HT transporter knockout mice was not significantly different from wildtype control mice. Similarly, survival of newly generated cells was not changed in 5HT transporter knockout mice compared to wildtype control mice. **Conclusions:** 5HT transporter knockout mice show no change in proliferation or survival of the newly generated cells; moreover the ratio of BrdU-positive neuronal versus glial cells is not altered. Ablation of the 5HT transporter does not appear to influence adult hippocampal neurogenesis These findings in 5HT transporter deficient mice have important implications for the mode of action of antidepressant drugs.

164. Vulnerability to Depression Secondary to Interferon-alpha: Genetic and Personality Factors

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A major depressive episode (MDE) can be precipitated by exposure to the cytokine interferon-alpha (IFN-) in about 25-33% of subjects. Predicting vulnerability to this effect may help target prophylactic antidepressant treatment. This common form of induced depression also offers the opportunity for prospectively examining the mechanisms underlying vulnerability to major depression in humans. Towards this end, we report initial findings from 15 subjects with hepatitis C treated with IFN-. All subjects were euthymic and in good general health at baseline. Following baseline personality, psychosocial, and psychiatric evaluations, subjects were assessed monthly, for four months after IFN- treatment was initiated, for the development of depression symptoms. 4/15 quickly developed a SCID-IV-diagnosed MDE. Using the maximal change in Beck Depression Inventory-II (BDI-II) from baseline as the primary outcome, pre-treatment measures on the Psychosocial Adjustment to Illness Scale and Openness on the NEO-FFI predicted maximal increase in BDI-II scores (combined r2=0.61, p<0.01). Initial data also suggested that the maximal increase in BDI-II could be predicted by polymorphisms in the serotonin transporter promoter (6.7+/-2.8 for the L/L genotype and 13.3+/-4.9 for the S allele) and tryptophan hydroxylase (6.3+/-3.8 for the A/A genotype and 13.4+/-4.8 for the G allele). Changes in peripheral C-reactive protein also correlated with the development of depression symptoms (r2=0.65, p<0.01). Moreover, there was a trend towards a correlation between IFN- concentration and depression symptoms. These preliminary results indicate that IFN- can induce depression in euthymic individuals, and that social, personality, and genetic factors may play a role in vulnerability to this effect.

165. Effects of Caloric Restriction on Antipsychotic-Induced Weight Gain

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Background: One of the most relevant side effects of treatment with antipsychotics (APs) is weight gain, mediated through serotonergic, dopaminergic, adrenergic, cholinergic, histaminergic and glutamatergic receptors. Sex hormone, dysregulation, and altered insuline sensitivity are also involved. Management of overweight and obesity due to APs includes pharmacological interventions, dietary suggestions and behavioural strategies. Nevertheless, the use of pharmacologic management of this specific type of obesity is not supported by current evidences, and very few studies have been published regarding prevention and treatment of weight gain with other strategies (namely diet and behavioural modifications). **Objective:** The aim of this study was to evaluate the effectiveness of caloric restriction diet on weight gain in a group of psychiatric patients treated with APs. **Method:** Overweight psychiatric patients treated with APs were enrolled in a 12-week weight reducing diet program, consisting of a reduction of 500 kcal per day (15% of calories from protein, 50-60% of calories from carbohydrates, and 20-25% of calories from fat). Regular counselling, and follow-up of enrolled patients occurred on a monthly basis. Weight and body mass index at baseline and after 3 months were compared, using a Paired Sample Student's T-test. **Results:** Thirty-seven patients were enrolled; 19 (51,4%) were females. Bipolar Disorder was the most frequent diagnosis (70,3%; n=26). Mean age of the sample was 40,3 years (±14,1). Twenty-two patients were treated with atypical APs (59,4%), 9/37 (24,3%) with typical and 6 with an association of typical and atypical APs (16,2%). Nineteen (19/37; 48,6%) patients did not complete the 12-week program. Completers (n=18) showed a significant mean decrease of body weight (from 94,1±18,8 to 91,0±17,6; p=.005) with a mean BMI reduction of 1,1 (from 33,3±6,3 to 32,2±5,7; p=.005). **Conclusions:** These results support the hypothesis that weight reducing diet is an important tool for the management of APs treated overweight patients.