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Poster Session II - Tuesday

1. Effect of Memantine on Behavioral Outcomes in Moderate to Severe Alzheimer's Disease

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Memantine is a low-moderate affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist approved for the treatment of moderate to severe Alzheimer's disease (AD). Excitotoxicity mediated by NMDA receptors is thought to play a role in the pathogenesis of AD. Memantine blocks prolonged pathological activation of NMDA receptors while allowing normal receptor function. This analysis of a 24-week double-blind, placebo-controlled trial conducted in moderate to severe AD patients (N=404) assessed the effect of memantine on behavioral symptoms in moderate to severe AD patients receiving stable donepezil treatment. The trial demonstrated significant benefits of memantine on functional, cognitive, and global measures. Behavioral symptoms were assessed using the Neuropsychiatric Inventory (NPI), administered at baseline, Week 12 and Week 24. The statistical analysis (ANCOVA) was based on the ITT population using an LOCF approach. Baseline characteristics between the placebo and memantine groups were comparable. At Week 24, there was a statistically significant treatment difference (P=.002), with a reduction in behavioral disturbances and psychiatric symptoms in memantine-treated patients and worsening in placebo-treated patients. In addition, several NPI domains demonstrated statistically significant treatment differences in favor of memantine at Week 24. These domains were agitation/aggression (P=.001), irritability/lability (P=.005) and appetite/eating change (P=.045). When patients asymptomatic at baseline were examined, significantly fewer memantine patients exhibited emergence of delusions (P=.011) and agitation/aggression (P=.032) at Week 12 and agitation/aggression (P=.016), irritability/lability (P=.041) and nighttime behavioral disturbances (P=.027) at Week 24 compared to placebo patients. When patients symptomatic at baseline were examined, there was significantly less worsening compared to placebo in symptoms of agitation/aggression (P=.018, Week 12; P=.021, Week 24) and appetite/eating changes (P=.012, Week 12). Effective treatment of these behaviors is important for this patient population with respect to both quality of life and the potential for reducing caregiver burden.

2. TC-1734: A Neuronal Nicotinic Acetylcholine Receptor Partial Agonist that Demonstrated an Excellent Safety/Tolerabililty Profile and Cognitive Enhancement in Early Studies in Humans

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Sponsor: Raymond Bartus

Background: Neuronal nicotinic acetylcholine receptor(NNR) agonists are believed capable of affecting various aspects of cognition, including attention, memory and learning, in both normal and cognitively impaired subjects. Previous NNR agonists have lacked sufficient selectivity for the CNS and their development terminated due to peripheral side effects like nausea/vomiting and cardiovascular (CV) changes. TC-1734 is a selective partial agonsit at the CNS $\alpha 4\beta 2$ NNR that does not activate ganglion or muscle-type nicotinic acetylcholine receptors. It is orally active, has shown long lasting cognitive effects in animal models and neuroprotective effects *in vitro.* **Methods:** Four early placebo-controlled studies in humans have been completed and partial data from a fifth are available (N=124). The completed studies include SRD, MRD, food interaction and a PK in the elderly. Single doses up to 320mg and multiple doses for 10 days up to 200mg, have been explored. An ongoing study in elderly subjects with age associated memory impairment (AAMI) involves three-week dosing up to 150mg. Safety/Tolerability: The drug was well tolerated overall. No changes of clinical significance were detected on biochemistry testing, urine analysis, vital signs, ECG or 24-hour Holter monitoring. Adverse events (AEs) were mild to moderate in intensity. Severe AEs were only seen at MTD - identifed in these studies as 320mg in the young and 150mg in the elderly. Dose limiting AEs included headache, dizziness, lightheadedness, and occasional nausea/vomiting. Since no changes in CV variables accompanied these AEs, we have concluded they were due to the central pharmacology of TC-1734. Central Activity: Clear evidence of CNS penetration was found after single dosing and multiple dosing (10 days). Pharmaco-EEG showed acceleration type changes with power shift from the high theta, low alpha range to high alpha, low beta range. There was good correlation between plasma levels of TC-1734 and pharmaco-EEG changes. Cognitive enhancement: Cognitive effects were evaluated using factors measured by the CDR cognitive test battery. In the MRD study, a difference was seen between drug and placebo at day 10 on the Power of Attention factor. In the elderly PK study, improvement was seen on the Quality of Episodic Memory factor. This effect was most pronounced in the period 36-48 hours (the last time points assessed) following a single 80mg dose. The long duration of action is similar to that seen in animal models and suggests dosing once daily may be appropriate. In elderly AAMI subjects who received 50mg doses, there were robust differences between drug and placebo on the Power of Attention and Continuity of Attention factors. A difference was also seen on the Speed of Memory factor. There were some differences seen on the Quality of Episodic Memory factor, but none on the Quality of Working Memory factor. These 50mg results were statistically significant. Improvements in the 100mg cohort were less prominent, suggesting a possible inverted U-dose response curve. Again this is consistent with animal findings and with results seen with many drugs that enhance cognition. **Conclusions:** TC-1734 was well tolerated in early studies in humans. Unlike other NNR agonists, it did not cause peripheral CV effects or, except at the MTD, nausea/vomiting. At a dose of 50mg, TC-1734 enhanced attention, memory and speed of cognition in a group of elderly subjects with AAMI.

3. Using The Tryptophan Depletion Paradigm to Examine The Relationship Between Estrogen and Serotonin In Modulating Mood and Cognition in Menopausal Women

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Sponsor: Stephanie O'Malley

Background: Changes in neuroendocrine function may predispose menopausal women to psychological disturbances characterized by depressed mood, anxiety, irritability, fatigue, insomnia, forgetfulness and decline in libido. The acute tryptophan (TRP) depletion

paradigm was employed to examine serotonergic contribution to mood and cognitive function in menopausal women who were within four weeks of recovery from an episode of major depression and in healthy menopausal women pre and post treatment with estrogen. **Methods:** Menopausal women with depression that was responsive to treatment with estradiol 75 ug/d (N=4); the selective serotonin reuptake inhibitor (SSRI) fluoxetine 20-40 mg/d (n=4); or estradiol 75 ug/d and fluoxetine 20 mg/d (N=3) and peri and post menopausal healthy controls (N=18) underwent active and sham TRP depletion sessions. Healthy menopausal women underwent the procedures both before and after estradiol 75 ug/d treatment (ET) for 3 months. Mood and cognition were assessed using standard clinician administered tests before and 6 hours after administration of the amino acid mixture. **Results:** Although active TRP depletion resulted in an 89% decline in total and free plasma TRP levels, neither menopausal women who had recently recovered from an episode of major depressive disorder (MDD) or healthy menopausal women pre or post estrogen administration experienced a worsening of their mood during active tryptophan depletion. In contrast, TRP depletion was associated with a worsening of performance on the delay paragraph recall subtest of the Wechsler Memory Scale (WMS) in both groups. In addition, the healthy menopausal women experienced a significant worsening in performance on the delayed paired associates subtask of the WMS during TRP depletion prior to estrogen administration. However, after estrogen administration, healthy controls showed no difference in performance on these measures between sham and active TRP depletion sessions. **Conclusions:** Results from this pilot study indicating that menopausal women who have recently recovered from a major depressive episode do not experience a worsening of mood with acute TRP depletion is in contradistinction to findings of mood worsening in other previously depressed populations undergoing the same procedures. While preliminary, the results are suggestive of a distinct, perhaps less serotonin mediated, pathophysiology for depression during the menopause. Consistent with previous literature, tryptophan depletion was associated with worsening of performance on several tasks of verbal working memory, in particular tasks requiring delayed recall of information. Importantly, estrogen administration appeared to provide protection against the effects of rapid TRP depletion and thus serotonin depletion in healthy controls who were tested before and after ET. While the perimenopausal women in this study appeared to benefit most from estrogen administration, baseline differences in performance may be responsible.

4. African Americans' Decision Making to Participate in Alzheimer's Disease Clinical Trials

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Sponsor: Past Travel Awardee, NIMH, 2003

Background: Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disease that impairs memory and cognitive function. The number of Americans suffering from AD is anticipated to increase from 4 million to 14 million by 2050. Clinical trials committed to address the prevention of AD or the development of effective AD therapeutics are critical to alleviate the devastating consequences of this disease. The prevalence of AD appears to be as high or higher in African Americans than Caucasians. Clinical trials should have a sufficient number of subjects from racially and ethnically diverse groups to allow for a scientifically appropriate evaluation of the effects in the intervention in a particular group. Despite the recognition of the importance of adequate representation of ethnic groups in Alzheimer's research, the under-representation of ethnic minority elders still remains a problem. **Methods**: 5 focus groups (N=30) consisting of four to seven participants each were conducted at the Medical University of South Carolina and community locations. A brief demographic survey was completed at the beginning of the focus groups. A seven-item focus group discussion guide was developed and focus groups were conducted by a trained moderator. All sessions were tape-recorded and transcribed. Nonnumerical Unstructured Data Indexing Search and Theory Building was utilized to code and analyze the transcripts. **Results**: All participants self-identified themselves as African American. Participants were 55 years of age and older. Analysis of transcripts revealed recurring focus groups themes that may influence the decision making process. Participants expressed similar beliefs and thoughts about Alzheimer's disease symptoms. They expressed self-concerns about their own memory often elaborating on their confusion about normal aging versus dementia. They stressed concerns about the length of time from awareness of symptoms to the physician's diagnosis. They appeared to lack the knowledge that there are medications indicated in the treatment of AD. Many participants reported reluctance to participate in clinical trials involving medications. Input of their physicians and family members were deemed important in the decision making process. Additionally, first-hand knowledge about the investigator was also deemed important. Participants reported distrust of the pharmaceutical industry, research, and their own health care providers. **Conclusions**: These focus groups have provided insights on African Americans'beliefs about Alzheimer's disease, research, and the decision making process to participate in Alzheimer's disease clinical trials. Hypotheses may be generated from these focus groups that will allow the development and evaluation of strategies to improve minority recruitment and retention into AD clinical trials.

5. A Multitracer PET Study of Dopaminergic Function and Regional Cerebral Blood Flow in Human Aging

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Sponsor: Karen Berman

Aging is thought to be associated with alterations in cognitive function and changes in dopaminergic function, but the existence and distribution of presynaptic dopaminergic age changes is controversial. Interactions between dopaminergic function and cortical activation have been little studied in vivo. We used PET to measure both cerebral blood flow (rCBF) during working memory (with [15O]-H2O and the N-back task) and presynaptic dopaminergic function (with 6-[18F]-DOPA after Carbidopa pretreatment) in 52 normal subjects aged 22-81 (mean 45 + 17) years, M:F 27:27. rCBF images were analyzed using SPM99. The kinetic rate constant Ki for striatal dopaminergic uptake was calculated voxel-by-voxel (occipital input function) using a linear fit based on the Patlak method. Significant decreasses of Ki with age were observed in pons, anterior midbrain and ventral striatal areas, whereas posterior midbrain, putamen and anterior cingulate showed increases. Prominent changes of rCBF with age were found in the anterior ciongulate, temporal pole, cerebellum, thalamus and brainstem. Three regions showed age-related changes in both rCBF and dopaminergic uptake: pons, midbrain and anterior cingulate. Of these, the cingulate region showed a signficant change of activation during the cognitive task with age. Our data indicate that age-related changes in dopmainergic function and cortical activation may play a role in functional alteration in the anterior cingulate, a region critical for error-monitoring widely implicated in cognitive features of both healthy aging and dementia.

6. Piracetam Stabilizes Mitochondrial Function In Vitro and In Vivo
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Sponsor: Steven H. Ferris

Piracetam's therapeutical efficacy in cognitive impairment is suggested by a recent meta-analysis of clinical studies. (1). The biochemical mechanism is not yet understood. Piracetam modifies neuronal as well as mitochondrial membrane properties in aged brain (2,3). Mitochondrial failure plays an important role in Alzheimer's disease (AD) and brain aging. Thus, we investigated the protective effects of piracetam on mitochondrial dysfunction. As cellular model we used PC 12 cells and dissociated brain cells of young and aged mice treated orally with piracetam under conditions associated with impaired mitochondrial function. Piracetam either given before or shortly after initiating mitochondrial damage by H2O2, serum deprivation, or sodium nitroprusside (SNP) improved mitochondrial membrane potential significantly and dose-dependently, with first effects already seen at rather low concentrations (50 μM). Piracetam also reversed the associated ATP reductions. Piracetam was also able to maintain mitochondrial function after extracellular beta-amyloid treatment. Piracetam also stabilizes mitochondrial membrane potential and ATP levels PC12 cells bearing the APP-Swedish double mutation and in dissociated brain cells of young and aged mice treated with piracetam for 3 weeks. In general, young animals did benefit much less from piracetam treatment. Our study clearly shows stabilization and protection of mitochondrial dysfunction as a specific and very sensitive property of piracetam giving a plausible mechanism for the use of piracetam in brain aging and AD. (1) Waegemans et al. Dement. Geriatr. Cogn. Disord. 13:217-224, 2002. (2) Muller et al. Biochem. Pharmacology 53:135-140, 1997; (3) Muller et al. Pharmacopsychiatry 32 Suppl 1:2-9, 1999;

7. 5-HT$_6$ Receptors Modulate Learning
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Inhibition of 5 HT6 receptors has been previously shown to improve memory consolidation in several types of learning tasks, although the mechanism for this observation has not been identified. We examined this issue using two strategies: viral overexpression of 5 HT6 receptors in rat striatum and systemic treatment with 5 HT6 antagonists. A hemagglutinin (HA) epitope tagged rat 5 HT6 receptor was introduced into a dual expression HSV vector. The HA tagged 5 HT6 receptor was fully functional in vitro, and was detectable by immunocytochemistry or coexpression of GFP. We injected this vector or a GFP-only control vector into rat striatum bilaterally since this is an area of high endogenous 5 HT6 expression. Animals were then tested using a three day autoshaping task. Increased expression of 5 HT6 receptor prevented learning of the autoshaping task as compared to control or sham operated animals. We also tested whether a novel 5 HT6 antagonist, PMDT, can reverse memory or mood dysfunction caused by scopolamine, a muscarinic antagonist, using a two-object discrimination test in young (2 mo.) and mature (6 mo.) rats. On Day 1, rats were habituated to an empty open field for 15 minutes and on Day 2 the rats explored a small object (bottle) in the center of the field. After exploration on Day 2, the rats were given either saline or scopolamine (0.2 mg/kg i.p.) and 30 minutes later either saline or PMDT (10 mg/kg i.p.). On Day 3 a new object (cylinder) was placed in the field near the familiar object from Day 2 and the amount of exploration (touches or climbs) of both objects was recorded. Young rats showed no significant effects of either the low dose of scopolamine or PMDT on recognition of the novel object. Mature rats' recognition of the novel object was improved after PMDT while scopolamine decreased novel object recognition and this effect of scopolamine was reversed by the addition of PMDT. We are currently examining the effects of PMDT on autoshaping and will also present data on the effect of 5 HT6 receptor overexpression in rat striatum in other learning paradigms. This is the first report of behavioral effects of increased 5 HT6 activation, and together with the antagonist data suggest that 5 HT6 receptors influence several striatum-dependent learning tasks that involve memory of learned material between testing sessions. Together, these data suggest that 5 HT6 receptors may be an important target for cognitive problems associated dementia and schizophrenia.

8. A Proteomic Approach to Identify Biomarkers of Pharmacotherapy in Patients with Alzheimers Disease
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Sponsor: Lon Schneider

Alzheimers disease (AD) etiopathogenesis is multi-factorial. Neuropsychiatric disturbances such as agitation are frequent features of the illness. Based on clinical evidence that valproic acid (VPA) may have symptomatic efficacy for agitation in dementia, and on preclinical evidence suggesting it may also be neuroprotective, we sought to identify cellular targets of VPA action in leukocytes from AD patients, comparing gene products at baseline and after 4 weeks of treatment. Leukocyte samples were obtained from subjects with probable AD receiving 700-1000 mg/day of divalproex sodium who were either enrolled in a study of divalproex sodium tolerability (n=12) or were being treated symptomatically for agitation in a nursing home setting (n=3). Total cellular proteins were subjected to 2-dimensional gel electrophoresis. Comparison of protein abundance at baseline and week 4 revealed significant changes for 10 proteins as a function of treatment. Following analysis by mass spectroscopy, 9 of the 10 spots were identified as novel targets of VPA treatment. These can be classified into pathways significant for anti-apoptotic, anti-oxidant and other potentially neuroprotective effects. Dose-dependent responsiveness of these proteins to VPA was confirmed in cultured non-AD lymphocytes by Western blotting for at least 4 of the 9 novel protein targets. Further confirmation of changes in RNA expression for these VPA targets following in vitro treatment is being carried out. These studies demonstrate the effectiveness of a combined proteomic approach in peripherally accessible tissues from patients undergoing pharmacotherapy, using validation by in vitro techniques for identifying novel cellular targets of drug responsiveness. Supported by an investigator-initiated grant from Abbott Laboratories.

9. Mild Cognitive Impairment assessed by [15O]water Positron Emission Tomography: Differences in Cerebral Blood Flow among Cognitive Subtypes
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Objective: This study measured cerebral blood flow using [15O]water PET imaging in persons with mild cognitive impairment (MCI) participating in an intervention study. In addition to PET imaging, subjects received neuropsychological testing at a screening visit as well as baseline and follow-up visits. **Methods:** [15O]water PET imaging was obtained during a baseline verbal production (counting) task and a verbal memory task. When the cognitive data were analyzed to characterize the sample, it was noted that a subset of participants displayed benefits from repeated exposure to the test materials (i.e., practice effects) between the screening and baseline visits, whereas another subset did not demonstrate benefits. Although both

groups were cognitively equivalent at the screening visit, one group i.e., the Test-Retest Improvement (TRI) group, n = 7, improved their performance on the BVMT-R (Total) at the 2-week baseline visit. The other group displayed minimal or no test-retest improvement (non-TRI group), n = 8. This trend continued at the 3 and 6-month follow-up sessions, with the TRI group continuing to outperform the non-TRI group. Differences in cerebral blood flow at intake were compared between these groups, specifically the relative increase in cerebral blood flow during the verbal recall task relative to the control task of verbal production. **Results:** Preliminary findings suggest a possible association between neuropsychological performance and change in global cerebral blood flow (gCBF) during the verbal memory recall task. For the TRI group, the mean change in gCBF during the memory task was 3.7 mL/min/100g and for the non-TRI group the mean change was -4.02 mL/min/100g. A Mann-Whitney U-test suggests a difference between the groups in gCBF change during the verbal memory task: U=45, exact two-sided p=0.054. **Discussion:** These preliminary findings suggest that there may be subtypes within the MCI population with unique prognostic features. These subtypes display differences in psychometric test performance and in global cerebral blood flow. Further characterization of these groups may help explain the heterogeneity in outcome across this diagnostic category, as well as the mechanisms behind this heterogeneity.

10. Quetiapine for the Treatment of Agitation in Elderly Institutionalized Patients with Dementia: A Randomized, Double-Blind Trial

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Introduction: Behavioral and psychological symptoms of dementia (BPSD), including agitation, are a major concern for patients in long-term care facilities and their caregivers. Currently available treatments for BPSD have variable efficacy and safety. **Objective:** To evaluate the efficacy, tolerability, and safety of quetiapine compared with placebo in the treatment of agitation associated with dementia in elderly patients residing in long-term care facilities. **Methods:** This was a 10-week, multicenter, double-blind, placebo-controlled, randomized, fixed-dose trial. Key inclusion criteria included a history of dementia and clinical symptoms of agitation requiring treatment with antipsychotic medication. Eligible patients were randomized (3:3:2) to quetiapine 100 mg/day, quetiapine 200 mg/day, or placebo. Quetiapine was initiated at 25 mg/day and increased by 25 mg/day to target doses of either 100 mg/day by Day 4 or 200 mg/day by Day 8. The primary efficacy measure was the change in the PANSS-Excitement Component (PANSS-EC) score from baseline to Week 10. Secondary efficacy measures included the CGI-C scores and the response rate (percentage of patients with either ≥40% reduction in the PANSS-EC score or a CGI-C rating of 'much improved' or 'very much improved'). Efficacy data were analyzed in the per protocol (PP) population. The key safety and tolerability measures included the incidence of treatment-emergent adverse events (AEs), such as somnolence, postural hypotension, falls, and extrapyramidal symptoms (EPS), and cerebrovascular adverse events (CVAEs). **Results:** A total of 333 patients were randomized to treatment with quetiapine 200 mg/day (n=117), quetiapine 100 mg/day (n=124), or placebo (n=92). The PP population included 294 patients (97, 109, and 86 for 200 mg/day, 100 mg/day, and placebo, respectively). The baseline characteristics of patients were comparable among treatment groups. The completion rates were similar in all groups: 63%, 65%, and 65% for quetiapine 200 mg/day, 100 mg/day, and placebo, respectively. Treatment with quetiapine 200 mg/day resulted in significantly greater reductions in PANSS-EC scores compared with placebo ($p<0.05$); the significant improvement was observed starting at Week 2 and was sustained at Weeks 4, 8, and 10 ($p<0.05$). Quetiapine 200 mg/day significantly improved the CGI-C scores compared with placebo and the response rate was significantly higher ($p<0.05$). In the Alzheimer's disease subgroup, the response rate was significantly greater in the 200 mg/day group compared with placebo. Improvements in PANSS-EC and CGI-C scores were numerically, but not statistically, superior with quetiapine 100 mg/day compared with placebo. The incidences of AEs (85%, 80%, and 80%), serious AEs (7%, 11%, and 10%), and AEs leading to withdrawal (12%, 7%, and 8%) were similar for quetiapine 200 mg/day, 100 mg/day, and placebo, respectively. No CVAEs were reported in the quetiapine groups; one patient in the placebo group had a transient ischemic attack. Although the incidence of somnolence was higher in the quetiapine groups compared with placebo, it was not dose-related and was associated with a low rate of withdrawal (<2%). The incidence of postural hypotension, falls, hip fractures, and EPS was similar among the treatment groups. **Conclusion:** Quetiapine 200 mg/day reduced agitation and improved the clinical global rating in patients with dementia. Treatment with quetiapine was generally well tolerated, and its use was not associated with CVAEs in this study. The dose can be titrated to 200 mg/day by Day 8 with good tolerability.

11. Neuroactive Steroids in Alzheimer's Disease: Investigations in Prefrontal Cortex

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Sponsor: Daniel Blazer

Background: Alzheimer's disease (AD) is the most common dementia in older adults, and it is expected to undergo a dramatic increase in prevalence in future decades as the population ages. A deficit in cholinergic function is believed to be an important component in the pathogenesis of AD, and several current treatments that increase synaptic concentrations of acetylcholine (cholinesterase inhibitors) appear to slow disease progression. The neuroactive steroids pregnenolone sulfate and dehydroepiandrosterone sulfate (DHEAS) appear to increase acetylcholine release in rodent models (Darnaudery et al 1998, 2002; Rhodes et al 1996) and may play a role in the regulation of this neurotransmitter system. The neuroactive steroids dehydroepiandrosterone (DHEA), pregnenolone, and their respective sulfates (DHEAS and pregnenolone sulfate) enhance learning and cognitive performance in rodent models (Vallee et al 2001; Akwa et al 2001; Flood et al 1992). It has also been hypothesized that an age-related dysregulation in myelination may contribute to the pathophysiology of AD (Bartzokis 2003; Benes 2004). The neuroactive steroid allopregnanolone increases myelin basic protein expression (Ghoumari 2003) and may enhance myelination. Since this literature is consistent with the possibility that neuroactive steroids may be relevant to the pathophysiology of Alzheimer's disease, we determined DHEA, pregnenolone, and allopregnanolone levels in prefrontal cortex tissue from male subjects with Alzheimer's disease and cognitively intact male control subjects. **Methods:** Prefrontal cortex (PFC) tissue from the Joseph and Kathleen Bryan Alzheimer's Disease Research Center at Duke University was analyzed for neuroactive steroids by a highly sensitive and specific gas chromatography/mass spectrometry (GC/MS) method, preceded by high performance liquid chromatography purification. Allopregnanolone, DHEA, and pregnenolone levels were determined in PFC from 15 male subjects with Alzheimer's disease and 14 cognitively intact male control subjects matched for age. Postmortem interval (PMI) was less than 20 hours for all specimens (median PMI=3.2 hours for the Alzheimer's group, median PMI=7.5 hours for the cognitively intact control group). Median age was 83 for both groups. Statistical analyses were performed by Mann-Whitney U test. **Results:** Allopregnanolone levels were significantly lower in PFC specimens from male subjects

with Alzheimer's disease (median=2.50 ng/g) compared to cognitively intact male control subjects (median=5.59 ng/g), Mann-Whitney p=0.02. In contrast, DHEA levels were significantly higher in PFC specimens from subjects with Alzheimer's disease (median=2.61 ng/g) compared to control subjects (median=1.12 ng/g), Mann-Whitney p=0.01. Neuroactive steroid levels did not vary by PMI. Pregnenolone levels tended to be higher (but not significantly) in Alzheimer's subjects compared to cognitively intact control subjects (Mann-Whitney p=0.07). **Conclusions:** Allopregnanolone levels are significantly lower and DHEA levels are significantly higher in PFC specimens from male subjects with Alzheimer's disease compared to cognitively intact control subjects. Alterations in these neuroactive steroid levels may be relevant to the pathophysiology of Alzheimer's disease. Allopregnanolone effects on myelination, and the effects of DHEA, pregnenolone, and their sulfates on memory, learning, and acetylcholine regulation merit further investigation.

12. Efficacy of Memantine for Cognitive Deficits of Mild to Severe Alzheimer's Disease

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Sponsor: Pierre Tariot

Memantine, a low-moderate affinity, uncompetitive NMDA receptor antagonist approved in the U.S. for moderate to severe Alzheimer's disease (AD), is thought to allow normal physiological activation of the NMDA receptor while blocking prolonged pathological overstimulation, one factor implicated in the pathology of AD. This report provides additional analyses of the efficacy of memantine for cognitive deficits of mild to severe AD. A 24-week, double-blind, placebo-controlled trial was conducted in patients with mild to moderate AD (N=403) randomized to memantine or placebo. Cognition was assessed with the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog). Another 24-week, double-blind, placebo-controlled trial was conducted in moderate to severe AD patients treated with ongoing donepezil therapy (N=404) and randomized to memantine or placebo. Cognitive abilities were assessed using the Severe Impairment Battery (SIB). ANCOVA tests were performed on total score, items and subscales using an LOCF approach. In both trials, memantine-treated patients showed significant cognitive improvement compared to placebo-treated patients. For mild to moderate AD, the 11 ADAS-cog items that revealed superior effects were commands (P=.02), orientation (P=.01), comprehension (P=.02) and recall of instructions (P=.001). Previously published factor analytically derived subscales revealed a significant effect of memantine on language (P=.01), memory (P=.01) and no effect of memantine on praxis. For moderate to severe AD, the 9 SIB subscales revealed significant effects of memantine on language (P=.009), memory (P=.042), and praxis (P=.003). When the subscales were aggregated into three areas: memory/attention/orientation/orienting to name (P=.003), language/social interaction (P=.009), and praxis/visuospatial ability/construction (P=.002), all reached statistical significance. Overall, these findings support the efficacy of memantine in moderate to severe AD and suggest the possibility that memantine provides cognitive benefits across disease severity through effects on memory and language.

13. MDMA Induced Acetylcholine Release in the Prefrontal Cortex is Mediated by Serotonergic and Dopaminergic Mechanisms

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The effect of MDMA on acetylcholine (ACh) release was examined in the prefrontal cortex (PFC) using in vivo microdialysis. Systemic administration of MDMA (3-20 mg/kg, ip) dose-dependently enhanced ACh release in this brain region. Since MDMA acutely increases the release of 5-HT and dopamine, the effect of disrupting 5-HT and dopamine neurotransmission on ACh release stimulated by MDMA was examined. Treatment of rats with the tryptophan hydroxylase inhibitor parachlorophenylalanine (150 mg/kg, ip x 3) significantly attenuated MDMA-induced release of ACh; amphetamine-induced ACh release was unaffected by parachlorophenylalanine. Administration of the tyrosine hydroxylase inhibitor alpha-methyl-p-tyrosine (120 mg/kg, ip) also significantly decreased MDMA-induced ACh release. Further experiments examined the role of specific 5-HT and dopamine receptor subtypes on the ACh response to MDMA. Administration of the 5-HT4 antagonist SDZ-205557 (1 mg/kg, ip) or reverse dialysis of the 5-HT4 antagonist RS-23,597 (50 uM) into the PFC significantly attenuated MDMA-induced ACh release by 40-45%. In addition, systemic administration of the D1 receptor antagonist SCH-23,390 (0.5 mg/kg, ip) significantly diminished MDMA-induced ACh release by 30%. These data suggest that MDMA-induced ACh release in the PFC is mediated by both serotonergic and dopaminergic mechanisms. Furthermore, it appears that receptors of the 5-HT4 and D1 subtypes contribute to the cholinergic response to MDMA.

14. Nociception in NET, SERT and NET/SERT Double Knockout Mice

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Roles for the endogenous norepinephrine and serotonin systems in nociception have been reinforced by the findings that drugs that block the norepinephrine transporter (NET) and serotonin transporter (SERT), such as amitriptyline, have analgesic effects and may enhance the analgesic effects of opiates. Furthermore, perhaps as a result of tonic regulation of opioid systems, these descending neurotransmitter systems may play a role in modulating baseline nociceptive sensitivity. Although much emphasis in descending pain modulation has been made on serotonin systems, the relative contribution of each of these systems to these effects has been a matter of some debate. To determine the role of NET and SERT in basal, morphine-induced, and amitriptyline-induced nociception, these effects were examined in all nine genotypes of NET/SERT double knockout mice. These mice have chronically elevated extracellular levels of norepinephrine (NET KO) and serotonin levels (SERT KO). Analgesia was assessed in the tail flick (53oC, 15 sec maximum) and hot plate (55oC, 30 sec maximum) tests. All pharmacological treatments were conducted using within-subjects cumulative dose effect curves after stabilization of baseline analgesia. Deletion of the gene for NET was found to induce a profound baseline hypoalgesia in both the tail flick and hot plate tests. Indeed, this hypoalgesia was so profound that more than one-half of the NET -/- subjects had to be excluded from further analgesic testing because they were at near ceiling levels of basal analgesia (the criteria was 2/3 of the maximum). By contrast, deletion of the gene for SERT produced some hypoalgesia, but this was much smaller, limited to the hot plate test and not observed in both sets of basal analgesia measures. There did not appear to be an interaction between SERT and NET gene knockout, but observation of such an interactive effect may have been impaired by the high baseline analgesia produced by NET alone. Hypoalgesia in NET KO mice was accompanied by increased sensitivity to the antinociceptive effects of morphine in both tests of analgesia and to the analgesic effects of amitriptyline in the hot plate test. However, this data must be considered with the caveat that a large number of subjects were excluded from this testing may have biased the sample of mice remaining. Nonetheless combined NET/SERT KO was not observed to reduce amitriptyline analgesia indicating that another molecular target

plays a major role in its effects. One interpretation might be that NET does play a major role in amitriptyline analgesia, but that this role cannot be observed in NET KO mice because the lack of transporter produces the same result, observed as high basal analgesia; effectively NET is already blocked. However, given the magnitude of amitriptyline analgesia observed even in NET KO mice this seems unlikely. In any case an interaction of norepinephrine systems with endogenous opioid systems appears likely. Interestingly, NET KO mice, under baseline conditions exhibited Straub tail, an effect observed after morphine treatment which may indicate high basal opioid tone in these mice. There was also some evidence for hind limb spasticity but motor testing (Screen Hang Test and Roto-Rod test) failed to find any impairments in NET KO mice. These data clearly indicate a major role for NET and norepinephrine systems, and a much smaller role for SERT and serotonin systems, in basal nociceptive sensitivity, which may involve an important interaction with endogenous opioidergic mechanisms.

15. Zolpidem Does Not Serve as a Reinforcer in Humans Subjected to Simulated Shift Work

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Sponsor: Past Travel Awardee, NIMH, 2001

Individuals who work irregular or rotating shifts often use sedatives to offset shift-change-related mood and performance decrements. Yet, the abuse potential of zolpidem, a non-benzodiazepine hypnotic and most widely prescribed sleep medication in the United States, has not been well characterized. Eleven volunteers completed this 16-day residential study that examined the effects of changing work shifts on zolpidem self-administration. Volunteers participated in two drug sample days that occurred before they moved into the laboratory. On the first sample day, participants received 10 mg zolpidem in the afternoon and on the second sample day, participants received 10 mg zolpidem at night. Day and night shifts alternated three times during the study. When participants worked the day shift, they were given the opportunity to self-administer zolpidem (10 mg) or receive a $1 voucher at 1500 and 2300. When participants worked the night shift, they were given the opportunity to self-administer zolpidem (10 mg) or receive a $1 voucher at 0700 and 1500. Despite dramatic night shift-related mood and performance disruptions, participants overwhelmingly chose the $1 voucher over zolpidem. Zolpidem was selected on fewer than 20% of choice opportunities. These data suggest that zolpidem has minimal abuse liability in individuals who work irregular shifts.

16. The Expression of a Simple Appetitive Response Becomes Dopamine-Independent with Overlearning

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Sponsor: Joseph Tecce

Dopamine is importantly involved in the acquisition and expression of behaviors directed toward both drug and natural rewards. However, recent data suggest that the execution of behavioral responses may become DA-independent with extended habit training. In the present studies, rats learned to associate a brief auditory CS with delivery of a food pellet. Well-trained animals responded to CS presentation with a short latency head-entry into a food compartment. D1 and D2 antagonists (SCH23390 and raclopride, respectively) were administered during early and late stages of training. Results showed that the conditioned head entry response is vulnerable to D1 (but not D2) receptor blockade during early stages of learning, and that the response becomes invulnerable to DA receptor blockade with overtraining. Therefore, while DA receptors critically mediate conditioned response expression, the expression of an overtrained response becomes DA independent.

17. Risk Factors for Cocaine-Induced Paranoia in Cocaine-Dependent Sibling Pairs

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Sponsor: Joel Gelernter

Background: Cocaine-induced paranoia (CIP) is a common clinical manifestation of cocaine dependence, in which both environmental and genetic factors are thought to play a role. However, the relative importance and specific nature of such contributions are poorly understood, in part due to the small samples studied to date. **Methods:** Demographic, diagnostic, and cocaine-use data were obtained from 280 cocaine-dependent sibling pairs (N=560 subjects) using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA). Full sib status was confirmed by PREST analysis. Probands (N=280) with or without CIP were compared; then, factors associated with sibling CIP status were analyzed by logistic regression methods, controlling for differences between probands and siblings on these factors (i.e., using a propensity score) and for possible familial effects (i.e., using CIP status in probands). **Results:** One hundred ninety (68%) of 280 probands experienced paranoia from cocaine. Probands with CIP spent more money for cocaine during periods of heaviest use ($p < 0.001$), had a younger age of first cocaine use ($p < 0.001$), and were more frequently diagnosed with marijuana dependence ($p = 0.03$) than probands without CIP. Probands with CIP did not differ from those without the trait with respect to age, race, sex, or route of cocaine administration. Although 68% of probands with CIP had siblings with CIP, only 58% of probands without CIP had siblings with the trait. The magnitude of this effect was not significant in the logistic regression analysis (odds ratio = 1.57, $p = 0.13$). **Conclusions:** Quantity of cocaine (i.e., dollars spent), age of first cocaine use, and a diagnosis of marijuana dependence predict risk for CIP. Concordance for CIP between siblings did not emerge as a significant factor in our analyses. Larger samples or different study designs may be helpful in demonstrating a role for genetic factors in the risk for CIP.

18. Effects of Treatment with a Cyclic Peptide That Targets PDZ Domain of PSD-95: Peptide Administration to the Ventral Tegmental Area Inhibits Opiate-Induced Motor Sensitization in C57BL/6 Mice

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Sponsor: Robert Swift

The postsynaptic density protein 95 (PSD-95) acts as a molecular scaffold protein that regulates glutamatergic signaling at postsynaptic densities of dendritic spines. PDZ domains in PSD-95 regulate protein-protein interactions including those with glutamate kainate receptors. A cyclic peptide (Tyr-Lys-c[Lys-Thr-Glu(betaAla)-]-Val) was developed that inhibits the clustering of kainate receptor in vitro (Piserchio et al., Chemistry & Biology 11:469, 2004). We hypothesize that repeated treatment with this cyclic PDZ peptide disrupts gluta-

matergic signaling and affects opiate induced sensitization. Treatment with this peptide may interrupt excitatory glutamatergic drive to VTA dopamine neurons that mediate addictive behaviors. We administered this peptide directly into the ventral tegmental area (VTA) of C57/BL6 mice to determine its effects (vs. control peptide) on the development of opiate-induced motor sensitization. Mice received morphine (10 mg/kg s.c.) and bilateral intra-VTA cyclic peptide administration (1 nmol/side) via indwelling cannulae. Cannulae to the VTA were placed in subjects via stereotaxic surgical procedures. Automated activity monitoring was performed for 180 min after drug administration on days 1, 3, 5, 8, 10, and 12. Mice received treatment with the cyclic peptide or a control peptide with each morphine administration. On day 15, all mice were challenged with morphine and received intra-VTA control peptide administration and then motor activity was monitored. Preliminary results indicate the peptide had no acute behavioral effects after a single administration of morphine. Repeated administration of morphine plus intra-VTA control peptide treatment produced a motor sensitization response with a several fold increase in motor activity (distance traveled in cm) on day 15 compared to day 1. However, repeated morphine plus intra-VTA cyclic peptide treatment resulted in no increase in motor activity on day 15 compared to day 1. On day 15 of the sensitization paradigm, mice receiving intra-VTA cyclic peptide showed only 35% of the motor activity of those mice receiving morphine plus the control peptide. Ongoing studies are comparing the effects of cyclic peptide vs. control peptide plus morphine treatments on activation of mesocorticolimbic dopaminergic cells via quantitative immunohistochemistry of immediate-early gene protein product Fos. This data and other studies suggest that this cyclic peptide inhibits the clustering of glutamate receptors in VTA by disrupting glumate receptor/PSD-95 interactions. This cyclic peptide may be an exciting new ligand that inhibits the development of opiate sensitization and possibly other addiction related behaviors. Support Contributed By: Brown University Seed Grant (JM and GBK), a Department of Veterans Affairs Merit Review Grant (GBK), a NIAAA T32 grant (KLM), and NIH grants RR-15578 (JM) and GM-63021 (MRS)

19. Progressive and Persistent Activation of Brain Reward Circuitries by Self-Administered Nicotine: Role of N-METHYL-D-ASPARTATE (NMDA) Receptors

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Sponsor: Travel Awardee, BMS, 2004

Nicotine-induced enhancement of brain reward pathways, measured by lowering of intracranial self-stimulation (ICSS) thresholds, is considered a crucial factor in establishing and maintaining the nicotine-taking habit (e.g., tobacco smoking). In addition, accumulating evidence indicates that the stimulatory effects of nicotine on glutamate transmission may mediate the addictive properties of nicotine. The above hypotheses were first tested by training rats to intravenously self-administer nicotine and also to respond for rewarding ICSS, and then examining the effects of nicotine self-administration (SA) on ICSS thresholds. Rats were permitted 1 h or 12 h daily access to nicotine SA (0.03 mg/kg/infusion, free-base). ICSS thresholds were assessed 1 h before (pre-nicotine) and 15 min after (post-nicotine) each SA session. Stable patterns of intake were rapidly established in 1 h and 12 h rats. These rats consumed approximately 0.38 mg/kg and 1.36 mg/kg nicotine per day, respectively. Reward thresholds remained stable and unaltered in nicotine-naïve control rats for the duration of the experiment. Post-nicotine reward thresholds were lowered, indicating increased brain reward function in 1 h and 12 h rats after nicotine SA. This effect was reversed by the nicotinic acetylcholine receptor antagonist dihydro-b-erythroidine (3 mg/kg). Interestingly, pre-nicotine thresholds became progressively lower as exposure to nicotine increased, indicating that baseline brain reward function gradually increased. Further, this enhancement of baseline reward function endured for at least 8 days after cessation of nicotine SA. To investigate the role of NMDA receptors in regulating the reinforcing properties of nicotine and in regulating nicotine-induced enhancement of brain reward function, we examined the effects of the competitive NMDA receptor antagonist LY235959 on nicotine SA and nicotine-induced lowering of ICSS thresholds. Systemic administration of LY235959 (0.1-5 mg/kg) dose-dependently decreased nicotine (0.03 mg/kg/infusion) SA. Similarly, microinfusion of LY235959 (1-10 ng/side) into the VTA, but not 2 mm above, also decreased nicotine SA. Further, doses of LY235959 (0.5-2.5 mg/kg) that decreased nicotine SA also reversed the lowering of ICSS thresholds associated with nicotine SA. Overall, the present data demonstrate that nicotine SA significantly increased brain reward function in rats, as measured by lowering of ICSS thresholds. These observations are consistent with the hypothesis that nicotine enhancement of brain reward function plays a crucial role in establishing and maintaining the nicotine-taking habit, and suggest that rats may regulate their pattern of nicotine intake to induce maximal increases in brain reward function. Further, nicotine produced an enduring plasticity in brain reward circuitries reflected in a progressive and persistent lowering of baseline ICSS thresholds. This previously unidentified action of nicotine on brain reward function suggests that the positive affective state associated with nicotine consumption persists for a surprisingly long duration. Finally, the present data demonstrate that NMDA receptors, particularly those in the VTA, play a crucial role in regulating nicotine SA and nicotine-enhancement of brain reward function.

20. Effects of Combined Dopamine and Serotonin Transporter Inhibitors on Cocaine Self-administration in Rhesus Monkeys

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The dopamine transporter (DAT) is a critical recognition site for cocaine and likely contributes to its significant abuse liability. Accordingly, the development of compounds that target the DAT represents a logical approach in the pharmacological treatment of cocaine abuse. Recent studies indicate that the behavioral profile of DAT inhibitors may be influenced by dual actions at the serotonin transporter (SERT) as well as at the DAT. The present study characterized the effects of a mixed-action DAT/SERT inhibitor (RTI-112) on self-administration behavior maintained under a second-order schedule of i.v. cocaine delivery in rhesus monkeys. Pretreatment with RTI-112 produced dose-related reductions in cocaine self-administration at low levels of DAT occupancy (<10%) determined by positron emission tomography imaging. In drug-substitution experiments, RTI-112 failed to maintain robust drug self-administration in any subject over a range of doses. Subsequent experiments evaluated the effects of co-administration of a selective DAT inhibitor, RTI-336, and a selective SERT inhibitor, fluoxetine. Pretreatment with RTI-336 alone produced dose-related reductions in cocaine self-administration. The dose of RTI-336 that reduced self-administration to 50% of baseline (ED50) was associated with high levels of DAT occupancy (>80%). In contrast, daily administration of fluoxetine alone for three consecutive weeks had no significant effect on cocaine self-administration. However, co-administration of fluoxetine with the ED50 dose of RTI-336 on week four completely suppressed cocaine self-administration in all subjects. Hence, the effectiveness of RTI-336 to suppress cocaine self-administration was enhanced with fluoxetine co-administration. Similar results were obtained when RTI-336 was co-administered with the selective SERT inhibitor, citalopram. The results indicate that mixed action inhibitors of DAT and SERT warrant consideration as potential pharmacotherapies in the treatment of cocaine abuse.

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21. Discriminative Stimulus Effects of Gamma-Hydroxybutyrate (GHB): Discriminating GHB from Baclofen and Diazepam

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Sponsor: Charles France

Gamma-hydroxybutyrate (GHB) abuse is likely related to its discriminative stimulus (DS) effects, which are thought to involve multiple mechanisms. Some of these mechanisms may be unique to GHB (i.e., those involving specific GHB receptors), whereas others may be in common with other compounds (i.e., those involving GABA-A and GABA-B receptors). The present studies are part of an effort to increase the pharmacological specificity of the DS effects of GHB by training rats to discriminate GHB not only from saline, but also from other drugs that share receptor mechanisms with GHB. Different groups of rats were trained to discriminate GHB from either saline or other drugs: group 1 was trained to discriminate 200 mg/kg GHB from saline and from the GABA-B agonist baclofen (3.2 mg/kg); group 2 was trained to discriminate 200 mg/kg GHB from saline, from baclofen, and from the GABA-A positive modulator diazepam (1 mg/kg). The results obtained in groups 1 and 2 were compared with those obtained previously in rats discriminating 200 mg/kg GHB from saline (group 3). Rats in groups 1 and 2 acquired the GHB versus other discriminations after a median number of 55 and 53 sessions, respectively, which was significantly slower than the acquisition of the GHB versus saline discrimination in group 3 (i.e., 35 sessions to criterion). Baclofen, which produced about 80% GHB-appropriate responding in group 3, produced less than 30 % GHB-appropriate responding in groups 1 and 2. Diazepam, which produced about 60% GHB-appropriate responding in group 3, produced 30 and 5% GHB-appropriate responding in groups 1 and 2, respectively. The GABA-B antagonist CGP35348 attenuated the DS effects of GHB, but was less potent to do so in groups 1 and 2 as compared with group 3. Similar differences were apparent with the GABA-B antagonist CGP52432. The GHB receptor antagonist NCS-382, which attenuated the DS effects of GHB only partially in group 3, appeared to be even less effective to attenuate the DS effects of GHB in groups 1 and 2. These results show that animals can discriminate GHB from baclofen, which is further evidence that the behavioral effects of GHB and baclofen are not identical. Because GHB is a drug of abuse, whereas baclofen is not, it is possible that animals discriminate GHB from baclofen based on the abuse-related effects of GHB. Thus, the discriminations in groups 1 and 2 may provide assays of (abuse-related) DS effects of GHB that are not like baclofen. Such effects may involve GHB receptors and/or differential interactions of GHB and baclofen with GABA-B receptors. Supported by: USPHS Grant DA14986, DA15692

22. Cue-Induced Brain Activity Changes and Treatment Outcome in Cocaine Dependent Patients

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This study used functional magnetic resonance imaging (fMRI) to examine the association between brain activation during exposure to cocaine-related cues and relapse to drug use in cocaine dependent (CD) patients. We imaged 17 CD subjects during a 2-week inpatient stay. The subjects then entered a 10 week outpatient placebo-controlled, double-blind randomized clinical trial where urine toxicologies were assessed three times weekly to calculate the Treatment Effectiveness Score (TES). Worse TES correlated with BOLD activation in the right pre-central, right posterior cingulate cortex (PCC), right superior temporal, and left middle temporal and lingual cortices ($R>0.65$; $P<0.005$). The right PCC activation also distinguished 8 responders (TES above mean and completed treatment) from 9 non-responders. The non-responders had significantly fewer cocaine-free urines (66%) than responders (92%) and remained in treatment an average of only 3.2 weeks. Self-reports of craving during fMRI did not differ between responders and non-responders and did not correlate with TES. Relapse to cocaine abuse was associated with increased activation in the sensory association cortex, the motor cortex, and PCC while viewing images of cocaine-related cues. These results suggest that relapse to cocaine abuse is associated with increased brain activation response to cocaine cues in sensory, motor and cognitive-emotional processing areas. This physiological response was a better predictor of treatment outcome than subjective reports of craving, and may be a useful target for treatment and marker of treatment response.

23. The Effect of Finasteride to Reduce the Stimulating Effects of Ethanol is Moderated by *GABRA2*

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Background: $GABA_A$ receptors mediate several behavioral effects of alcohol. Because alcohol elevates plasma and brain concentrations of GABAergic neuroactive steroids, including 3α-hydroxy-5α-pregnan-20-one (allopregnanolone), it has been hypothesized that these compounds may contribute to specific behavioral actions of ethanol. Recently, COGA investigators have shown a haplotypic association of a gene encoding the GABAA receptor alpha-2 subunit (*GABRA2*) to alcohol dependence. We have replicated this haplotypic association (Covault et al., 2004). In the present study, we sought to examine 1) the effect of finasteride, which reduces allopregnanolone concentrations, on the subjective responses to alcohol and 2) the allelic association of *GABRA2* to the effects of finasteride on the subjective responses to alcohol. **Methods:** This study used a within-subject design to investigate the effects of finasteride or placebo on the subjective response to an intoxicating dose of alcohol. Twenty-seven healthy subjects (15 males) with no personal history of a substance use disorder completed two laboratory sessions separated by one month. Twice before each session (i.e., 24 and 2 hours before), subjects received, in randomized order and under double-blind conditions, a capsule containing finasteride (100 mg) or a matching placebo followed by a beverage containing alcohol (0.8 g/kg for men or 0.7 g/kg for women). Primary outcome measures included the Central Stimulant Subscale of the Alcohol Sensation Scale (SS), the Stimulation Subscale of the Biphasic Alcohol Effects Scale (BAES), and the Drug Effect Questionnaire (DEQ). We used repeated measures ANOVA to examine the main and interactive effects of session (finasteride vs. placebo), genotype (using the most informative of the SNPs in *GABRA2*), and time (baseline and 30 and 40 minutes following alcohol administration) on the above measures. **Results:** We observed significant effects of time, session, genotype, all two-way interactions and the three-way interaction on the SS Central Stimulant Subscale. There was also a significant three-way interaction on the BAES Stimulation Subscale. **Conclusions:** Finasteride reduced the stimulating effects of alcohol in healthy individuals, though its effects varied as a function of *GABRA2* genotype. Together, these findings underscore the potential significance of GABA neurotransmission in determining risk for alcohol dependence and the potential utility of

medications that modify neuroactive steroids for use in the treatment of the disorder. Supported by NIH grants P50-AA03510, M01-RR06192 and K24-AA13736 (to HRK)

24. Enhanced Behavioral and Neurochemical Response to Binge Cocaine in Adolescent Rats.

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Drug use that begins during adolescence is more likely to progress to addiction than use which begins later in life. Age-related differences in the neural substrates mediating the behavioral responses to addictive drugs might contribute to this vulnerability. The purpose of the present study was to investigate this possibility. Twenty eight, 42 and 65 day old male rats were treated with saline or a "binge" cocaine regimen of 3 doses of cocaine (15 mg/kg) delivered ip at hourly intervals. Horizontal and vertical locomotion were quantitated in a photocell apparatus, and individual behaviors were scored by an observer to obtain an integrated stereotypy score. Another cohort of rats (days 28, 42, and 65) was treated identically with cocaine, and plasma and brain collected for determination of cocaine levels 30 minutes after each of the three injections. In a companion experiment, fast scan cyclic voltammetry was used to evaluate dopamine release and clearance in 28, 42 and 65 day old rats at baseline and after 15 mg/kg of cocaine. There was no age-related difference in cocaine-stimulated horizontal locomotion. However, adolescent rats showed two dramatic differences from adults: they received significantly greater stereotypy scores after each dose and they exhibited a novel "burst" type locomotion that was never observed in adults. Dopamine release after cocaine (% baseline) was markedly elevated in 28-day old rats, although electrically-stimulated dopamine release at this age was lower than that of adults. Blood and brain cocaine levels were comparable in adolescents and adults. These findings suggest that decreased baseline dopaminergic function during adolescence could lead to exaggerated responses to drugs that activate dopamine systems and enhanced vulnerability to progression of drug use during adolescence. Supported by DA09079.

25. Nicotine-Induced Up-Regulation and Desensitization of a4b2 Neuronal Nicotinic Receptors Depend on Subunit Ratio

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Sponsor: ACNP Secretariat

Desensitization induced by chronic nicotine exposure may trigger the up-regulation of a4b2 nicotinic acetylcholine receptor (nAChR). We studied the effect of acute and chronic nicotine exposure on the desensitization and up-regulation of different a4b2 subunit ratios expressed in Xenopus oocytes. The presence of a4 subunit in the oocyte plasmatic membrane increased linearly with the amount of a4 mRNA injected. nAChR function and expression were assessed using voltage clamp and whole-mount immunofluorescence assay for detection of a4 subunit. The 2a4:3b2 subunit ratio displayed the highest ACh sensitivity. Nicotine dose-response curves for the 1a4:4b2 and 2a4:3b2 subunit ratios displayed a biphasic behavior at concentrations from 0.1 to 300 μM. A biphasic curve for 4a4:1b2 was obtained at nicotine concentrations higher than 300 μM. The 1a4:4b2 subunit ratio exhibited the lowest ACh- and nicotine-induced macroscopic current, whereas 4a4:1b2 presented the largest currents at all agonist concentrations tested. Desensitization by acute nicotine exposure was more evident as the ratio of b2/a4 subunits increased. All three a4b2 subunit ratios displayed a reduced state of activation after chronic nicotine exposure. Chronic nicotine-induced up-regulation was obvious only for the 2a4:3b2 subunit ratio. Our data suggest that subunit ratio of a4b2 determines the functional state of activation, desensitization, and up-regulation of this neuronal nAChR.

26. Rimonabant, a CB1 Antagonist, Blocks Nicotine Conditioned Place Preferences Without Altering Nicotine Discrimination

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Sponsor: Richard Rothman

Environmental stimuli repeatedly associated with drug taking acquire conditioned properties and, by themselves, may cause reports of craving for drug in abstinent drug users and lead to drug-seeking behavior, resulting in relapse to drug taking. Since environmental stimuli associated with drug self-administration appear to be particularly important in the development and subsequent maintenance of nicotine self-administration behavior, persistent effects of these conditioned stimuli may be a major determinant of relapse to smoking behavior in ex-smokers. One candidate treatment for decreasing the facilitatory effects of conditioned stimuli on drug-seeking behavior is the cannabinoid CB1-receptor antagonist, N-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl) -4-methyl-pyrazole-3-carboxamide (SR141716, Rimonabant). We have evaluated the effects of Rimonabant in animal models for subjective and rewarding effects of nicotine. To assess the rewarding effects of nicotine, we used the conditioned place preference paradigm. A standard two-compartment (mesh vs. bar floors) CPP apparatus was used. Infrared photocells interfaced to a computer tabulated time spent per side and distance traveled during test sessions. Pre-test (one session), conditioning (2 sessions/day over 3 days, nicotine 0.1 mg/kg), and post-test (one session) were conducted over 5 consecutive days. Acute administration of 1 or 3 mg/kg SR141716 blocked expression of nicotine-induced conditioned place preferences ($P<0.05$). SR141716 had no effect on locomotor activity of nicotine conditioned rats. SR141716 (0.3-3 mg/kg) was also studied in rats trained to discriminate nicotine from saline under a fixed-ratio schedule of food delivery. In contrast to nicotine replacement therapy and bupropion, SR141716 did not have nicotine-like discriminative effects and did not alter the dose response curve for nicotine discrimination. These findings support the proposed use of SR141716 for smoking cessation and indicate that it would selectively reduce the influence of environmental stimuli that contribute to persistent smoking behavior, without affecting subjective responses to nicotine.

27. Patterns of Transcriptoin in Human Orbitofrontal Cortex in Drug Abuse: Changes in the CCK-B Receptor

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Sponsor: William J. Freed

We previously reported that individual cases of cocaine abuse are characterized by changes in a consistent subset of transcripts in postmortem dorsolateral prefrontal cortex, which differ in the direction and magnitude of change (*Pharmacogenomics J.* 2003, 3, 27-40). We hypothesized that underlying differences in the abuse mode and/or chronicity as well as time since last drug dose accounted for the direction of change. Currently, we extend these studies to a larger group of cases and to the orbitofrontal cortex (OFC), a region centrally involved in various abuse-associated states such as intoxication, craving, bingeing and withdrawal (*Am J Psychiatry* 2002 159:1642-1652). Thirty-four drug abuse cases (primarily cocaine and THC) and fifty controls were assessed using the NIA Mammalian Gene Collection (MGC) Array and ^{33}P-labeled cDNA reverse transcribed from 8 μg total RNA. A broad panel of toxicological screens and case histories were obtained to characterize factors responsible for individual

differences. Each drug abuse case was compared to the four demographically best-matched controls, and to a pool of all controls utilized. Hierarchical clustering was used to classify the drug abuse cases. Three main case clusters, or subgroups, of drug abuse cases were identified by sets of transcripts which demonstrated similar regulation within the subgroup, but differed in the other subgroups. We examined the expression of a transcript belonging to one of these transcriptional sets, the cholecystokinin (CCK) B receptor (CCKBR), which was strongly down-regulated within one subgroup and up-regulated in more than 75% of the cases in the second subgroup. There was no consistent change in the third subgroup. CCKBR transcripts were substantially altered in 22 of the 34 drug abuse cases (numerical z-ratio changes > 1.5), with changes in expression ranging from a 4-fold decrease to a 4-fold increase. The magnitude and direction of change was validated by real-time PCR (QPCR). In conclusion, we suggest that subgroups of drug abusers can be identified by the presence of similar transcriptional patterns in the postmortem human OFC. Specifically, the present data suggests that altered expression of the CCK-B receptor may be characteristic of specific types and/or phases of drug abuse.

28. Cocaine Craving, Euphoria, and Self-Administration: the Effect of Dopamine Depletion

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Sponsor: Paul Vezina

Cocaine-induced increases in dopamine (DA) neurotransmission are thought to affect various aspects of drug taking behavior. To investigate these associations, we used the acute phenylalanine/tyrosine depletion method (APTD)[1,2] to measure the effect of transient DA depletion on cocaine craving, euphoria, and self-administration. Eight non-dependent, non-treatment seeking cocaine users self-administered three doses of cocaine (0.6, 1.5, 3.0 mg/kg, taken intra-nasally) following ingestion of (i) a nutritionally balanced amino acid mixture, (ii) APTD, and (iii) APTD followed by L-DOPA/carbidopa (2 x 100mg/25mg). APTD decreased both cue- and cocaine-induced drug craving but not euphoria or rate of self-administration. Drug craving was also decreased by L-DOPA, possibly reflecting its ability to transiently decrease DA cell firing. Together, the results suggest that the craving elicited by cocaine and cocaine cues may be closely related to DA neurotransmission. Euphoria and the self-administration of freely available drug, in comparison, might be better accounted for by other mechanisms. 1. Leyton M, Dagher A, Boileau I, Casey K, Baker GB, Diksic M, Gunn R, Young SN, Benkelfat C. Decreasing amphetamine-induced dopamine release by acute phenylalanine/tyrosine depletion: A PET/[11C]raclopride study in healthy men. Neuropsychopharmacology 2004;29:427-432 2. McTavish SF, Raumann B, Cowen PJ, Sharp T. Tyrosine depletion attenuates the behavioural stimulant effects of amphetamine and cocaine in rats. Eur J Pharmacol 2001;424:115-119

29. Cerebral Metabolic Dysfunction and Impaired Vigilance in Recently Abstinent Methamphetamine Abusers

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Chronic methamphetamine (MA) use has been linked to cognitive deficits, and to abnormalities in cerebral glucose metabolism and in the structure of the hippocampus, and limbic and paralimbic cortices. The links between these cognitive deficits and cerebral abnormalities have not been well defined. In the present study, 17 newly abstinent (4-7 days) chronic MA users and 16 comparison subjects performed an auditory vigilance task during the uptake of [F-18]fluorodeoxyglucose (a tracer for cerebral glucose metabolism) and had structural magnetic resonance scans of their brains. Radioactivity in pre-selected regions (relative to global radioactivity), measured by positron emission tomography, served as a surrogate marker for glucose metabolism. Task performance was related to regional radioactivity and to hippocampal morphology. MA users made more errors on the vigilance task than did controls and had lower relative activity in the anterior cingulate and insular cortices, but higher activity in lateral orbitofrontal cortex and middle and posterior regions of the cingulate cortex. Combining groups, relative activities in the left insula and bilateral hippocampus as well as the local radial size and volume of the hippocampus were negatively associated with errors. The groups differed in the relationships between performance and relative activity of the anterior and middle cingulate gyrus and the insula; error rate was negatively related to relative activity in these regions among MA subjects, and positively related to activity in the cingulate cortex among controls. The results indicate that dysfunction in the cingulate and insular cortices of recently abstinent MA abusers may contribute to impaired vigilance and other cognitive functions requiring sustained attention. This work was supported by grants from the National Institutes of Health (RO1 DA 15179 to EDL and National Center for Research Resources Grants RR12169, RR08655, and MOI RR 00865), and a contract from the National Institute on Drug Abuse (1 Y01 DA 50038 to EDL, WL). The Ahmanson-Lovelace Brain Mapping Center, where the imaging data were collected, is supported by the Brain Mapping Medical Research Organization, the Brain Mapping Support Foundation, the Pierson-Lovelace Foundation, the Ahmanson Foundation, the Tamkin Foundation, the Jennifer Jones-Simon Foundation, the Capital Group Companies Charitable Foundation, the Robson Family, and the Northstar Fund. The authors thank Leyla Khenissi for technical support.

30. Eph/ephrin Family Members, Implicated in Cocaine-mediated Neuroadaptation, are Expressed in Adult Primate Brain

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The Eph/ephrins, a large family of tyrosine kinase receptors/ligands, facilitate topographic guidance in developing brain, including the nigrostriatal and mesolimbic dopamine pathways. In adult rodent brain, the ephrin family is implicated in neuronal plasticity associated with learning, memory and in cocaine-induced neuroadaptation. As the potential contribution of the ephrin family to drug-induced neuroadaptation in primate brain is unknown, we initially investigated whether ephrin receptors and their ligands are expressed in adult monkey brain. mRNA encoding EphA4 (the only receptor that cross talks with ephrin-A, ephrin-B ligands), ephrin-B2 (modulated by dopaminergic projection systems) were expressed robustly in medial and orbitofrontal cortices, hippocampus, amygdala, nucleus accumbens, thalamus, caudate/putamen, and cerebellum, and to a lesser extent in globus pallidus. Weak expression of EphB1 mRNA was found in selective regions (cerebellum) and its ligand, ephrin-B1, was not detected in adult monkey brain. To secure the distribution data, we also conducted immunohistochemical analysis of EphA4 protein expression. EphA4 was expressed discretely in the Purkinje cells in cerebellum, fusiform cells in dentate gyrus of hippocampus, pyramidal cells in frontal cortices (mainly in layers II, III and V), globus pallidus and substantia nigra. EphA4 positive neurons were found to co-localize with tyrosine hydroxylase positive terminals in striatum and cell bodies in substantia nigra. Preliminary data suggest that EphA4 in putamen was altered by cocaine-treated monkeys. The contribution

of the ephrin family to neuronal plasticity in general, and to dopamine neurons in cocaine-induced adaptation mediated is under investigation. Supported by: DA06303, DA15305, DA11558, RR00168.

31. Attention Deficit Hyperactivity Disorder (ADHD): New Roles for old Trace Amines and Monoamine Transporters

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Introduction: Although the pathophysiology of ADHD is poorly understood, the pharmacological effects of ADHD medications are more explicable. ADHD medications (e.g. methylphenidate, d-amphetamine, atomoxetine) are robust inhibitors of the dopamine and norepinephrine transporters, and trigger a significant rise in extracellular levels of the monoamines dopamine and norepinephrine levels in brain. The trace amine phenylethylamine (PEA) has also been implicated in ADHD pathology and pharmacology, but its mechanisms are unknown. PEA levels are reduced in urine of children with ADHD and significantly elevated following treatment with methylphenidate or d-amphetamine. To explore the neurobiology of PEA, we investigated whether PEA is a substrate for the dopamine and norepinephrine transporters, whether methylphenidate blocks PEA transport, and whether PEA is an agonist at the newly cloned trace amine receptor. **Results:** This is the first report demonstrating [3H]PEA transport by the dopamine (DAT) and norepinephrine (NET) transporters in a concentration-, time- and temperature-dependent manner. The affinities of PEA as a substrate for DAT and NET were similar to corresponding dopamine or norepinephrine affinities at DAT and NET. Methylphenidate potently inhibited [3H]PEA transport by the DAT and NET, indicating that PEA levels may also be increased in brain following treatment with ADHD medications. In addition to functioning as transporter substrates, PEA, d- and l-amphetamine activated the recently cloned trace amine receptor subtype1, whereas methylphenidate was inactive. Intriguingly, co-expression of the dopamine transporter and the trace amine receptor enhanced receptor activation, possibly indicating that the trace amine receptor is localized intracellularly and activated by translocation of PEA. **Conclusions:** 1. PEA is a potent substrate for catecholamine transporters. Drug development for novel ADHD medications should consider PEA transport in screening assays. 2. PEA levels may be deficient in ADHD brain and catecholamine transport inhibitors may increase brain levels of PEA by transport blockade. Consequently, elevated PEA levels may enhance trace amine receptor activity and produce a therapeutic response. 3. Conversely, if the DAT and trace amine receptor1 are co-localized, inadequate release of PEA in ADHD may lead to overactivity of PEA at an intracellular trace amine receptor1. Under these conditions, transport blockade by nthylphenidate may reduce trace amine receptor1 activity by blocking access of PEA to the intracellular milieu. In summary, as a substrate for monoamine transporters and an agonist at the trace amine receptor1, PEA may contribute to the pathophysiology and therapeutic efficacy of ADHD medications. Support: DA06303, DA15305, DA 11558, DA 16606, RR00168.

32. Regulation of Dopaminergic Transmission and Cocaine Reward by the Clock Gene

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Sponsor: Eric Nestler

Although drug addiction is associated with pronounced disruptions of sleep and circadian rhythmicity, a modulatory role for the circadian Clock gene or its downstream products on the dopamine system has not been previously described. Given the importance of the midbrain dopamine neurons in reward and addictive processes we focused on possible dopamine neural adaptations in mice lacking a functional Clock gene. We found a novel role for the circadian Clock gene in regulating dopamine and cocaine reward-related behaviors. Mice with a mutation in the Clock gene have increased dopamine neurotransmission consisting of increased basal dopamine neuronal impulse activity, locomotor hyperactivity and increased sensitivity to the rewarding effects of cocaine. Our results indicate that midbrain ventral tegmental area dopamine neurons express the CLOCK protein which apparently exerts inhibitory control over the rate limiting enzyme in the production of dopamine, tyrosine hydroxylase. The dopamine neurons in the Clock mutant mice show a dramatic increase in tyrosine hydroxylase mRNA and protein. In addition, our DNA microarray analysis of the ventral tegmental area indicates that compared to wild type controls, Clock mutants have altered expression of several genes known to regulate dopamine neuronal excitability. These results provide the first evidence for a direct involvement of the circadian Clock gene in regulating dopamine neuronal excitability and cocaine reward possibly linking it to circadian pathologies associated with drug addiction.

33. Contribution of Cortico-Striato-Limbic Circuitry to Heroin-Seeking Behavior

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While the contribution of cortico-striato-limbic circuitry to cocaine-seeking behavior has been established, its role in heroin-seeking behavior has yet to be examined. For this reason, mapping and microdialysis studies were conducted to examine the circuitry and pharmacology subserving heroin-induced reinstatement of heroin seeking. Animals previously trained to self-administer heroin had their operant responding extinguished. Then on a single trial, the ability of a noncontingent priming injection of heroin was tested for its ability to reinstate drug-seeking behavior. Transient inhibition of both motor (the dorsal prefrontal cortex and nucleus accumbens core) and limbic (ventral tegmental area and basolateral amygdala) nuclei prevented heroin-induced reinstatement circuitry. Conversely, inhibition of the ventral pallidum increased reinstatement responding. Inhibition of any of other the other nuclei tested (including the shell of the nucleus accumbens, ventral prefrontal cortex, ventral bed nucleus of the stria terminals, central amygdala, mediodorsal thalamus and substantia nigra) had no effect on reinstatement responding. Subsequent microdialysis studies examined the contribution of the glutamatergic projection from the prefrontal cortex to the nucleus accumbens in heroin-seeking behavior. Notably, there was considerable overlap in the circuitry found to underlie heroin-seeking behavior with that previously found to be important for cocaine-seeking behavior, suggesting a potential "final common pathway" for drug seeking behavior in reinstatement models of relapse.

34. Effects of Buprenorphine and d-amphetamine on "Speedball" Self-Administration By Rhesus Monkeys

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The simultaneous i.v. administration of heroin and cocaine, called a "speedball", is often reported clinically, and we have modeled this type of polydrug abuse in the rhesus monkey (Mello et al., 1995). The development of effective pharmacotherapies for "speedball" and other forms of polydrug abuse is a continuing challenge, and we have

found that treatment with combinations of medications that target the cocaine and heroin component may reduce speedball self-administration more effectively than either drug alone (Mello and Negus, 1999, 2001). Speedballs (0.01 mg/kg/inj cocaine + 0.0032 mg/kg/inj heroin) and food (1 gm banana-flavored pellets) were available in four daily sessions on a second-order schedule of reinforcement [FR2 (VR16:S)]. Monkeys were treated for 10 days with saline, the monamine releaser d-amphetamine alone (0.032 mg/kg/hr), or with a combination of the partial mu agonist buprenorphine (0.075 or 0.237 mg/kg/day) and amphetamine (0.0032-0.032 mg/kg/hr). Both buprenorphine doses + d-amphetamine produced an amphetamine dose-dependent decrease in speedball self-administration in comparison to the saline treatment baseline. Buprenorphine (0.237 mg/kg/day) + d-amphetamine (0.01 mg/kg/hr) also produced a rightward and downward shift in the speedball self-administration dose-effect curve with minimal effect on food-maintained responding. This buprenorphine + d-amphetamine combination produced a sustained decrease in self-administration of all speedball combinations over 10 days with minimal effects on food-maintained responding. These findings extend our previous reports that d-amphetamine significantly decreased cocaine self-administration under several conditions (Negus 2003, Negus and Mello 2003 a, b). These data are also consistent with our previous findings that combinations of two or more medications, designed to target each component of the speedball combination, are an effective approach to polydrug abuse treatment (Mello and Negus 1999, 2001). This research was supported in part by P01-DA14528, RO1-DA02519 and KO5-DA00101 from NIDA, NIH.

35. Menstrual Cycle Phase Influences the Effects of Cigarette Smoking on Mood States and the HPA Axis

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Twelve healthy adult women who met DSM-IV criteria for nicotine dependence provided informed consent for participation in studies designed to examine if menstrual cycle phase influenced the acute effects of cigarette smoking on subjective and neuroendocrine measures. Six follicular phase women (progesterone = 0.73 ± 0.15 ng/ml) and six luteal phase women (progesterone = 9.18 ± 1.55 ng/ml) were studied after overnight abstinence from smoking. Baseline carbon monoxide levels were less than 5 ppm and did not differ significantly between the two groups. Women smoked a commercially available, high dose nicotine cigarette under controlled conditions. Subjects took one 5 sec puff every 30 sec for 12 min. Serum nicotine levels increased significantly within 4 min ($P < 0.05$), and remained significantly above baseline levels throughout the 120 min study session. Peak serum nicotine levels were equivalent in the two groups of women, and averaged 23.4 ± 5.4 ng/ml and 24.3 ± 2.2 ng/ml. Heart rate increased significantly from baseline within 2 min ($P < 0.05$) and there were no differences between follicular and luteal phase women. However, cigarette smoking produced higher ratings of positive subjective effects on a Visual Analogue Scale (VAS) in follicular phase women than in luteal phase women. VAS ratings of High and Rush were higher in follicular than in luteal phase women. ACTH peak levels were also higher in follicular than in luteal phase women. Serum levels of ACTH increased significantly within 14 min after smoking began and ACTH increases were followed by significant increases in cortisol and DHEA ($P < 0.05$). Cortisol and DHEA were also higher in follicular phase women than in luteal phase women. These findings suggest that menstrual cycle phase modulates the effects of cigarette smoking on mood states and neuroendocrine hormones in women. There are many similarities between the subjective and endocrine effects of cigarette smoking and i.v. cocaine (Jones et al., 1999; Mendelson et al., 2003). These preliminary findings are consistent with clinical and preclinical reports that high levels of progesterone during the luteal phase and/or progesterone administration may attenuate subjective reactions to cocaine and decrease cocaine self-administration (Evans and Foltin, 2002; Mello et al., 2004). This research was supported by grants T32-DA07252, R01-DA15067, P01-DA14528, K05-DA00064 and K05-DA00101 from the National Institute on Drug Abuse, NIH.

36. Is There a Therapeutic Window for Methylphenidate in Children with ADHD: A PK/PD Analysis

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Methylphenidate (MPH) is the most commonly prescribed stimulant for treating ADHD in the US. It acts predominantly as an inhibitor of the dopamine transporter (DAT). Volkow et al (1998) reported that d-MPH plasma levels of 10 ng/ml resulted in 75% occupancy of DAT in normal young adults, and that higher plasma levels were not associated with any greater degree of DAT binding. This suggests that at levels beyond the minimum plateau point that MPH would lose specificity, and that this could represent the potential peak of a therapeutic window. To test this hypothesis we examined the pharmacokinetic/pharmacodynamic profile of MPH response in children with ADHD. Thirty-eight boys from 9-12 years of age who met DSM-IV criteria for ADHD combined subtype (K-SADS-E interview), and who were objectively hyperactive (Teicher et al 1996), were enrolled in this IRB-approved study. Each child received a total daily dose of 1 mg/kg MPH that was administered in different amounts at different times to produce 4 distinct pharmacokinetic profiles. One profile produced 6-8 hours of rising blood levels, another produced an initial peak and a sustained blood level, a third had a three-pulse pattern with moderate fluctuations, and the fourth had a three-pulse pattern with large fluctuations. Subjects were tested immediately prior to medication administration and every hour thereafter (for 12 hours) with a 5 minute CPT test coupled to an infrared motion analysis system to track their degree of hyperactivity (Teicher et al 1996). Blood samples were also collected at hour intervals and were assayed using GC-MS for levels of d-MPH. The response profile of each subject was analyzed to ascertain on which of the 12 CPT-motion analysis tests they had their best performance, their worst performance, and their response at their peak plasma level. Overall, best response occurred at a mean plasma level of 11.3 ng/ml. At this level there was a 68% reduction in fidgeting (position changes) versus pre-drug baseline ($F_{1,34} = 46.5$, $p < 0.0001$). On average, the highest MPH plasma level obtained was 14.2 ng/ml (optimal vs. peak $F_{1,34} = 50.7$, $p < 0.0001$). Fidgeting at peak level was significantly better than pre-drug baseline (44% reduction; $F_{1,34} = 17.9$, $p < 0.0001$), but 77% higher (worse) than response at their optimal level ($F_{1,34} = 23.6$, $p < 0.0001$). Interestingly, their poorest non-baseline response occurred at a mean plasma level of 8.4 ng/ml (optimal vs. worst blood $F_{1,34} = 10.6$, $p = 0.003$). At this level they fidgeted 24% more than during pre-drug baseline, although not significantly so ($F_{1,34} = 3.7$, $p = 0.06$). Seventy-one percent of subjects fidgeted the most at MPH levels that were on average 5.4 ng/ml below optimal. Twenty-nine percent fidgeted the most at levels 2.8 ng/ml above optimal. CPT accuracy showed the same profile with an optimal plasma level of 11.0 ng/ml. These findings held across the 4 different pharmacokinetic administration profiles. There were no significant differences between the regimens in terms of plasma-level associated with optimal response ($F_{3,34} = 1.0$, $p = 0.4$), or poorest non-baseline response ($F_{3,34} = 0.7$, $p = 0.5$). Overall, these findings suggest that optimal response to MPH occurs at a plasma level (11 ng/ml)

remarkably similar to the minimum plasma level found by Volkow et al (1998) to be associated with maximal binding to DAT. As hypothesized higher plasma levels were associated with a significant decline in efficacy, but plasma levels approximately 5.4 ng/ml below optimal were associated with loss of efficacy and possible worsening of symptoms in a substantial number of subjects.

37. Late Pregnancy Exposure to Serotonin Reuptake Inhibitors (SSRIs) is Associated with Neonatal Adjustment Problems and Subtle Motor Changes in Infancy Compared to Early Pregnancy Exposure to SSRIs or No Drug Exposure

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Antidepressant drug treatment during pregnancy, specifically with Serotonin Reuptake Inhibitors (SSRIs) has been associated with a reduced acute pain response, motor symptoms in the newborn and motor changes in the infant at follow-up. The primary objective of the present study was to compare newborn functioning and the developmental outcome of children of depressed mothers who either did not take medication, took SSRIs during the first trimester only, or took SSRIs during the third trimester of pregnancy. **Methods:** Information regarding delivery and neonatal course of 78 newborns were collected from obstetric and neonatal medical records. At follow-up, mean age 15.5 months, children underwent neurologic and dysmorphology examinations and were tested using the Bayley Scales of Infant Development (BSID-II). Children (N=24) of unmedicated mothers, were compared to children (N=13) exposed during the first trimester to sertraline (31%), paroxetine (39%) fluoxetine (5%) and one each to citalopram and fluvoxamine and to children exposed during the third trimester or longer during gestation (N= 41) to sertraline (42%), fluoxetine (34 %), paroxetine (17%), two to fluoxetine and sertraline and one to citalopram. Eighty-five percent of control mothers and of mothers who took SSRIs during the first trimester of pregnancy compared to 93 % of mothers who took SSRIs during the third trimester breastfed their children. Among mothers, who breastfed, 27% (controls), 36% (first trimester) and 84 % (late pregnancy) took SSRI antidepressants. **Results:** The mothers demographic and clinical characteristics were similar. Specifically, nearly all mothers took prenatal vitamins and virtually no mothers smoked, used alcohol or used illicit drugs. Birth outcome: No between group differences were observed for preterm births, major and minor malformations, or birth weights and lengths. Newborns with late exposure had significantly lower Apgar scores at 1 min and at 5 min than un-medicated controls and newborns with first trimester exposure. Among the newborns with third trimester exposure 27% were admitted to neonatal care units as opposed to 8.3% among the controls and none with first trimester exposure. Follow-up: Infants in the three groups were not different in their mental development and children with early SSRI exposure were not different from unexposed children in their psychomotor development. Children with late exposure showed lower scores on the Behavioral Rating Scale for behavioral motor quality, specifically they had lower scores on the subscales for gross and fine motor movements compared to the children with first trimester exposure and compared to the children of unmedicated mothers. **Conclusions:** The higher rate of neonatal adaptation problems in children, who were exposed to SSRIs during late gestation as opposed to unexposed children or to those exposed during the first trimester emphasizes the need for close neonatal monitoring of newborns of mothers taking SSRIs prenatally. Further studies are required to clarify the extent to which the subtle motor signs at follow-up in children exposed late in pregnancy to SSRIs are related to neonatal adjustment problems or to direct drug effects.

38. Mice with Human Mutations of the MeCP2 Gene as Animal Models of Rett Syndrome

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Rett syndrome (RS) is an X-linked disorder in the spectrum of the pervasive developmental disorders that affects predominantly females and is characterized by cognitive decline commencing at two years after birth, stereotypic movements and breathing abnormalities. RS is caused by mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2), which is involved in transcriptional repression. To understand the pathophysiology of RS, we have created mice with the symptomatic human mutations inserted into the MeCP2 gene (knock-in). The D156E mutation affects the methyl CpG binding domain and R168X and R255X have truncation mutations in the transcription repression domain. As early as 4 weeks after birth, the male mutants developed stereotypic forepaw movements, psychomotor retardation, hind limb clasping, body tremors, piloerection, and periods of labored breathing. Female heterozygous mutants developed a similar phenotype starting at 4 months, but some remained asymptomatic up to 6 months. All male mice carrying the point mutations died around 10 weeks of age and were infertile. The mutant mice were more severely affected than mice with a null mutation (knock-out) of the MeCP2 gene, suggesting that the mutant proteins may exert dominant negative effects. We found that the expression of tyrosine hydroxylase is reduced in the nucleus tractus solitarius of the knock-in mutant mice, which may contribute to the pathophysiology of the respiratory abnormality in RS. The female knock-in mutants were impaired in their performance of a working memory task as assessed by the T-maze. Skewing of X chromosome inactivation correlates with the behavioral and respiratory phenotype in females as determined by RT-PCR measures of X chromosome inactivation in lymphocytes. These studies provide insights into the relationship between the human MeCP2 mutations and their behavioral and phenotypic consequences resulting in RS. (Supported by the International Rett Syndrome Foundation)

39. Maturational Alterations in G (olf) Alpha Protein Expression in the Striatum of an Animal Model of ADHD

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Sponsor: Travel Awardee, NIMH, 2004

Attention-deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in the pediatric population with a prevalence of 5 to 7.5 %. Systematic clinical observations demonstrate that hyperactivity symptoms decrease markedly during adolescence, while inattention symptoms persist into adulthood in 30-50%. Accumulating evidence supports the hypothesis that ADHD reflects, in part, a dysregulation of the central catecholaminergic systems, in particular, the dopaminergic pathways. Of potential interest for ADHD is the G (olf) alpha protein, which has recently been found to mediate D1R signaling in the striatum. We studied potential maturational alterations in G (olf) alpha in spontaneously hypertensive rats (SHR), an inbred animal model of ADHD and Wistar-Kyoto (WKY) rats, the strain from which SHR were derived. Striatal G (olf) alpha protein expression was evaluated by western blot technique in prepubertal (3-weeks old), adolescent (5 weeks old), and young adult (8 weeks old) SHR and WKY rats. Preliminary data (N= 6/cell) indicate that during the prepubertal period there is higher expression of G (olf) alpha in the striatum of SHR as compared to WKY rats. However, this pattern is reversed by adulthood, when SHR express less G (olf) alpha than WKY rats. We are currently exploring the implications of these intriguing results.

40. A Shift from Diffuse to Focal Cortical Activity with Development

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Sponsor: Enoch Callaway

Recent imaging studies have suggested that development may parallel patterns of adult learning in cortical activation becoming less diffuse and more focal over time. However, while adult learning studies have examined changes within subjects, developmental findings have been based on cross-sectional samples and comparisons across studies. In the present study, we used longitudinal functional MRI to test directly for shifts in cortical activity. Children aged 7 to 12 years participated in two functional MRI sessions two years apart, when they were on average 9 and 11 years of age. On both occasions, they were instructed to press a button to a string of targets, but not to a rare non-target. A second set of subjects participated in an fMRI session once, when they were 11 years of age, allowing us to perform a cross-sectional analysis in addition to the longitudinal one. Behaviorally, subjects became more accurate and faster at detecting the target from time 1 to time 2, although subjects made a similar number of false alarms. Our longitudinal MR findings, relative to our cross-sectional ones, suggested a decrease in global cortical activity. The only region where MR signal increased was in right inferior frontal gyrus. MR signal in this region correlated with performance. These results suggest that as children begin to reach adolescence, simple target detection ability is improving, while other aspects of cognition are still developing. Behavioral changes are paralleled by an increase in recruitment of ventral prefrontal regions over other cortical regions, consistent with less diffuse and more focal patterns of activity in regions that correlate with performance across development. Understanding normal progressions in behavioral and neural systems will have a significant impact in determining the biological substrates of clinical disorders and targeting effective treatments and interventions. This work was supported by a NIMH R01 award to BJC and a stipend from the Netherlands Organisation for Scientific Research (NWO) to SD.

41. Repeated Methamphetamine Treatment Reveals the Existence of Resilient Dopaminergic Neurons: Implications for Development and Neurotoxicity

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High-dose methamphetamine (METH) administration differentially affects dopaminergic neuronal parameters as a function of development. For example, METH treatment causes persistent dopaminergic neuronal deficits in young adult (postnatal day (PND 90)), but not adolescent (PND 40) rats, as evidenced by findings that high-dose METH treatment results in persistent decreases in dopamine (DA) content, and the activities of the DA transporter, tyrosine hydroxylase, and the vesicular monoamine transporter-2 (VMAT-2) in PND 90, but not PND 40 rats. Findings from the present study confirm that high-dose METH treatment (4 x 7.5 mg/kg/injection, s.c., 2-h intervals) causes persistent dopaminergic deficits in rats aged approximately PND 90, as evidenced by decreased tissue DA content and VMAT-2 activity 7 d post-treatment. Reminiscent of a lack of persistent effects of METH in PND 40 rats, administration of a challenge METH treatment (4 x 7.5 mg/kg/injection, s.c., 2-h intervals) 7 d after the initial METH insult did not further decrease DA content nor VMAT-2 activity, as assessed 7 d after the second treatment. These data suggest the existence of a population of DA neurons resistant to the neurotoxic METH regimen; a population that may have been present throughout development. Mechanisms underlying this resistance, as well as the relevance of this resistant population with regard to the etiology of neurodegenerative disorders such as Parkinson's disease, will be discussed. (Supported by DA00869, DA11389, DA04222, DA13367).

42. Genetic Analysis of Hypothalamic Corticotropin Releasing Factor (CRF) System

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The goal of this study was to use BxD recombinant inbred (RI) mice to search for genes that control the hypothalamic corticotropin releasing factor (CRF) system. The specific phenotype that was measured was abundance of transcripts that encode various components of the hypothalamic CRF system in total hypothalamic RNA. Transcript abundances for CRF, CRF receptor (Crf-R1), CRF binding protein (Crf-BP) and argenine vasopressin (AVP) were measured in total hypothalamic RNA with real-time RT-PCR assays. The phenotype measured, transcript abundance for each target in total hypothalamic RNA, was chosen because it is not constrained to any particular molecular mechanism. Genes that control biological processes at many different levels, from target-gene specific transcriptional mechanisms through cellular differentiation of paraventricular nucleus neurons and stress responsivity could be detected with this phenotype. The strain distribution patterns (SDP) for the hypothalamic transcript abundances for each target were continuously distributed, consistent with these being quantitative traits. Marker regression at a genome-wide significance of $p<0.0001$ revealed associations with quantitative trait loci (QTL) for CRF transcript abundance (CRFta) on chromosome 1 at P1Ehs1 and Mtv7 and on chromosome 12 at D12Mit233 and D12Mit79; for Crf-R1ta on chromosome 12 at D12Mit14 and chromosome X at Oat-rs1; for Crf-BPta on chromosome 2 at D2Mit412 and D2Mit229, chromosome 4 at Cd72, chromosome 5 at Spp1, chromosome 8 at D8Mit75, and chromosome 17 at D17Mit39; and for AVPta on chromosome 2 at D2Mit235. The transcript abundance QTL were not linked to the structural genes for their respective targets. Significance levels (suggestive, significant and highly significant) for interval mapping for QTL controlling expression of each target were set empirically with the permutation test run through 10,000 iterations for each data set. Interval mapping was carried out on chromosomes that had significant genetic associations detected in the marker regression analysis and this revealed a number of significant and suggestive likelihood ratio statistic (LRS) linkage peaks. Interval mapping on chromosome 12 reveals substantial overlap between QTL that control CRF and Crf-R1 transcript abundance, which may indicate shared genetic regulation of the hormone and receptor. The QTL Hipp1A, which controls hippocampal weight and cellularity, is located at a map position in very close proximity to the CRFta LRS peak. Comparison of the CRFta data to the WebQTL phenotypes database revealed modest, uncorrected correlations of CRF-Ct values to a number of hippocampal phenotypes and these correlations indicate an inverse relationship between hypothalamic CRF transcript abundance and hippocampal volume and cellularity. Thus strains with larger hippocampal measures (weight, cellularity, etc) exhibit lower quantities of hypothalamic

CRF transcript. There are other behavioral QTL on chromosome 1 that map in very close proximity to CRFta peaks including Cfcd, which controls contextual fear conditioning, Emotionality (Emo1), escape latencies during navigation (Elnt1), alcohol withdrawal 1 (Alcw1), and pentobarbital withdrawal 1 (Pbw1). The phenotypes associated with any of these QTL could be alternative manifestations of the CRFta phenotype. The QTL, Axtofa4 that impacts anxiety behaviors in the open field is coincident with the LRS peak on chromosome 12 that controls Crf-R1ta, in the region of apparent shared genetic regulation between CRF and Crf-R1 transcript abundance, suggesting that the behavioral and molecular phenotypes are manifestations of the same fundamental biological process.

43. Gabaergic Neurosteroid Administration Alters Cortical Development

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Sponsor: Past Travel Awardee, MEM, 2002

GABA receptors ($GABA_A$and $GABA_B$) have been shown to affect neuronal migration in several systems. $GABA_A$ receptors are thought to be mediate some aspects of migration and axon pathfinding of developing cortical neurons. However, the role of GABA receptor modulators in these systems is not well characterized. The neurosteroid, 3α-hydroxy-5α-pregnane-20-one (3α, 5α-THP, allopregnanolone), is a potent endogenous modulator of $GABA_A$ receptor function whose levels fluctuate dramatically in the perinatal period. Previous work from this lab has shown that neonatal administration of allopregnanolone alters adult prefrontal cortex and thalamus (J. Neurosci 23:1832). BrdU labeling of E17 mitotic cells was used to investigate the effects of neurosteroid administration on lamination of the parvalbumin-positive neuron population in P21 animals. Immunohistochemical staining and analysis of variance revealed that allopregnanolone administration (10 mg/kg, i.p.) during the first week of life alters the localization of the E17-born cells in the prefrontal cortex ($F=6.743$, $p<0.01$, n= 9-13 animals/group) without altering the number of BrdU-positive cells ($F=0.8263$, p=n.s.) or the volume of the cortex ($F=0.025$, p=n.s.). The localization of the parvalbumin-positive subpopulation of BrdU-labeled cells was not changed ($F= 0.4937$, p= n.s., n= 9-13 animals/group). Neurosteroid administration decreased the in vitro migration of GABAergic cells in cortex but not in striatum. Heterochronic co-cultures of GFP+ mouse MGE explants on embryonic rat cortical slices were exposed to different concentrations of allopregnanolone in the culture media. The number of cells migrating out of the MGE explant into the dorsal/ventral boundary was less than the number migrating into the striatum in the presence of 3 nM allopregnanolone. The neurosteroid-associated shift in cellular localization in the ILPFC without a change in total cell number is consistent with the notion that neurosteroid levels play a role in late-phase developmental events, including migration through the cortical plate and cortical lamination. Decreased migration through the cortical plate, but not the striatum in vitro in response to low levels of allopregnanolone in culture indicates that neurosteroid levels may affect the velocity of neuronal migration though the developing cortex, with implications for later developmental processes, including the laminar placement of specific cell populations. Neurosteroid levels may be important in the late events of normal CNS development, including lamination, and could therefore play a role in abnormal development. Supported by: Stanley Medical Research Institute Stanley Scholars Grant to SSG and MH065470 to ACG and the UNC Silvio Conte Center

44. The Role of Neurogenesis in Mediating Vulnerability to Stress in Mice Exposed to Low Levels of Maternal Care Early in Life

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Sponsor: George Heninger

Good parental care during early development is necessary for appropriate cognitive, emotional, and physical development of the child. Children that have experienced abuse or poor parental bonding during early development are at greater risk to develop numerous psychopathologies including anxiety and depression later in life. Similar observations have also been documented in primates and rodents, supporting the use of rodents to study the molecular mechanisms by which postnatal-parental care influences neurodevelopment and vulnerability to stress in humans. Elegant work in rats has shown that offspring exposed to lower levels of postnatal maternal care (PMC) have increase in hypothalamic-pituitary axis (HPA) reactivity, as well as an increase in anxiety and depression-like behaviors. These effects are stable and persist throughout the adult life of the animal. However, the mechanism by which PMC leads to these behavioral changes is unclear. Few studies have demonstrated similar results in the mouse but no group has used transgenic animals to study this process. Here we report preliminary results on establishing this paradigm in the mouse and provide examples to demonstrate the potential of using mouse molecular genetics to study this problem. More specifically, we wish to study whether some of the effects of PMC are mediated through its ability to regulate neurogenesis during development and/or throughout the adult life of the animal. Recent work from several labs has demonstrated that low levels of PMC are associated with a decrease in neurogenesis/neuronal survival in young and adult rodents. Given that the postnatal period is characterized by a second wave of neurogenesis, some of the behavioral consequences of poor PMC might be due to its effect on neurogenesis during development and/or in the adult animal. This is consistent with data suggesting that higher levels of neurogenesis have protective effect against some forms of depression and anxiety, and neuroimaging studies showing that reduced hippocampal size is associated with a vulnerability to several psychopathologies. Here we propose to study the effect of PMC on neurogenesis in the mouse and determine whether some of the behavioral sequelae of poor PMC are due to its ability to regulate neurogenesis.

45. A Voxel-Based Morphometry Study of Brain Anatomy in Tourette Syndrome

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Sponsor: Past Travel Awardee, BMS, 2002

Introduction: Previous anatomical neuroimaging studies have suggested abnormalities of cortical gray matter and white matter in Tourette syndrome (TS). However, voxel-based methods, which permit the detection of localized gray and white matter differences across the entire brain, have not been employed in TS. In this study, whole-brain voxel-based morphometry was used to examine the local gray and white matter abnormalities. **Methods:** Twenty-five males with TS (age: 10.9±2.7 years) and 31 male controls (age: 11.2±2.7 years) participated in this study. The diagnosis of TS was made using DSM IV criteria, and all patients had a full-scale intelligence greater than 70. All control subjects were assessed using the K-SADS to exclude the presence of any psychiatric disorders. Controls with a family history

of a tic disorder, obsessive-compulsive disorder or attention-deficit/hyperactivity disorder were excluded. The groups did not differ significantly in age, race, or handedness. T1-weighted 3D MP-RAGE images (1.2-mm isotropic voxels, TI/TE/TR=200/5/11 ms, flip angle 12 degrees) were acquired on all subjects using a 3 Tesla MRI scanner. The images were then warped to stereotactic space, segmented into cerebral spinal fluid (CSF), white and gray-matter, and then smoothed. Regionally specific gray matter and white matter differences between the groups were assessed using voxel-wise parametric statistical tests, using a threshold of $p \leq 0.001$ (uncorrected). **Results:** Compared with controls, patients with TS had localized increases in left and right frontal gray matter and reductions in left parietal gray matter and right cingulated cortex. Additionally, patients had increased white matter in the left frontal lobe and bilaterally in the parietal lobe. **Conclusions:** Patients with TS had gray and white matter abnormalities in regions which are parts of neural circuits involved in the inhibition of unwanted impulses. Further, abnormalities were detected in regions which are components of the cortical-striatal-thalamic-cortical circuits believed to be involved in the pathophysiology of TS. These results, which need to be interpreted cautiously due to several limitations (small sample size, lack of female subjects, comorbid attention-deficit/hyperactivity disorder in many patients with TS) suggest abnormalities in cortical regions participating in the regulation of appropriate motor behaviour.

46. Brain Structure in Preclinical Huntington's Disease: Evidence for Abnormal Brain Development

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Background: Huntington's Disease (HD) has consistently been conceptualized as a degenerative disease of the striatum. Recent scientific advances have begun to reshape this construct, both in regard to whether or not this disease has a significant neurodevelopmental component as well as to whether the striatum is the primary region of pathology. The current study was designed to comprehensively assess the morphology of the brain in participants who had previously undergone elective DNA analyses for the CAG expansion in the HD gene ("presymptomatic testing") and who did not currently have a clinical diagnosis of HD (preclinical HD subjects). **Methods:** 24 preclinical participants with the gene expansion for HD underwent brain MRI and were compared to a group of 24 healthy control subjects, matched by sex and age. Quantitative measures of general and regional tissue volumes for the entire brain were obtained. In addition, using a unique image processing method, quantitative measures of the cerebral cortex were obtained. **Results:** Compared to controls, HD preclinical participants had substantial morphologic changes throughout the cerebrum. Volume of the cerebral cortex was significantly increased in preclinical HD compared to controls whereas the basal ganglia and cerebral white matter volume were substantially decreased. Further analysis of the cerebral cortex morphology showed that the increase in cortical volume was accounted for by an increase in surface area and thickness of the cortex, localized to the gyri. This abnormal thickening of the cortex was generalized throughout the cerebrum and therefore not regionally specific. **Conclusion:** In individuals with the HD gene mutation who are considered healthy (preclinical for manifest disease), the morphology of the brain is substantially altered in comparison to matched controls. Although some of these findings such as decreased volumes of the striatum and cerebral white matter could represent early degenerative changes, the novel finding of enlarged cortex suggests that developmental pathology occurs in HD. These findings support recent reports from basic science research in HD suggesting a neurodevelopmental component to the pathoetiology of the classic "neurodegenerative" disease.

47. A Retrospective Analysis of Quetiapine in the Treatment of Pervasive Developmental Disorders

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Sponsor: Christopher McDougle

Background: The purpose of this study was to examine the effectiveness and tolerability of quetiapine for aggression, hyperactivity and self-injury in pervasive developmental disorders (PDDs).
Method: Records of all patients with PDDs treated within an autism clinic were retrospectively reviewed to determine whether a subject had been treated with quetiapine. Patients who received quetiapine for at least 4 weeks, and who were not concurrently treated with another antipsychotic or mood stabilizer were included. Improvement was measured with the Clinical Global Impressions-Improvement (CGI-I) scale, with response determined by ratings of much improved or very much improved. **Results:** Of 857 records reviewed, 20 patients (16 males, 4 females) (mean age +/- SD, 12.1 +/- 6.7 years; range, 5-28 years) received a quetiapine trial (mean dosage +/- SD, 248.7 +/- 198.4 mg/day; range, 25-600 mg/day) over a mean duration of 59.8 +/- 55.1 weeks (range, 4-180 weeks). Eight (40%) of 20 patients were judged responders to quetiapine; the mean CGI-I score for the entire group was 3.0 +/- 1.1 (minimally improved). A statistically significant improvement was found between a mean pre-trial CGI-Severity (S) score of 5.1 +/- 0.6 (markedly ill) and a post-trial CGI-S score of 4.2 +/- 1.1 (moderately ill) (p=.002). Adverse effects occurred in 50% of patients and led to drug discontinuation in 15% of patients. **Conclusion:** Quetiapine was modestly effective for maladaptive behavior in patients with a PDD. A substantial minority of patients (40%) improved significantly during treatment. Quetiapine was associated with adverse effects in 50% of the patients. Controlled studies are needed to further assess these preliminary findings.

48. A Randomized, Double-blind, Placebo-controlled, Crossover Trial of Methylphenidate in Children with Hyperactivity Associated with Pervasive Developmental Disorders

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Sponsor: Travel Awardee, NIMH, 2004

Background: Studies on the use of methylphenidate to treat hyperactivity in autism and related pervasive developmental disorders (PDDs) have been inconclusive. The objective of this study was to determine the efficacy and safety of methylphenidate in children with PDDs and hyperactivity. **Methods:** Drug-free children with autistic disorder, Aspergers disorder, or PDD not otherwise specified presenting with significant hyperactivity were enrolled in a 4-week, randomized, placebo-controlled, crossover trial. Subjects initially entered a one-week single-blind test dose phase to determine tolerability. Subjects then received one week each of placebo and three different doses of methylphenidate (low, medium, high) in random order during the crossover phase. Responders to methylphenidate then received an additional 8 weeks of open-label methylphenidate treatment at the best dose. The primary outcome measure was the teacher-rated Hyperactivity subscale of the Aberrant Behavior Checklist (ABC). In addition, the parent- and teacher-rated ABC Hyperactivity subscales and the Clinical Global Impressions scale global improvement item were used to classify subjects as either responders or nonresponders to treatment. **Results:** Medium and high dose methylphenidate was more efficacious than placebo on the primary outcome measure. Thirty-five of 72 (49%) enrolled sub-

jects were classified as methylphenidate responders. Adverse effects led to discontinuation of study medication in 13 of 72 (18%) subjects. **Conclusions:** Methylphenidate was often efficacious in treating hyperactivity associated with PDD, but the rate and magnitude of response was less than that seen in typically developing children with attention-deficit/hyperactivity disorder. Adverse effects were also more frequent.

49. Neurocognitive Function in Pediatric Bipolar Disorder

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Sponsor: Ghanshyam Pandey

Background: It is critical to evaluate neurocognitive functioning in individuals with pediatric bipolar disorder (BD) given the neurodevelopmental abnormalities and educational difficulties in this population. Our hypothesis is that pediatric BD is marked by impaired cognition, including deficits in spatial working memory, verbal learning and memory, executive control of working memory, set shifting, and sustained attention, similar to that we and others have reported in adult BD. **Methods:** Forty age, sex, and race matched pediatric BD and healthy subjects entered the study (mean age: 11± 2.7 years). Groups were matched in word reading ability on the Wide Range Achievement Test-III. All subjects were euthymic during the testing period (Young Mania Rating Scale score ≤8 and Revised Child Depression Rating Scale Score ≤40). A computerized neurocognitive battery was administered, along with neuropsychological tests including the California Verbal Learning Test (CVLT-C), subtests from the Wechsler Memory Scale-III (WMS-III) and Wechsler Abbreviated Scale of Intelligence (WASI), and Trails A and B. Group comparison was done for the five composites of subsets: executive functioning, attention, working memory, verbal memory and visual memory. **Results:** Subjects with pediatric BD showed marked impairments on executive functioning. Verbal memory and attention were also significantly different across groups. Working memory and visual memory were not significant after controlling for IQ. **Conclusions:** There are a wide range of neurocognitive deficits in pediatric BD subjects, even in the euthymic phase of illness, that underscore the complexity of neuronal networks involved in pediatric BD beyond affective brain systems.

50. Birthweight and Hypothalamic-Pituitary-Adrenal (HPA) Axis Function in Young Rhesus Macaques (Macaca Mulatta)

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Sponsor: Dee Higley

Research with humans has indicated a relationship between low birth weight and dysregulation of HPA-axis function in childhood as well as later in adulthood. The specific results of such studies involving humans have not been consistent, however. Furthermore, very few studies have investigated the effect of low birth weight on HPA-axis function in response to stress. This study investigates the effects of low birth weight on baseline and stress-induced plasma cortisol and ACTH levels in rhesus macaques. Birthweight categories were determined from a sample of 257 (118 females, 139 males) rhesus monkey infants. Low birth weight (LBW) infants fell below the 25th percentile in birthweight for their respective sex. Average birth weight (ABW) infants fell between the 25th and 75th percentile, and high birth weight (HBW) infants fell above the 75th percentile. The effect of birthweight (BW) category on plasma cortisol and ACTH levels was evaluated in a subsample of subjects under three conditions: 1) a non-stressed baseline condition at 60 days of age, 2) under conditions of mild stress at 14, 30, 90, 120, and 150 days of age, and 3) under a 4-week long social separation paradigm at roughly six months of age. Data were analyzed using analysis of variance (ANOVA). Where possible, rearing history (mother-reared, peer-reared, or surrogate peer-reared) was included as a factor in the analysis. No significant effects were found for plasma cortisol levels under any of the conditions. For the Day 60 baseline ACTH measure, there was a significant interaction of BW and rearing condition (ANOVA, $F = 2.766$, $p = 0.029$). LBW infants had significantly higher ACTH levels than ABW infants, but only among mother-reared subjects. Under the conditions of mild stress from Day 14 to Day 150, there was a significant interaction of BW and sample day on ACTH levels (mixed-design repeated measures ANOVA, $F = 2.347$, $p = 0.0174$). LBW infants had higher ACTH levels on Day 14 compared to ABW and HBW infants, while on Days 90, 120, and 150, LBW infants had lower ACTH levels. During the 4-week social separation stressor, LBW infants exhibited lower ACTH levels in response to chronic stress compared to both ABW and HBW infants (mixed-design repeated measures ANOVA, $F = 3.757$, $p = 0.0276$). These results suggest that the relationship between low birth weight and HPA-axis function is not clear-cut. Contrary to studies in humans, LBW was not associated with alterations in cortisol levels in young rhesus macaques. Furthermore, effects of LBW on the ACTH response to stress varied depending upon the age of the infant and the type and duration of stress.

51. The Impact of Maternal Deprivation on Brain Corticotropin Releasing Hormone (CRH), CRH Receptor 1, and CRH Binding Protein mRNA in the Limbic System of the Infant Rat

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Sponsor: Huda Akil

The corticotropin releasing hormone (CRH) brain system is viewed as a central coordinator of endocrinological, autonomic, and behavioral responses to stress. Early in life, there is a delicate and critical balance of LHPA activity in the infant rat to maintain low stress hormone levels. From postnatal day 4 to 14, the adrenal response to mild stress is minimal; therefore, this period has been termed the stress-hyporesponsive-period (SHRP). Over the last two decades it has been evident that the neural substrate that orchestrates stress responses in the infant is not completely stress-unresponsive, but rather the response is limited in magnitude, and the appearance of a response at the different levels of the axis is time and stressor specific. Levine and co-workers have altered the developmental pattern of stress responsiveness using prolonged maternal deprivation (MD) during the SHRP. In view of the role of CRH as a neuro-transmitter mediating behavior associated with stress and anxiety, we investigated the maternal deprivation effects on brain regions known to constitute a part of the extrahypothalamic CRH system (i.e. the CRH neurons not directly involved in ACTH secretion). We examined the time course of stress-induced CRH, CRH receptor 1, CRH receptor 2 and CRH binding protein mRNA in structures related to the limbic system (prefrontal cortex, hippocampus, amygdala, septum). We compared non-deprived animals to animals subjected to MD at postnatal days 6, 12, and 18. Restraint was used as the stressor. We find that developmental patterns are observed which are idiosyncratic to the anatomical area examined. In maternally deprived animals, we observed that the temporal response of mRNA levels is also dependent on the anatomical area. In specific regions genomic changes may be rapid and sustained, while in others the initial alteration in gene expression may show recovery to its initial starting point. Our data shows that genomic changes are not always related to maternal deprivation status, in fact MD may enhance, suppress or have no consequence on the underlying ontogenic progression of these CRH related molecules. This data once again challenges the basic assumption of a

stress hyporesponsiveness in the infant rat. Supported by NIH grant HD/DK37431 to DMV and JFL and NIMH grant MH-45006 to SL.

52. Relapse Prevention of Panic Disorder in Adult Outpatient Responders to Venlafaxine XR

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Objective: The primary objective was to compare the long-term safety and efficacy of venlafaxine extended release (XR) with placebo for preventing relapse in outpatients with panic disorder (PD). The secondary objective was to evaluate short-term safety and efficacy of open-label venlafaxine XR in outpatients with PD. Methodology: Outpatients aged ≥18 years, who met DSM-IV criteria for PD (with or without agoraphobia) for ≥3 months before study day 1, who had a score ≥4 on the Clinical Global Impression-Severity (CGI-S) subscale, had ≥6 full-symptom panic attacks in the 2 weeks before the screening visit, had ≥3 full-symptom panic attacks in the 2 weeks prior to baseline, and had a Covi Anxiety Scale score greater than their Raskin Depression Scale score were eligible for the study. Patients who completed the 12-week, open-label treatment phase and met criteria for 'responder' (ie, had ≤1 full-symptom panic attack per week in the last 2 weeks of open-label treatment and a CGI-Improvement [CGI-I] score of 1 or 2) in the last 2 weeks of the open-label phase were randomly assigned to receive either double-blind venlafaxine XR or placebo for up to 6 additional months. The primary endpoint for efficacy analysis was time to relapse during the double-blind phase. Relapse was defined as ≥2 full-symptom panic attacks per week for 2 consecutive weeks as assessed by the Panic and Anticipatory Anxiety Scale (PAAS) or discontinuation from the double-blind phase due to investigator-determined loss of effectiveness from the patient termination record. Secondary efficacy variables included the percentage of patients with no full-symptom panic attacks (PAAS) per 2-week period; Panic Disorder Severity Scale (PDSS) score; number of full-symptom panic attacks per 2-week period; CGI-S; Phobia Scale (PS) fear and avoidance; and anticipatory anxiety. Health outcomes included the Sheehan Disability Index (SDI) and Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Time to relapse was analyzed using Kaplan-Meier survival analysis. Multiple logistic regression was used for rates and proportions. The number of full-symptom panic attacks and mean scores on the PDSS, PS, and CGI-S were analyzed by ANCOVA with baseline as covariate. The CGI-I was analyzed by ANOVA. Final on-therapy analyses are reported. Results: The ITT population had 291 patients in the open-label treatment phase, and 169 patients in the double-blind phase (placebo group = 80, venlafaxine XR group = 89). Mean daily doses of venlafaxine XR ranged from 75.5 to 172.1 and 164.9 to 170.8 mg during the open-label and double-blind phase respectively. Venlafaxine XR prevented relapse significantly better than placebo. The primary efficacy variable and most secondary efficacy variables showed strong statistical separation of venlafaxine XR from placebo with P values ≤0.001 at final on-therapy evaluation. In addition to preventing relapse, the overall efficacy of venlafaxine XR continued in the double-blind phase as evidenced by reduction of panic attack frequency. Improvement in important symptoms of PD, including anticipatory anxiety, fear and avoidance, psychic anxiety, and somatic anxiety were maintained to a greater extent in the venlafaxine XR group than in the placebo group. Improvement was also greater with venlafaxine XR than placebo in the CGI-S, SDI subscales (P<0.001), and 9 of 10 Q-LES-Q subscales. Adverse events for venlafaxine XR were similar to those observed in premarketing studies for depression, GAD, and SAD. Conclusion: In this study, venlafaxine XR was safe, well tolerated, and effective in preventing relapse in patients with PD.

53. Antidepressant Use During Mixed States: Naturalistic Outcome Data from the STEP-1000

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Background: Practice guidelines generally advise against the use of antidepressants to target depressive symptoms during bipolar mixed states. However, there exists little empirical data on the risks versus benefits of antidepressants added to mood stabilizers when depressive symptoms accompany mania. **Method:** From among the first 1000 enrollees in the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), illness parameters and naturalistic treatment outcomes were examined for those who entered in a DSM-IV mixed/cycling state. Initial analyses compared demographic and clinical factors associated with the use or non-use of antidepressants in conjunction with lithium, divalproex, or atypical antipsychotics. Times until achieving a "recovering" or "recovered" clinical status for those taking or not taking antidepressants were compared by Kaplan-Meier analyses with log rank statistics. **Results:** Eighty-seven subjects (8.7%) entered the study in a mixed/cycling state. Upon entry, 47 (54%) were taking antidepressants either with (25 [53%]) or without (22 [47%]) a standard mood stabilizer. No specific clinical factors differentiated patients who did versus did not receive an antidepressant. Log rank tests revealed that the time until reaching a "recovering" or "recovered" status was no different when lithium or divalproex was taken with versus without an antidepressant (p=.125), or when an atypical antipsychotic was taken with versus without an antidepressant (p=.261). **Conclusions:** In this naturalistic dataset, use of antidepressants in conjunction with standard mood stabilizers or with atypical antipsychotics did not appreciably hasten or delay the time until achieving signs of recovery from a mixed manic episode. The findings do not support an advantage for the use of antidepressants when depression accompanies a manic or hypomanic syndrome.

54. Top-Down vs. Bottom-Up Regulation of Frontal Cortical Memory Networks in the Context of Emotion

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Sponsor: ACNP Secretariat

Introduction: Emotion and memory are intimately linked but the mechanisms by which emotional brain circuits affect cognitive circuitry are relatively unexplored. While a top-down hierarchical model has been in favor for many years, it is unclear how this would relate to recent findings of bottom-up activation in cognitive paradigms using emotional stimuli. We hypothesized that these two principals reflect at least in part two different states of brain activity. We developed a neuropsychological paradigm for measuring working memory in the context of varying emotional valences of the memoranda. We hypothesized a bottom-up regulation based on memory parsed by emotional valence, and a top-down regulation during the 'resting state' reflected in functional connectivity between processing circuits. **Methods:** Eighty-two normal volunteers performed two cognitive tasks, a labeling task and a two-back working memory task, within an event-related fMRI design. For both tasks, the stimuli were photographs of positive, neutral, and negative valence chosen and carefully matched from the IAPS. Brain activations were then compared via a 4-way ANOVA, with task, valence, and gender as fixed factors, and subjects as random factor. 'Resting-state' connectivity was measured after removing these effects. The following reference regions were defined and a time series averaged within these regions: amygdala, hippocampus, DLPFC,

subgenual cingulate, medial prefrontal cortex. One-sample t-tests were used to detect differences from baseline. All statistics are corrected for multiple comparisons for the whole brain. A significance level of $p<0.05$ was then applied. **Results:** As hypothesized, emotional stimuli, which activated limbic regions such as bilateral amygdalae (less for pleasant than unpleasant stimuli) and hippocampus, showed a significantly higher activation during the 2-back task in bilateral dorsolateral prefrontal regions adjacent to BA 46/9, indicating a bottom-up regulation of neural activity fundamental to working memory. Also in accordance with our hypothesis we found that during the resting condition the BOLD signal within several frontal regions such as DLPFC, medial PFC and subgenual cingulate was negatively correlated with deeper limbic structures such as hippocampus, parahippocampal gyrus and amygdalae indicating a top-down regulation. **Conclusion:** Our results support the conclusion that top-down regulation by frontal cortical areas of limbic structures such as hippocampus, amygdalae and parhippocampal gyrus might reflect an inhibitory control of these structures in the absence of emotion-laden stimuli. However, this top-down regulation principle can be disrupted and inverted in the presence of emotion-laden stimuli mediated by limbic structures such as hippocampus and amygdala. These data provide insights into the mechanisms of emotional modulation of cognitive processes. Damasio, A.R. Descartes' error : emotion, reason, and the human brain, (G.P. Putnam, New York, 1994). Dolan, R.J. Emotion, cognition, and behavior. Science 298, 1191-4 (2002). Gray, J.R., Braver, T.S. & Raichle, M.E. Integration of emotion and cognition in the lateral prefrontal cortex. Proc Natl Acad Sci U S A 99, 4115-20 (2002). Perlstein, W.M., Elbert, T. & Stenger, V.A. Dissociation in human prefrontal cortex of affective influences on working memory-related activity. Proc Natl Acad Sci U S A 99, 1736-41 (2002). Phillips, M.L., Drevets, W.C., Rauch, S.L. & Lane, R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. Biol Psychiatry 54, 504-14 (2003).

55. The Effect of Cognitive Behavioral Therapy on Brain Imaging and Neuroendocrine Responses in Patients with Panic Disorder

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Background: Preclinical research has demonstrated that the amygdala is a crucial brain structure for the acquisition and expression of conditioned fear. Using this lead, a number of investigators have employed several different brain imaging methods to show that amygdala activation commonly occurs during the induction of fear and anxiety in humans. Some studies suggest that the threshold for amygdala activation is lower in patients with anxiety disorder. An increasing number of preclinical studies have also now shown that areas within the prefrontal cortex exert control over the amygdala. Neuroimaging data also indicate that this is the case in humans and that one feature of patients with anxiety disorder is an alteration in activity of prefrontal cortical areas, including the anterior cingulate and the orbitofrontal cortex (OFC). In a positron emission tomography (PET) study using ^{15}O-H20, we found that immediately prior to the administration of the respiratory stimulant doxapram, which reliably produces panic attacks in patients with panic disorder but not normal controls, subjects who subsequently panicked after doxapram administration showed marked reduction in OFC activity. This finding led us to consider the need to further study the relationship between the amygdala and prefrontal cortex in patients with panic disorder. The substantial vasoconstriction caused by doxapram-induced hyperventilation made it impossible to image amygdala activation during the actual panic attack, however. Therefore, we have adapted ^{18}fluorodeoxyglucose (FDG) PET to doxapram administration and shown in a pilot study that by measuring metabolic rate instead of blood flow we are able to image the amygdala and OFC during panic attacks. We found differences between panic patients and normal comparison subjects in amygdala and OFC response to anticipation of panic and to doxapram-induced panic and that cognitive behavioral therapy (CBT) normalized the patients' OFC response. **Methods:** Four panic patients and three normal control subjects underwent baseline PET imaging first with placebo injection and second with doxapram injection to induce a panic attack. The same sequence was repeated after treatment with CBT for 12 weeks in patients and after 12 weeks for controls. Measures including the Acute Panic Inventory (API), Borg Scale of Exertion (a measure of dyspnea), and the 10-point Anxiety Scale and data from both sets of PET scans were collected. Salivary cortisol was measured, as were heart rate and respiration using a continuous recording device. **Results:** All patients showed improved prefrontal panic inhibition during doxapram injection on repeat PET scan, and decreases in Borg, API and Anxiety Scale scores compared to baseline. After treatment, cortisol levels, heart rate, and respiration were all reduced in panic patients. **Conclusion:** This small pilot study shows that CBT normalized brain activity (prefrontal cortex, amygdala), autonomic and hormonal responses to panic, and lowered scores on anxiety scales.

56. Analysis of Ingestion and Activity Patterns Exhibited by Sixteen Inbred Strains of Mice Reveals Distinct Behavioral Groups

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Sponsor: Past Travel Awardee Memorial, 2002

The regulation of ingestion and activity are essential to the survival of animals. This regulation produces a temporal pattern of ingestion and activity that represents an adaptation of animals to their habitat. The classically derived inbred mouse strains are derived largely from two sub-species of mice from distinct regions of the world and thus from potentially distinct habitats. As a result, it is possible that these sub-species of mice may have distinct temporal patterns of ingestion and activity. To investigate this possibility, continuous home cage behavioral monitoring of ingestion and activity was performed with mice from two wild derived inbred strains (CZECH and WSB) originating from these two sub-species. In addition, a survey of ingestion and activity patterns was performed with fourteen additional inbred strains of mice. A technique was developed to classify the behavior of the mice into active states characterized by bouts of feeding, drinking, and locomotion and inactive states characterized by prolonged immobility at the nest. The temporal patterns of these states exhibit clear differences between the two sub-species. In addition, clustering of the inbred strains based on the temporal patterns of their active states reveals that many of the inbred strains can be grouped based on their similarity to one of the wild derived inbred strains. New approaches to the quantitative description of behavioral patterns exhibited by mice in their home cages thus provides a means to identify genes involved in the regulation of ingestion and activity.

57. Thyroid Hormone Metabolites and Depression - A New Twist on an Old Tale

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One of the most consistent findings in individuals with severe hypothyroidism is depression. Furthermore, it has been well documented that the administration of thyroid hormone (TH) in the form of T3 can significantly hasten the responsiveness of many, but not all, depressed individuals undergoing tricyclic antidepressant

therapy. The underlying mechanism of this potentiation remains to be elucidated. Other physiological manifestations of depression that may also have a TH component include thermoregulatory disturbances, decreased metabolic rate, decreased cardiorespiratory fitness, inactivity, and hyperglycemia. Recently we discovered 3-iodothyronamine (T1AM), a novel endogenous metabolite of TH (Scanlan et al. nature medicine 10: 638; 2004) that is a potent agonist of rodent G protein-coupled trace amine receptors heterologously expressed in HEK cells. We have begun to explore the actions of this molecule in wild-type C57Bl/6J mice and have found that in addition to profoundly interfering with the ability of a mouse to thermoregulate and maintain normal cardiovascular tone at room temperature, locomotor activity and metabolic rate are significantly depressed while blood sugar is significantly elevated. This spectrum of in vivo responses suggests that further study of T1AM and related compounds in rodent models of depression is warranted. Supported by MH67497 & DA107803 (DKG) and DK52798 (TSS).

58. A Novel Approach to Measuring Onset of Efficacy of Duloxetine in Mood and Painful Symptoms of Depression

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Sponsor: Barry Blackwell

Background: Interactive Voice Response (IVR) technology enables computer-based processing and retrieval of information through touchtone telephones. IVR systems have been developed for a range of clinical applications, including screening for axis I psychiatric disorders and monitoring patients recovering from alcohol dependence. Using the telephone to gather patient responses, IVR systems can efficiently and reliably collect data at greater frequencies than weekly office visits. Duloxetine, a dual-reuptake inhibitor of serotonin and norepinephrine, has demonstrated significant improvement in traditionally recognized symptoms of depression and has shown efficacy in treating painful physical symptoms in patients with MDD. In previous studies, duloxetine demonstrated significant differences from placebo on self-reported measures of depression, pain, and global functioning by the end of one week of treatment. As the first data collection in these studies occurred after seven days of treatment, the exact timing of onset of these improvements was unknown. The current study examined the tolerability and efficacy within the first week of treatment of two starting doses of duloxetine (30 mg QD and 60 mg QD) in currently untreated patients meeting DSM-IV criteria for MDD with an entry HAM-D17 rating >/=15 and CGI >/=4 as part of an open-label trial. It was hypothesized that during the first week of treatment, patients starting duloxetine at 30 mg QD would report fewer adverse events, but patients starting duloxetine at 60mg QD would show greater improvements in emotional and painful physical symptom ratings. **Methods:** For the first week of treatment, patients were randomized to begin duloxetine at either 30 (n=67) or 60 (n=70) mg QD. Daily, patients called an IVR system that administered an adapted Visual Analog Scale (VAS) for pain (0-10 score) and the Patient Global Impression of Improvement (PGI-I). Safety and tolerability were measured at the site by reports of adverse events, and by blood pressure and pulse recordings during scheduled office visits. **Results:** Compared to patients started at duloxetine 30 mg, patients started at 60 mg reported their first observed significantly greater improvement in shoulder pain (p=.008) and back pain (p =.01) by day one, pain while awake by day three (p=.03), global emotional improvement by day five (p=.03), and global physical improvement by day seven (p=.04). Although significantly more patients receiving a 60 mg starting dose reported nausea in the first week of treatment than patients receiving duloxetine 30 mg (p=.03), there were no significant differences between the groups in discontinuation due to nausea or any other adverse event within the first week. Moreover, the groups did not significantly differ on mean changes in pulse, blood pressure, weight, or any other reported adverse event. **Conclusions:** In this study, a starting dose of 60 mg QD of duloxetine demonstrated onset of efficacy in both emotional and physical symptoms of MDD, within one week of treatment, with improvement significantly superior to a 30 mg QD starting dose beginning as early as day one after initiation of treatment. Daily IVR made evident the immediacy of onset of action not measurable with standard assessment methods in previous studies. The 30 mg starting dose of duloxetine was shown to produce less nausea, suggesting greater initial tolerability. Using daily IVR, this study provided previously unknown data about early symptom improvement and initial dosing tolerability of duloxetine that may enable clinicians to make more educated decisions about treatment.

59. The Longitudinal Associations Between Panic and Asthma. The Zurich Cohort Study

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Sponsor: Jules Angst

Context: Cross-sectional studies have consistently shown that panic and asthma co-occur more frequently than expected by chance. Longitudinal studies are required to increase our understanding of the temporal association and potentially causal mechanisms relating panic to asthma. **Objective:** To examine longitudinal associations between panic and asthma in young adults. Design and Subjects: Prospective community-based cohort study of young adults (N=591) followed between ages 19/20 and 40/41. Information was derived from six subsequent semi-structured diagnostic interviews conducted by professionals over twenty years. Main Outcome Measures: Repeated panic attacks, panic disorder, and asthma disease activity. Longitudinal associations between cumulative exposure variables and lagged outcome variables were estimated by robust estimates of repeated measures by generalized estimating equations (GEE). **Results:** Combining the data from all 6 interviews, asthma was more strongly associated with panic disorder (OR = 4.0 [95% CI 1.7, 9.3]) than with any panic, which included both panic disorder and panic attacks (OR = 2.1 [1.1, 4.5]). Longitudinally, after adjusting for potentially confounding variables, the presence of panic disorder predicted subsequent asthma activity (OR = 6.3 [95% CI 2.8, 14.0], and active asthma predicted subsequent panic disorder (OR = 6.3 [1.9, 20.9]). Associations were stronger in females than in males, and smoking was found to be an important mediator of the asthma-panic comorbidity. Among the confounding variables, pre-school onset anxiety was consistently associated with adult asthma suggesting the involvement of additional shared etiologic factors. **Conclusion:** This is the first long-term follow-up study on panic and asthma. The severity of panic appeared to be an important determinant of the strength of the panic-asthma relationship. Showing longitudinal associations between panic and asthma might have important clinical implications.

60. Proton Magnetic Resonance Spectroscopy of the Prefrontal Cortex in Remitted Depressed Patients

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Sponsor: Dennis Charney

Context: Recent magnetic resonance spectroscopy studies have found reduced gamma-aminobutyric acid (GABA) levels and altered

glutamate/glutamine (Glx) levels in the occipital cortex of symptomatic patients with major depression. **Objective:** To investigate whether altered GABA levels in the prefrontal cortex represent a trait characteristic of MDD, GABA levels in the prefrontal cortex were determined in unmedicated remitted subjects with MDD (rMDD) and controls. Design and Subjects: Sixteen rMDD subjects and fourteen healthy controls underwent 3 Tesla proton magnetic resonance spectroscopy. Main Outcome Measures: GABA levels were measured in the ventromedial prefrontal and dorsolateral/anterior medial prefrontal cortex. **Results:** There was no difference in prefrontal GABA levels between rMDD subjects and healthy controls in the ventromedial prefrontal and dorsolateral/anterior medial prefrontal cortex. Secondary analyses revealed a negative relationship between the Glx/GABA ratio and age of onset of MDD in the ventromedial prefrontal cortex ($r=-0.65$, $p<0.01$). **Conclusion:** This result suggests that GABA concentrations in the prefrontal cortex are not altered in remitted depressed subjects. Further research is needed to determine brain GABA levels in different brain regions, in different stages of depressive illness and in different depressive subtypes.

61. Duloxetine at Doses of 60 mg Once Daily and 60 mg Twice Daily is Effective in Treatment of Diabetic Neuropathic Pain

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Sponsor: David T. Wong

Objective: Serotonin (5-HT) and norepinephrine (NE) are involved in pain modulation via descending inhibitory pathways in the brain and spinal cord. This study assessed the efficacy of duloxetine, a potent, selective, and balanced inhibitor of 5-HT and NE reuptake, on the reduction of pain severity, in patients with diabetic neuropathic pain (DNP). **Methods:** Patients with DNP and without comorbid depression were randomized to treatment with duloxetine 60 mg QD, 60 mg BID, or placebo for 12 weeks. The primary outcome measure was the weekly mean score of 24-hour average pain severity on the 11-point Likert scale. Secondary measures included night and 24-hour worst pain severity, Brief Pain Inventory (BPI), Clinical Global Impression of Severity (CGI-Severity), Patient Global Impression of Improvement (PGI-Improvement), Short-form McGill Pain Questionnaire, Dynamic Allodynia, and Average Daily Intake of Acetaminophen. **Results:** Duloxetine 60 mg QD and 60 mg BID demonstrated significant improvement in the treatment of DNP and showed rapid onset of action, with separation from placebo occurring at week one on the 24-hour average pain severity score. For all secondary measures for pain (except allodynia), mean changes showed superiority of duloxetine over placebo, with no significant difference between 60 mg QD and 60 mg BID. Reduction in 24-hour average pain severity was caused by direct treatment effect. CGI and PGI evaluation also demonstrated greater improvement on duloxetine- versus placebo-treated patients. Duloxetine showed no notable interference on diabetic control, and both doses were safely administered and well tolerated. **Conclusion:** This study confirms previous findings that duloxetine at 60 mg QD and 60 mg BID is safe and effective in treating DNP.

62. Collection of Traumatic and Stressful Life Events in an Urban Low-Income African-American Population

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Sponsor: Past Travel Awardee, Aventis, 2003

Traumatic and stressful life events, which can contribute to causation or exacerbation of mental health disorders, are common in urban low-income, mostly African American populations. This population may be vulnerable to traumatic or stressful life events related to socioeconomic status. Although research efforts have been made in collecting this data, the full range of traumatic or stressful events is not always explored. The impact of multiple stressful events at once is often difficult to assess using existing standard measures. For example, one may experience lack of adequate resources for providing proper nutrition, while at the same time suddenly have to take care of an orphaned or disabled family member. Because it is often a transient population, experiencing multiple stressful life events at once, or similar traumatic events repeatedly, there are difficulties in gathering a complete record of traumatic and stressful life events over a lifetime. It would be helpful to superimpose the occurrence of stressful life events with the occurrence of Post Traumatic Stress Disorder or Major Depressive disorder symptoms. Therefore, in order to thoroughly study the impact of these life events on mental health, research methods must be developed to accurately gather chronologies of traumatic or stressful life events on urban low-income, African American populations. We are piloting one approach to gathering such data in an ecologically-valid manner. This approach involves interviews anchored by a life history calendar. Specific, idiosyncratic traumatic and stressful life events, salient for that person and place, will be superimposed onto that person's calendar. Episodes of Major depressive disorder and Post traumatic stress disorder will be added to the life history calendar to allow a longitudinal view of the subject's traumatic and stressful life events as they relate to episodes of depression and PTSD. This poster will present an outline of the method currently being used in a pilot study, as well as the initial results of how effective the method is, a description of potential modifications, and further implications for clinical use.

63. Quetiapine and Citalopram in the Treatment of Psychotic Depression

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Sponsor: ACNP Secretariat

Purpose The objective of this study was to investigate the efficacy and safety of quetiapine in combination with citalopram in patients with psychotic depression. **Methods** In this open, multicenter study, adult patients with an ICD-10/DSM-IV diagnosis of psychotic depression (unipolar or bipolar) receiving citalopram treatment (20 to 60 mg/d) were administered quetiapine (50 to 750 mg/d, BID) for 6 weeks. The recommended dosing administration for quetiapine was 50mg on Day 1, 100 mg on Day 2, 150 mg on Day 3, 200 mg on Day 4 and up to 750 mg/d from Day 5 onward. The primary efficacy measure was change from baseline to Week 6 in Hamilton Depression Rating Scale (HAM-D-21) scores. Secondary efficacy measures were changed from baseline to Week 6 in Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI) Scale scores. Safety measures included spontaneously reported adverse events (AEs), clinical laboratory data, physical exams, and vital signs. Extrapyramidal symptom (EPS)-related AEs were measured by the Simpson-Angus Scale (SAS) and the other side effects with the Udvalg for Kliniske Undersogelser (UKU) side effects rating scale. All assessments were carried out at baseline and Weeks 2, 4, and 6. **Results** Twenty-five patients were enrolled in the study, 1 patient discontinued due to a misdiagnosis (ITT population consisted of 24 patients). Three patients withdrew from the study due to treatment-related AEs and 1 patient due to relocation. The average age was 51.4 years and baseline weight was 72.6 kg. The majority of patients (79%) had a diagnosis of recurrent depressive disorder, current episode severe with psychotic symptoms (F33.3). Twenty-one percent were diagnosed

with a severe depressive episode with psychotic symptoms (F32.3)- Patients received a mean dose of 303+/-118 mg/d quetiapine and 34+/-12 mg/d citalopram during the study. Combination treatment with citalopram and quetiapine over 6 weeks was associated with a highly significant improvement in HAM-D scores from baseline (31.21+/-5.18) to Week 2 (21.04+/-7.76), Week 4(14.88+/-9.94), and Week 6 (13.25+/-10.87) (all P<0.05). A significant improvement of psychotic symptoms was also observed, as measured by the decrease from baseline (59.25+/-6.6) to Week 6 (30.65+/-11.55) in BPRS scores (P<0.001). Clinical improvement of symptoms was confirmed by the significant difference in CGI scores from baseline to Week 6. Twelve (48%) patients experienced at least 1 AE but none were severe. Liver and biliary system disorders were reported in 3 patients and were the most frequently reported AEs. The mean change in body weight from baseline to Week 6 was +2.0 kg (NS). There was a non-significant decrease in EPS from baseline (1.44+/-2.97) to endpoint (1.40+/-3.69) (P=0.979). Both baseline serum prolactin levels and UKU side effects scores normalized by the end of the study. **Conclusions** Quetiapine in combination with citalopram is effective and well tolerated in the treatment of psychotic depression, in both unipolar and bipolar depressed patients. Larger, controlled studies to confirm these findings are warranted.

64. Comparing the Efficacy of Venlafaxine XR and Fluoxetine for Acute, Continuation, and Maintenance Therapy in Recurrent Unipolar Major Depression

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Background/Objectives: Reliance on modern antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine XR for acute, continuation, and maintenance therapy of unipolar major depression underscores the urgent clinical relevance of data on long-term efficacy and safety. This study compared the efficacy and safety of venlafaxine XR and the SSRI fluoxetine in acute, continuation, and maintenance therapy in patients with recurrent unipolar major depression (RMD). **Methods:** In this 3-phase, large multicenter, double blind study, outpatients with RMD were randomly assigned to receive venlafaxine XR (75-300 mg/day; n=821) or fluoxetine (20-60 mg/day; n=275). After a 10-week acute treatment phase, responders entered a 6-month continuation phase of therapy with venlafaxine (n=530) or fluoxetine (n=185). Patients still responding at the end of the continuation phase entered the first of two consecutive 12-month periods composing the maintenance phase of the study. At the start of each of the maintenance periods, the venlafaxine XR responders were randomly assigned to receive double-blind treatment with venlafaxine XR or placebo and the fluoxetine responders were continued on the SSRI. Data from the acute treatment and continuation phases of the study are now presented. **Results:** In the acute treatment phase, rates of end point remission (HAM-D_{17} ≤7) and response (HAM-D_{17} ≤12 or ≥50% decrease from baseline score) were 49% and 79% for venlafaxine XR and 50% and 79% for fluoxetine, respectively (P=NS). In the continuation phase, remission and response rates were 72% and 90% for venlafaxine XR and 69% and 92% for fluoxetine, respectively (P=NS). Rates of discontinuation due to adverse events were comparable for both treatment groups. **Conclusion:** Both venlafaxine XR and fluoxetine were efficacious in producing and maintaining therapeutic response in depressed patients during acute and continuation therapy. Although well powered, the study was limited by the absence of a placebo control during the acute treatment and continuation phases of the study for venlafaxine XR and throughout the study for fluoxetine.

65. Sequence Variants in the NTRK2 Gene Predict Response to Lithium in Bipolar Disorder

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Bipolar patients display robust differences in response to different mood stabilizers. Several clinical features, such as positive family history, absence of rapid cycling and absence of dysphoric mania, have been shown to be associated with lithium response. It is also likely that genetic variation explains a substantial portion of the variation in response. DNA markers that could predict response to lithium would be of great clinical utility in matching patients to the most efficacious medication. To date, however, few molecular studies have addressed this issue. Previous studies have associated two genes with lithium response: the serotonin transporter (HTT) and inositol polyphosphatase 1 (INPP1). We identified 92 lithium responders and 92 non-responders from retrospective data on bipolar patients ascertained primarily for genetic linkage studies. Data from SCID interview, medical records and family informants were used to construct a lifechart, and lithium response was assessed by consensus review. These data were also used to assess several clinical variables related to course of illness. 88 markers were then genotyped in 9 genes in pathways hypothesized to be related to lithium's mechanism of action. Consistent with previous literature, dysphoric mania (p=0.001) and rapid cycling (p=0.017), were associated with poor response to lithium. Co-morbid PTSD was associated with poor response (p=0.029). The age of first symptoms was also significantly lower in non-responders (p=0.048). Genetic polymorphisms were analyzed using chi square analysis, and COCAPHASE (Dudbridge 2003). Contrary to previous reports, neither the promoter repeat in HTT (HTTLPR), nor SNPs in INPP1 were associated with response. Four SNPs in three genes were nominally significant (IMPA1, IMPA2, NTRK2). A SNP in the 3'UTR of the NTRK2 gene showed the strongest association (p=0.006). This association derived almost entirely from patients with euphoric mania (p=0.0005) and was unassociated in patients with primarily dysphoric mania. This result was also significant using a 2 SNP sliding haplotype window (p=0.0027), and when corrected for the number of SNPs examined in the NTRK2 gene (p=0.03). NTRK2 (tropomyosin receptor kinase 2, also TRKb) protein product is the receptor for two neurotrophins: brain derived neurotrophic factor (BDNF) and neurotrophin 4/5 (NT 4/5). Lithium has been shown to induce BDNF and activate NTRK2 possible as part of its neuroprotective role (Hashimoto 2002). BDNF has been associated with risk for bipolar disorder (Sklar 2002). Our data not only support the role of the BDNF/TRKb system in the mechanism of action of lithium, but also suggest that variation in the NTRK2 gene may influence response to lithium.

66. Differences in Sexual Dysfunction between Men and Women with Depression: A Comparison Before and After Treatment with Bupropion and Paroxetine

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Sponsor: James Kennedy

Sexual dysfunction is commmonly associated with Major Depressive Disorder (MDD) and may also be caused or exacerbated by various medications. The primary purpose of this study was to compare the effects on sexual functioning of bupropion sustained (SR) and paroxetine in depressed men and women before and over the course of an 8-week trial. A secondary purpose was to compare antidepressant effectiveness between bupropion SR and paroxetine. **Methods:** In this multicentre, double-blind study, patients with DSM-IV Major Depression (N=141, 73 males, 68 females) were ran-

domly assigned to a flexible dosing of bupropion SR (150-399mg/day) or paroxetine (20-40mg/day). Patients were assessed at baseline and after 2, 4, 6 and 8 weeks using the 17-item Hamilton Rating Scale for Depression (HAMD17), the Sex Effects scale for sexual dysfunction in males and females (Sex FX M/F) and the Investigator Rated Sexual Desire/Functioning assessment (IRSD/F). **Results:** Bupropion SR and paroxetine were equally effective in the treatment of depressive symptoms. Women had significantly higher levels of sexual dysfunction than menat baseline. Bupropion SR did not significantly alter sexual dysfunction scores in men or women. In contrast, there was an increase in SD overtime in men treated with paroxetine. **Conclusion:** Sexual dysfunction differentially effects depressed ment and women both before and during antidepressant treatment. While women consistently reported higher levels of sexual dsyfunction, antidepressant-induced or exacerbated sexual dysfunction was only apparent in males treated with paroxetine. Bupropion SR did not significantly alter sexual dysfunction in men or women. Results for Sex FX correlated highly with IRSD/F assessments.

67. Gender Differences in SSRI Antidepressant Response Among Outpatients Participating in Antidepressant Clinical Trials

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Sponsor: Walter Brown

Previous reports have yielded mixed results regarding gender differences in antidepressant treatment response. Much of the literature compares men and womens response to tricyclics to that of newer antidepressants (SSRIs, venlafaxine) or only examines one particular antidepressant. The purpose of this study was to further examine the differences between men and womens response to eight newer antidepressants. We also investigated whether the disparity in men and womens weight coupled with treatment dosage may contribute to gender differences in antidepressant response. A total of 15 randomized, placebo-controlled trials that included 323 depressed patients were examined for gender differences in antidepressant treatment response. The magnitude of change with SSRIs compared to placebo was approximately 605% larger among women than men, although the magnitude of response to SSRIs compared to placebo was robust among men also. Such a pattern was not discernable for venlafaxine. There were no differences in dose of SSRIs or venlafaxine, based on weight among men and women. These findings suggest that mechanism of action of SSRIs may be different from other antidepressants. It is possible that the serotonergic system may be more sensitive to SSRI effects among women compared to men.

68. Stress-Related Changes in GABAergic Inhibitory Inputs to the Dorsal Raphe Nucleus

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Sponsor: Sheryl Beck

Stress regulates the serotonin (5-hydroxytryptamine; 5-HT) system in a complex manner. Some of the effects of stress may be mediated through regulation of GABAergic neurotransmission in the raphe nuclei. We examined GABAergic function in the dorsal raphe nucleus (DRN) using a combination of electrophysiological, immunohistochemical and molecular techniques. Visualized whole-cell recording techniques were used to measure spontaneous and miniature (TTX-sensitive) GABA IPSCs in the DRN slice preparation. Amplified antisense RNA techniques were used to measure $GABA_A$ receptor subunit composition within the DRN. Both GABA physiology and receptor subunit composition were compared between the stress hyperresponsive Wistar-Kyoto (WKY) rat strain and controls. Finally, the IPSC response to bath application of the stress neurohormone corticotropin-releasing factor (CRF) was compared in the two rat strains. Immunohistochemistry was used following electrophysiology experiments to determine the neurochemical identity of the recorded cells as 5-HT or non-5-HT containing. 5-HT DRN neurons from WKY rats had significantly shorter IPSC decay times than controls, indicating a change in postsynaptic $GABA_A$ receptor-ionophore kinetics. This electrophysiological change was coupled with an increase in gamma subunits of $GABA_A$ receptors in the DRN from WKY rats compared to controls. Within the control group, IPSC frequency and amplitude were slightly reduced and IPSC decay time significantly elevated in 5-HT compared to non-5-HT DRN neurons, indicating potential differences in both presynaptic GABA release and postsynaptic $GABA_A$ receptor sensitivity and kinetics. Preliminary results also indicate a differential IPSC response to CRF: CRF produced a small increase in IPSC frequency selectively in 5-HT DRN neurons. Since our laboratory has previously shown an inhibitory effect of CRF on 5-HT DRN neurons *in vivo*, these data indicate that this effect may be indirect, mediated by an increase in GABA release. Interestingly, 5-HT DRN neurons from WKY rats did not show an IPSC response to CRF, indicating a potential desensitization of CRF receptors of the DRN in this strain know to have altered hypothalamo-pituitary adrenal axis activity under both basal and stress conditions. Taken together, these data indicate that stress regulates different aspects of GABA neurotransmission within the DRN, an effect with potential consequences for 5-HT neuronal excitability and 5-HT release in forebrain targets.

69. Escitalopram Treatment of Dysthymic Disorder

James Kocsis

Abstract Not Available

70. Safety of Sertraline in Childhood Depression and Obsessive-Compulsive Disorder

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Sponsor: John March

Objective: To evaluate the overall safety of sertraline as a treatment of major depression (MDD) and obsessive-compulsive disorder (OCD) in children ages 6-18. **Method:** Safety data was analyzed from 3 placebo-controlled trials of sertraline in MDD and OCD (total N=560). The NNTH [+95%-CI] was calculated to provide an estimate of the number needed to treat before a drug-specific adverse event could be expected to occur. **Results:** Discontinuation due to adverse events occurred on sertraline at a rate of 9.6% [95%CI: 6.4-13.7] and on placebo at a rate of 2.2% [0.8-4.6], with an NNTH of 13. Serious adverse events occurred on sertraline at a rate of 3.2% [1.5-6.0] and on placebo at a rate of 2.2% [0.8-4.6], with an NNTH of 95. No suicides occurred in this program, while suicide attempts occurred at a rate of 0.71% vs 0.72% (NNTH not calculable). Suicidal ideation occurred on sertraline at a rate of 1.1% [0.2-3.1] and on placebo at a rate of 0.4% [0.01-2.0], with an NNTH of 141. **Conclusions:** Treatment with sertraline was associated with high NNTH values, especially for serious adverse events, indicating a large margin of safety in the treatment of childhood MDD and OCD.

71. Cognitive Function In Middle-Aged And Older Depressed Adults With Type-2 Diabetes

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Objective: Diabetes mellitus is a common metabolic disorder characterized by glycemic dyscontrol and microvascular disease, two

mechanisms that are associated with neuronal compromise. Both cognitive abnormalities and depression have been identified in patients with diabetes, though the mechanisms contributing to these behavioral changes are poorly understood. The aim of the study was to examine the relationship between major depression and cognitive functioning among middle- and older-aged adults with Type-2 diabetes. **Method:** Cognitive profiles were compared between 17 Type-2 diabetics with major depression, 20 non-depressed Type-2 diabetics and 29 non-depressed/non-diabetic controls. Diabetics were recruited from diabetes clinics in Los Angeles and were matched on age and gender to non-diabetics recruited from the community. Participants were screened for dementia, other CNS diseases, other Axis I disorders, and medications believed to produce depression. All depressed patients met DSM criteria for major depression and had Hamilton depression scores of 15 or greater on the 17 item scale. Mean age was 59 for depressed and non-depressed diabetics, and 62 for non-diabetics. Mean education for the entire sample was 15 years; most were women. The neurocognitive battery included measures of attention/information processing speed, verbal memory, and executive functioning. Individual test scores were combined to create specific cognitive domains that were compared across groups. **Results:** Using standardized scores, composite variables were created for each domain, with overall reliability ranging from α = .78-.94. A MANOVA, which assessed between-group differences was significant (F=2.16 (6,120), p=.05). Individual ANOVA's revealed differences in attention/information processing and executive functioning. Depressed and non-depressed diabetics demonstrated greater executive dysfunction than controls, specifically working memory (p=.005). Depressed diabetics also had poorer performances in attention/information processing than both non-depressed diabetics and controls (p<.05). **Conclusions:** Type-2 diabetics – depressed and non-depressed — had poorer cognitive functioning relative to controls. Depression resulted in additional cognitive impairments, beyond that caused by diabetes alone. Glycemic dyscontrol and microvascular disease might compromise specific circuits thereby leading to both cognitive and mood changes in patients with diabetes. These findings have implications for neuronal circuitry and the neurobiology of mood disorders.

72. The Schizophrenias are Severe Mood Disorders with Psychotic Features

Raymond Lake

Abstract Not Available

73. Methylphenidate Enhanced Antidepressant Response in Geriatric Depression

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Sponsor: Gary Small

Background: Accelerated treatment response may be particularly beneficial in elderly depressed patients prone to increased frailty and suicide. Different treatment strategies of depression in these patients may be warranted. There is presently a lack of prospective controlled augmentation antidepressant trials in elderly depressed patients. **Objectives:** The main goal of the 10-week randomized, double-blind, placebo-controlled clinical trial of a low-dose mehylphenidate (MPH) augmentation of citalopram, is to determine whether the addition of low-dose MPH to citalopram would increase efficacy and decrease the time to antidepressant response in the depressed elderly. **Methods:** We recruited 19 elderly outpatients (9 women, mean age=74.13 years) diagnosed with major depression. Three women changed their minds prior to randomization and 16 were treated with citalopram in an open-label fashion and were randomized to receive MPH (n=10) or placebo (n=6) for 10 weeks. We followed all patients up to 4 months following discontinuation of MPH or placebo. Response was defined as HAM-D< 10. We compared the treatment groups with regard to the number of responders; improvement in depression at weeks 3 and 8; improvement in functioning and cognition; early relapse; and the number of dropouts. Repeated measures ANOVA and Chi-square analyses were used. **Results:** Thirteen patients (7 on MPH) completed 3 weeks and 12 patients (6 on MPH) completed 8 weeks. Four subjects in the MPH group dropped out, three due to side-effects. The mean dose of citalopram did not differ between the groups at weeks 3 and 8 and ranged from 20 to 40 mg. The mean dose of MPH at week 3 was 10.6 (5.3) mg and at week 8, 8.3 (7.5) mg. Five of 9 subjects on MPH responded at week 3 and none of 6 subjects receiving placebo responded (C2=5.0; df=1; p=0.04). At week 8, 4 of 6 patients on MPH and 2 of 6 on placebo responded (C2=3.1; df=1; p=0.1). In the repeated measures ANOVA, the MPH group showed a significant improvement over the course of treatment compared to those on CIT+PBO (F=8.5; df=1,5; p=0.03). At week 8, MPH group had greater improvement in anxiety, apathy, psychomotor slowing, energy, emotional well-being. Side-effects responsible for dropouts included anxiety, nausea, and urinary hesitancy. Two of 4 (50%) MPH responders experienced early relapse within 4 month, after MPH was discontinued. **Conclusions:** Combined treatment with MPH resulted in accelerated and enhanced antidepressant response compared to those on placebo. In addition, a greater improvement in other functional outcomes was observed in the patients receiving MPH compared to those on placebo.

74. Functional Neuroanatomy of Sertaline and Placebo Effects in PTSD: A fMRI Investigation

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Sponsor: Past Travel Awardee, ADAA, 2003

Objective: The goal of this study was to characterize functional brain correlates of placebo and sertraline effects in Posttraumatic Stress Disorder (PTSD) using functional magnetic resonance imaging (fMRI). **Method:** 4.0 Tesla fMRI was used to assess brain activation patterns during script-driven symptom provocation in traumatized subjects with PTSD before and after eight weeks of treatment with either sertraline or placebo. Subjects were randomly assigned and assessed with a full battery at pre- and post-treatment, including the Clinician-Administered PTSD Scale (CAPS). **Results:** Significant differences in brain activations in response to trauma scripts were found in PTSD subjects after eight weeks of treatment with sertraline. After successful treatment with sertraline, PTSD subjects showed increased activation in the inferior prefrontal cortex (BA 9 and 47) and the superior and middle temporal gyri (BA 21 and 38). Significant differences in brain activations in response to trauma scripts were also found in PTSD subjects after placebo response. However, some of these brain activation patterns were different from the changes observed after successful treatment with sertraline, that is, PTSD subjects showed increased activation in the anterior cingulate gyrus (BA 24 and 32), the medial prefrontal cortex (BA 11), the insula (BA 13), and the inferior prefrontal cortex (BA 47). **Conclusions:** In this preliminary fMRI study, PTSD patients responding to sertraline and placebo exhibited changes in brain activations to script-driven imagery that were overlapping (BA 47) and divergent (e.g., BA 11, BA 13, BA 24, BA 32). To date there are no published studies on function neural correlates of successful PTSD treatment. Our placebo response findings are partially consistent with those of Mayberg et al's (2002) functional neuroimaging study of the placebo effect in a sample of depressed patients. These results are consistent with changes in dysfunctional corticolimbic circuitry resulting from successful treatment by either modality.

75. Paroxetine-induced Changes in Levels of Plasma Nitric Oxide Metabolites and Platelet Nitric Oxide Synthase Activity in Subjects with Major Depressive Disorder Compared to Healthy Controls

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Sponsor: Past Travel Awardee, ADAA, 2001

Objective: Major depression (MD) and cardiovascular disease (CVD) have been conclusively linked in the literature. Although the biological mechanisms underlying the relationship between MD and CVD remains to be identified, both endothelial dysfunction and platelet hyperactivity have been suggested as two of the main mechanistic explanations for the link between MD and CVD. NO produced from either the endothelium or from platelets plays a major role in cardiovascular regulation and cardiovascular pathology. Indeed, numerous cardiovascular diseases, such as hypertension, heart failure and coronary artery disease, have been associated with alterations in the NO system. Recent studies allude to a potential role of nitric oxide (NO) in the relationship between major depression and cardiovascular risk as well as an effect of antidepressants on NO production. The purpose of this investigation is to further investigate a potential mechanism involving nitric oxide (NO) and to examine the effect of the selective serotonin reuptake inhibitor paroxetine on NO production by both platelets and the endothelium. **Methods:** In total, 17 subjects with MD and 12 healthy controls (HCs) with no known history of cardiovascular illness were included in the study. Paroxetine was administered to both the MD patients and HCs over an 8-week period, and then medication was discontinued. Blood samples were taken at various times throughout paroxetine treatment and after discontinuation. Plasma NO metabolite (NOx) levels were measured by the chemiluminescence method. Platelet endothelial NO synthase (eNOS) activity was examined through the conversion of L-[14C]arginine to L-[14C]citrulline. Data were analyzed using t-tests and a linear mixed effects model. **Results:** Baseline levels of both plasma NOx and platelet NOS activity were significantly lower in subjects with MD compared to HCs (5.74 + 6.01 micromol/L and 23.33+ 13.01 micromol/L respectively, $p<0.001$ and 1.25+1.33 pmol/min/mg protein versus 16.41+ 9.68 pmol/min/mg protein respectively, $p<0.001$). Throughout treatment, plasma NOx levels increased in both HCs and MD patients. However, platelet eNOS activity decreased in HCs while no change was evidenced in MD patients. **Conclusions:** These data suggest that decreased NO production, a potential contributor to increased cardiovascular risk, is modified by administration of the antidepressant paroxetine.

76. Triiodothyronine (T3) Significantly Enhances the Antidepressant Effect of Sertraline in Patients with Unipolar Major Depression

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Multiple lines of evidence point to a relationship between thyroid function, depression and response to antidepressant treatment. An effect of the thyroid hormone, triiodothyronine (T3) to potentiate the therapeutic effect of tricyclic antidepressants (TCAs) was supported by a meta-analysis of prior studies (Aronson et al, Arch Gen Psychiatry. 1996; 53:842-8), as was an effect of T3 to accelerate the onset of action of TCAs (Altshuler et al, Am J Psychiatry. 2001;158:1617-22). These studies were relatively small and encompassed patients with bipolar as well as unipolar depression. As yet there is no controlled evidence that T3 enhances the therapeutic action of selective serotonin reuptake inhibitors (SSRIs). We are conducting a double blind, controlled trial in which patients with unipolar, non-psychotic, major depression are randomized to treatment with sertraline (50mg per 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) or sertraline plus placebo, for 8 weeks. The primary outcome criteria for a potentiation effect are the proportion of responders (21 item Hamilton Depression Scale [HAM-D] improvement >50%) or remitters (final HAM-D <7) in the two treatment groups, based on intent to treat analysis. We have conducted an interim data analysis of the first 64 patients to complete the research protocol, 36 of whom were randomized to sertraline plus T3 (SERT-T3) and 28 to sertraline plus placebo (SERT-PLAC). The groups were well matched in terms of age (SERT-T3: 45.1 yrs. [SD 12.9], SERT-PLAC: 41.3 [SD 11.7], $p>0.1$). Because of reports that T3 augmentation may be more effective in females, random assignment was stratified for gender (SERT-T3: 60.0% female, SERT-PLAC: 52.8% female; $p>0.1$). HAM-D scores of the SERT-PLAC group were slightly but significantly higher than SERT-T3 at baseline (SERT-PLAC 22.2 [SD 5.2], SERT-T3: 19.8 [SD 3.9], $p=.03$). Both treatments were well tolerated and there was no significant difference in dropouts between the groups. The antidepressant effect of sertraline, as defined by the proportion of responders (HAM-D improvement >50%) was significantly enhanced in patients concomitantly treated with T3 as compared to patients concomitantly treated with placebo (SERT-T3: 80.6%, SERT-PLAC: 50.0%, $p=.009$). The difference in the effect of the treatments to induce remission (final HAM-D<7) was even more striking (SERT-T3: 75.0%, SERT-PLAC: 35.7%, $p=.001$). In fact, all but two of the 29 SERT-T3 patients who fulfilled criteria for response also fulfilled criteria for remission. Analysis of covariance (ANCOVA) with baseline HAM-D score as covariate showed a significant effect of T3 supplementation ($F[\text{treatment}]=7.8$, df 1,61, $p=.007$; $F[\text{time}]=25.2$, df 4, 248; $F[\text{interaction}]=21.7$, df 4, 248, $p=.09$). A significant difference in HAM-D scores between the groups was already evident by two weeks of treatment ($F[\text{treatment}]=5.6$, df 1,61, $p=.02$ by ANCOVA with baseline HAM-D as covariate). These findings support a clear-cut effect of T3 to enhance the outcome of antidepressant treatment with sertraline in patients with unipolar, non-psychotic major depression and suggest that the onset of antidepressant effect is accelerated by the combination treatment. [Supported by a grant from the Stanley Medical Research Institute]

77. The Apoptotic Molecule P53 is Regulated by Chronic Unpredictable Stress and by Antidepressants in Rat Hippocampus

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Sponsor: Stanley Watson

P53 is a cell-cycle protein known to have two major signaling roles: cell cycle arrest, and apoptosis during cellular stress. It is possible that P53 may mediate some of the deleterious effects of chronic stress in the brain. To determine this, P53 mRNA and protein were mapped in normal male rat forebrain using in situ hybridization and immunohistochemistry. Intense levels were observed in hippocampus and high levels were observed in piriform cortex. There were moderate levels in habenular nuclei, supraoptic nuclei, and arcuate nuclei. We also examined the regulation of P53 in the hippocampus in response to a chronic unpredictable stress (CUS) paradigm. Male, female, and ovarectomized female rats underwent the CUS paradigm for four weeks. P53 mRNA levels measured by in situ hybridization showed a significant upregulation in male hippocampus. Levels were slightly upregulated in the hippocampus of ovarectomized females but this was not statically significant. No change was seen in P53 mRNA levels in female rat hippocampus compared to unstressed controls. In a second study, P53 mRNA and protein expression were

examined in male rats in response to CUS and to antidepressant treatment (desipramine 10 mg/kg/day and fluoxetine 10 mg/kg/day). Again, four weeks of CUS significantly upregulated P53 mRNA levels, as well as P53 immunoreactivity, in male rat hippocampus. When desipramine was administered in conjunction with CUS, it inhibited the upregulation of P53 gene expression and protein observed during the chronic stress paradigm. Fluoxetine co-administration did not prevent the CUS-induced increases in P53 gene expression, but it prevented the increase in P53 immunoreactivity. Since P53 expression is induced by CUS in male hippocampus, this may indicate an increased vulnerability to apoptosis during conditions of chronic and/or uncontrollable stress, which may be prevented by antidepressant administration. Therefore, induction of P53 may be one of mechanisms by which stress increases the vulnerability of the hippocampus to neuronal atrophy and/or cell death. P53 may also be mediating the known suppressive effect of stress on hippocampal neurogenesis. Finally, there seems to be a strong gender difference in P53 mRNA regulation in the rat hippocampus, perhaps due to the neuroprotective effects of estrogen in female animals.

78. Behavioral Effects of Insulin Like Growth Factor-1 Are Mediated Through Activation of Serotonin Transmission

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The neurotrophin insulin-like growth factor-I (IGF-1) increases neurogenesis and cell survival and is a substrate underlying the effects of physical exercise. These studies examined the behavioral and neurochemical effects of (IGF-1) after intraventricular administration to rats. IGF-1 produced novel antidepressant and anxiolytic behavioral effects. In the modified rat forced swimming test, infusion of IGF-I (1.0 μg) produced long-lasting antidepressant-like effects: reduced immobility and increased swimming were present 3 - 6 days after infusion. The antidepressant-like effects of IGF-1 were prevented by the prior depletion of serotonin (5-HT) using the biosynthesis inhibitor para-chlorophenylalanine. IGF-1 also produced anxiolytic effects 3 days after infusion, as measured in the rat conditioned burying test. The effects of IGF-1 (1.0 μg) on extracellular 5-HT levels were examined in the ventral hippocampus 3 days after i.c.v. infusion. IGF-I increased basal levels of 5-HT 4-fold in the hippocampus 3 days after injection, and the increase of hippocampal 5-HT produced by citalopram (2.5 mg/kg, i.p.). These results suggest that some of the behavioral effects of IGF-1 may derive from prolonged activation of 5-HT transmission. IGF-1 may be a unique mediator of antidepressant and anxiolytic activity.

79. The Implication of 5-HT2 Receptor Subtypes in the Mechanism of Action of Antidepressants in the Four-Plates Test

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The selective serotonin reuptake inhibitor (SSRIs) and the serotonin and noradrenaline reuptake inhibitor (SNRIs) increase synaptic levels of 5-HT, leading to an increased activation of a multitude of specific postsynaptic serotonin (5-HT) receptors. However, it is not yet known which 5-HT receptor subtypes mediate the therapeutic effects of antidepressants. Methods: The effects of the SSRI, paroxetine and SNRI, venlafaxine were evaluated in the mouse four plate test (FPT). Results: Paroxetine administered intraperitoneally (i.p.) (0.5, 2-8 mg/kg) potently augmented the number of punished passages accepted by mice in this paradigm. The effects of paroxetine (8 mg/kg) were not reversed by the selective 5-HT2C receptor antagonist, RS 102221 (0.1 and 1 mg/kg) or the selective 5-HT2B/2C receptor antagonist SB 206553 (0.1 and 1 mg/kg), at doses which lack an effect when administered alone. In contrast, the selective 5-HT2A receptor antagonist, SR 46349B (0.1 and 1 mg/kg) completely abolished the paroxetine-induced increase in punished passages. The acute administration of venlafaxine induced an anxiolytic-like effect in the FPT at the doses of 2 to 16 mg/kg. This effect was reversed by the 5-HT2B/2C receptor antagonist as did SR 46349B, for both doses administered. Our results strongly suggest that activation of 5-HT2A receptors is critically involved in the anxiolytic activity of paroxetine, whereas the 5-HT2A and 5-HT2B receptors are involved in the anti-punishment action of venlafaxine in the FPT. The co-administration of selective 5-HT2A, 2B, 2C receptor agonists (DOI, 0.06 and 0.25 mg/kg; BW 723C86, 0.5 and 2 mg/kg and RO 60-0175, 0.06 and 0.25 mg/kg) respectively, was subsequently investigated. The effects of sub-active doses of paroxetine (0.25 and 1 mg/kg) were augmented by BW 723C86 and RO 60-0175 receptor agonist challenge. The anti-punishment effects of venlafaxine (0.25 and 1 mg/kg) were potentialised only by DOI co-administration. Conclusion: These results indicate that the co-administration of 5-HT2 receptor agonists with paroxetine and venlafaxine may provide a powerful tool for enhancing the clinical efficacy of these antidepressants.

80. Regulation of Synaptic Localization and Trafficking of AMPA Glutamate Receptor Subunit GluR2 by Mood Stabilizers and Antidepressants:Avenues for the Development of Novel Therapeutics

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Background: A growing body of data from clinical and preclinical studies suggests that the glutamatergic system may represent a novel therapeutic target for severe recurrent mood disorders. AMPA glutamate receptor trafficking is critical in regulating various forms of synaptic plasticity and may therefore modulates the throughput in neuronal circuitry involved in regulating affective, cognitive and motoric symptoms. It is now known that AMPA receptor subunit trafficking is regulated by the very same signaling cascades that are major targets for mood stabilizers. We have therefore investigated the effects of mood stabilizers on GluR2 synaptic expression/trafficking. The GluR2 is known to regulate calcium permeability, rectification, and single channel conductance of AMPA receptors; notably, these receptors are dominantly influenced by inclusion of a GluR2 subunit in the receptor complex - suggesting that alterations in synaptic GluR2 trafficking would have a major effect on synaptic plasticity. **Methods:** Rats were treated with lithium, or valproate, or imipramine for 4 weeks and synaptosomal fractions from the hippocampus were prepared. Western blot analysis with an anti-GluR2 antibody was performed to determine the GluR2 content at synapses and in the brain. In order to understand the underlining mechanism, GluR-2 expression at the neuronal surface were determined by biotinylation assay and GluR2 levels at the synapses was investigated by double immunostaining with anti-GluR2 and anti-synaptotagmin antibodies in cultured hippocampal neurons. **Results:** Both lithium and valproate reduced hippocampal synaptosomal levels of GluR2 after chronic administration. Lithium significantly reduced GluR2 total protein levels in chronically treated animals, while valproate did not. In cultured hippocampal neurons, both lithium and VPA also significantly down-regulated the surface expression of GluR2 in a time-dependent manner. Double-immunostaining of GluR2 and synaptotagmin showed that the GluR2 immunostaining at synapses of lithium and valproate-treated neurons was attenuated after 4 days of treatment. Total protein level of GluR2 was also significantly attenuated by lithium, but not valproate, confirming the in vivo data. In striking contrast, drugs, which are known to provoke mania, such as imipramine increase the synaptic expression of GluR2 in vivo in hip-

pocampus. **Conclusions:** These studies suggest that regulation of glutamatergically mediated synaptic plasticity may play a role in the treatment of mood disorders, and raises the possibility that agents more directly affecting synaptic GluR2 may represent novel therapies for this devastating illness.

81. Transcranial Magnetic Stimulation (TMS) in the Treatment of Resistant Obsessive-Compulsive Disorder (OCD): Clinical Outcomes and Neurophysiological Correlates

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Sponsor: Sarah Lisanby

Despite major advances in the study and treatment of Obsessive-Compulsive Disorder (OCD), patients often do not respond or experience only partial remission from pharmacotherapy or cognitive behavioral therapy. Imaging and neurophysiological data suggest that cognitive involvement and motor intrusive and repetitive behaviours in OCD may be a consequence of a reduction of thalamo-cortical inhibition and a higher than normal level of cortical excitability involving motor circuits. The Supplementary Motor Area (SMA) may be a useful target for inhibitory stimulation in the treatment of OCD because it has extensive connections with regions implicated in OCD and in motor control (e.g., anterior cingulate cortex, the dorsolateral prefrontal cortex, anterior lateral premotor cortices, posterior parietal areas, and the basal ganglia). Data from a variety of sources suggest the SMA plays a central role in the higher cortical control of motor subroutines and the organization of motor actions in sequential order. To test whether focal inhibitory stimulation applied to the SMA could improve the symptoms of OCD, we performed a preliminary study of low frequency transcranial magnetic stimulation (TMS) in patients with resistant Obsessive Compulsive Spectrum Disorders, including OCD and Tourette Syndrome. TMS was applied daily for 2 weeks at 1 Hz, 100% of motor threshold (MT), 1200 stimuli/day, in 10 daily sessions. Seven patients (2 female, mean age: 37.3 ± 13.5 yrs) were treated in this open-label study. TMS was added onto ongoing pharmacotherapy that had to be at a stable dose for 12 weeks. TMS was well-tolerated with no significant side effects. Suggestions of clinical improvement were apparent as early as the first week of TMS with significant reduction in the Clinical Global Impression (CGI) (p=0.017), Hamilton Anxiety Rating Scale (HARS) (p=0.007), Hamilton Depression Rating Scale (HDRS) (p=0.009). At the 2nd week of treatment, marked improvements were seen, including significant reduction in the CGI (53% reduction, p=0.002), HARS (61% reduction, p=0.001), HDRS (57% reduction, p=0.002), Yale-Brown Obsessive Compulsive Scale (32% reduction, p=0.046), Self-Evaluation Scale for Depression (40% reduction, p=0.007), Beck Depression Inventory (48% reduction, p=0.006), and Symptoms Check-List (35% reduction, p=0.009). CGI improvement was maintained 3 months post-TMS. There was a hemispheric asymmetry in resting MT at baseline (R⟨L). Following 2 weeks of TMS, right MT increased (14% increase, p=0.001) but there was no change in the left MT, restoring symmetry. These open pilot data suggest that TMS applied to the SMA improved symptoms, and normalized motor physiological measures associated with the illness. To follow up these pilot data, we are currently conducting a randomized sham-controlled multicenter study to determine whether 1 Hz TMS to the SMA can be useful as an augmentation strategy for OCD patients resistant to conventional therapies. Patients are followed up at 3 months to determine the persistence of benefit. We are collecting measures of motor cortex excitability (resting and active MT, cortical silent period, intracortical inhibition and intracortical facilitation curves) at baseline and after treatment to determine whether changes in these measures will reveal inhibitory effects of 1 Hz TMS, and whether such changes may be correlated with clinical improvement. Preliminary results from this first controlled study to test the theory that restoring inhibitory control in SMA over motor-limbic circuits improves OCD symptoms will be presented.

82. Regulation of Cortical 5-Hydroxytryptamine$_{2A}$ Receptor Mediated Responses by Chronic Imipramine, Fluoxetine and Electroconvulsive Shock

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Sponsor: George Aghajanian

Down-regulation of prefrontal cortical 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptors is known to occur following chronic administration of tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, serotonin/norepinephrine reuptake inhibitors, and atypical antidepressants which are 5-HT$_{2A}$ receptor antagonists. Some, but not all, investigators have noted 5-HT$_{2A}$ receptor down-regulation with SSRIs. In contrast, convincing evidence exists for up-regulation of 5-HT$_{2A}$ receptor mRNA and protein following repeated electroconvulsive shock (ECS). However, the direct effects of these treatments regarding activating 5-HT$_{2A}$ receptors on cortical neuron function has not been well characterized. The purpose of the present study was to examine the effects of daily administration of the TCA imipramine (15 mg/kg/day x 21 days), the SSRI fluoxetine (10 mg/kg/day x 21 days) and ECS (10 daily treatments) on modulating 5-HT$_{2A}$-mediated responses in prefrontal cortical layer V pyramidal cells and GABAergic interneurons in the piriform cortex. Experiments were performed by preparing 500 μm slices of either the prefrontal cortex or the piriform cortex 24 hours after the last drug or 17 hours after the last ECS treatment in adult male Sprague-Dawley rats. Extracellular recordings were made from a subpopulation of GABAergic interneurons between the border of layers II and III in the piriform cortex (primary olfactory cortex) as previously characterized by the Aghajanian laboratory. 5-hydroxytryptamine (5-HT) excites these interneurons by activating 5-HT$_{2A}$ receptors. Intracellular recordings from prefrontal cortical pyramidal cells were made in the voltage clamp mode using K^+-acetate containing sharp electrodes to measure 5-HT-induced excitatory postsynaptic currents (EPSCs; Aghajanian & Marek, 1997). These two cortical electrophysiological signals were chosen as they appear to represent relatively pure 5-HT$_{2A}$ responses. Chronic administration of imipramine decreased the magnitude of the 5-HT$_{2A}$ responses in both cortical regions as expected. Chronic administration of the SSRI fluoxetine did not alter 5-HT$_{2A}$ responses in either cortical region. ECS increased the magnitude of 5-HT$_{2A}$ excitation of piriform cortical interneurons, but paradoxically tended to decrease the potency and/or magnitude of 5-HT-induced EPSCs in prefrontal pyramidal neurons. The ECS data suggests that 5-HT$_{2A}$ responses can be differentially regulated depending on cellular phenotype (principal cell vs interneuron) and/or brain region. Further, these findings with ECS are consistent with a general theoretical framework that the inhibitory effects of 5-HT are enhanced by chronic antidepressant drug administration. The support of George Aghajanian during the conduct of these studies is gratefully acknowledged. The present studies were performed in the Department of Psychiatry at the Yale University School of Medicine.

83. Adult Life Consequences of Early Trauma Are Alleviated by Escitalopram Pretreatment in a Rat Model of Depression

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Background: A wealth of data indicates that both genes and environment play a role in human depression. The exact mechanisms

have not been identifed and it is not known whether early treatment could alleviate/prevent the disorder. Animal models have been developed to study etiology and pathophysiology of depression: (a) a genetic model, the Flinders Sensitive Line (FSL) rat, and (b) an environmental model, early maternal separation, in rodents and primates; it mimics the early life neglect/parent loss in humans - experiences that best predict adult life psychopathology. Consequently, we investigated gene-environment interactions and effects of treatment with the antidepressant escitalopram in FSL rats and their controls, the resistant FRL line. **Methods:** In a novel design we superimposed early life maternal separation on the genetically "depressed" FSL and the control FRL rats and studied behavior when the animals reached adulthood and brain neurochemistry post-mortem. On postnatal days (PND) 2-14, FSL and FRL pups were maternally separated for 180 min. Comparison groups were not separated. On PND-44 a thirty day escitalopram/vehicle diet was started. Behavioral tests, e.g. Porsolt swim test, were carried out 8 days before the end of treatment. The brains were frozen for neurochemistry , e.g. neuropeptide Y (NPY) and corticotropin releasing hormone (CRH) assays. **Results:** FSL and FRL differed in the baseline swim percent of total test time (percent ST) (considered to be an inverse index of depression) ($p<0.001$). In the resistant FRL strain, separation only moderately decreased the percent ST ($p=0.06$) and escitalopram had no antidepressant effect, a finding parallel to the absence of its effects on mood in euthymic persons. In the genetically vulnerable FSL strain, maternal separation further decreased the percent ST ($p<0.001$). Escitalopram significantly increased the percent ST in both non-separated and separated FSL groups (ps <0.001). Neuropeptide analyses are ongoing. **Conclusions:** (1) While both genes and environment play a role in depression, the consequences of early adverse life events are significantly more deleterious in genetically vulnerable individuals, (2) regional brain changes in NPY and CRH may be markers for depression and stress vulnerability, (3) prophylactic antidepressant treatment to modify consequences of early adverse events should be considered in humans. Support. European Commission, GENDEP LSHB-CT-2003-503428; Swedish Medical Research Council # 10414; Lundbeck Foundation.

84. Neuropeptide Y Has Marked Antidepressant Properties in a Rat Model of Depression

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Background: While a dysregulation of the monoaminergic systems may be sufficient to cause depression there is no proof that it is also a necessary causative factor. A growing body of clinical & experimental data indicates that neuropeptides, in particular neuropeptide Y (NPY), play a role in pathophysiology of affective disorders. We have demonstrated that NPY, both mRNA and protein are decreased in hippocampus of Fawn Hooded and Flinders Sensitive Line (FSL) genetic rat models of depression as well as in adult rats that were exposed to early life stress (e.g., maternal separation). Furthermore, we and others have shown that antidepressant treatment modalities: antidepressant drugs, lithium, antiepileptics and ECS/ECT all reproducibly elevate NPY in rat hippocampus and in human brain and cerebrospinal fluid. These results have suggested that a dysregulated NPY may constitute one of the biological correlates of depression and that increased expression of NPY might be one common pathway of antidepressant treatments. **Methods:** To explore this hypothesis we tested the effects of NPY given intracerebroventricularly (ICV) to depressed FSL and the control resistant line (FRL) rats in Porsolt swim test. ICV cannulae were implanted to FSL and FRL rats and one week later each strain randomly divided into four subgroups receiving (1) NPY, (2) BIBP3226, a blocker of the NPY-Y1 receptor, (3) BIBP3226 + NPY, or (4) vehicle only. The Porsolt swim test was run 45 min following ICV administration. The procedure was repeated after an 8 day recovery period. **Results:** The mean percent basal total swim time (%ST) was 53 and 19 for FRL and FSL, respectively, confirming the differences between the two strains ($p=0.001$). No effects of NPY were observed in the resistant FRL. However, in the depressed FSL, NPY increased the %ST to 49 ($p=0.001$). NPY-Y1 blocker BIBP3226 had no effect per se but antagonized the effect of NPY in a dose-response manner. Repeated testing showed test-retest correlation Rho values >0.78(ps<0.001). **Conclusion:** The data confirm our hypothesis that (1) NPY has anti- depressant properties, (2) these effects are most likely exerted via an agonistic action on the NPY-Y1 receptor, and (3) in similarity to the action of antidepressant drugs on mood in humans, the effects will be apparent only in subjects showing signs of depression. **Significance:** The results will likely contribute to development of novel strategies to treat depressive disorders. Supported by the Swedish Medical Research Council grant 10414 and the G.&Z. Costakis Swedish Foundation for Medical Research

85. Riluzole in Generalized Anxiety Disorder: An Open-Label Trial

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Sponsor: Past Travel Awardee, Memorial, 2003

Objective: There is a need to identify novel pharmacotherapies for anxiety disorders. We examined the safety and efficacy of riluzole, an anti-glutamatergic agent, in adult outpatients with generalized anxiety disorder (GAD). **Method:** In this 8-week open-label fixed dose study, 18 medically-healthy patients with DSM-IV GAD received treatment with riluzole (100 mg/day), following a 2-week drug-free period. The primary efficacy measure was the Hamilton Anxiety Rating Scale (HAM-A) score at endpoint. **Results:** Response rates at week 8 for the intent-to-treat sample and trial completers (n=15) were 67% and 80%, respectively, while the week 8 remission rates (HAM-A ≤ 7) for all patients and trial completers were 44% and 53%, respectively. Median time to response was 2.5 weeks. **Conclusions:** Riluzole appears to be an effective, well-tolerated, and rapidly-acting anxiolytic medication in some patients with GAD. Larger, placebo-controlled studies are indicated.

86. Abnormalities in the Fatty Acid Composition of Postmortem Temporal Cortex, but not Prefrontal Cortex, of Patients with Bipolar Disorder

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Previous studies have documented significant reductions in omega-3 (n-3) fatty acid (FA) content in erythrocyte membranes of schizophrenic and bipolar disorder patients, and placebo-controlled clinical trials have demonstrated a therapeutic benefit of n-3 fatty acid supplementation in medicated bipolar and schizophrenic patients. These findings suggest that these disorders are associated with brain n-3 FA deficiency. In the present study we examined the FA composition of postmortem temporal cortex (BA 20-21) and prefrontal cortex (BA 10) from normal subjects (n=15), bipolar patients (n=13), and schizophrenic patients (n=14) by HPLC (Shimadzu GC-17A). Major saturated FAs (14:0, 16:0, 17:0, 18:0), n-3 FA (22:6n-3), n-6 FAs (18:2n-6, 20:2n-6, 20:3n-6, 20:4n-6, 22:2n-6), n-7 FAs (16:1n-7, 17:1n-7), and n-9 FAs (18:1n-9, 20:1n-9) were detected in postmortem brain tissue and represent ~80 percent of total fatty acid composition. Group differences in individual FAs were analyzed with a one-way ANOVA followed by Bonferroni post-hoc tests. Significant elevations in stearic acid (18:0), linoleic acid (18:2n-6), and arachidonic acid (AA)(20:4n-6), and significant reductions in eicosadienoic

acid (20:2n-6), docosadecadienoic acid (22:2n-6), oleic acid (18:9n-9), and eicosapentaenoic acid (20:1n-9), were found in the temporal cortex of bipolar patients compared with normal controls. No significant differences in temporal cortex FA levels were observed in bipolar patients taking vs. not taking lithium, valproate, antidepressants, or antipsychotic medications at the time-of-death. No significant differences were observed for any FA in the prefrontal cortex of bipolar patients relative to normal controls. No significant differences were observed in either prefrontal or temporal cortex FA levels of schizophrenics compared to normal controls. There were no significant group differences in the AA:docosahexaenoic acid (DHA) ratio in temporal cortex (Normal:1.0; Bipolar: 0.77; Schizophrenia; 0.99) or prefrontal cortex (Normal: 0.76; Bipolar: 0.97; Schizophrenia: 0.80). FA levels in prefrontal and temporal cortices of patients with psychosis (bipolar patients with psychosis and schizophrenics, n=23) and those without psychosis (non-psychotic bipolars and normals, n=19) did not differ significantly. No significant within group correlations were found between individual FA levels in prefrontal cortex or temporal cortex and postmortem interval, tissue pH, days in storage, lifetime exposure to antipsychotic medication (in fluphenazine mg equivalents), or age of onset of disease. Interestingly, age was found to be significantly negatively correlated with the levels of several FAs, including AA and DHA, in the prefrontal cortex, but not temporal cortex, of normal controls but not in either bipolar or schizophrenic groups. Collectively, these results do not support the hypothesis that bipolar disorder and schizophrenia are associated with brain n-3 fatty acid deficiency. However, these data do indicate that the temporal cortex of bipolar patients has significant abnormalities in FA composition which may contribute to, or be a consequence of, dysregulated signal transduction pathways in this brain region. (Postmortem brain tissue was donated by The Stanley Medical Research Institute Brain Collection).

87. Repeated Treatment with SKF-83959, a Selective Agonist at PI-Linked Dopamine D1 Receptors, Induces Sensitization to the Locomotor Stimulating Effect of Amphetamine

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A dysregulation in dopaminergic neurotransmission has been implicated in movement disorders, substance abuse disorders, and recurrent neuropsychiatric illnesses including schizophrenia. The actions of dopamine are mediated via D1 and D2 receptor families, and the dopamine D1-like receptor family consists of at least two molecular isoforms, the D1A receptor and the D1B receptor (human D5). Recent studies suggest that a subtype of the D1B receptor is coupled to the phosphatidylinositol (PI) hydrolysis signal transduction pathway via phospholipase C-beta. However, the functional role of PI-linked D1 receptors remains poorly understood. In the present study, we investigated the effect of acute and chronic treatment with SKF-83959 (R,S-3-methyl-6-chloro-7,8-dihydroxy-1-[3'-methylphenyl]-2,3,4,5-tetrahydro-1H-benzazepine), a selective agonist at PI-linked D1 receptors, on locomotor activity and cross-sensitization to amphetamine. Locomotor activity was monitored for 3 h with a 16x16 photo beam array (SD Instruments) located in residential activity chambers and expressed as crossovers. All rats were placed in the activity chambers 3 d prior to drug administration, and all rats received saline injections on days 2-3. On days 4-8, rats were administered saline (1 ml/kg 0.9% NaCl, s.c., n=10) or SKF-83959 (1 mg/ml/kg, s.c., n=9). All rats received saline injections on days 13-14 to assess conditioned locomotor response, and on day 15 all rats received a challenge with AMPH (1 mg/ml/kg). On days 1-3, there were no significant group differences. Following acute drug administration (day 4), SKF-83959 produced a significant and sustained (3 h) elevation in locomotor activity compared with saline. Similarly, on days 5-8 SKF-83959 produced a significant elevation in locomotor activity compared with saline but did not result in either sensitization or tolerance with repeated administration (day 4 vs. day 8, $p>0.05$). In response to AMPH challenge, locomotor activity in the SKF-83959 pretreated group was significantly elevated compared to the saline pretreated group at 30-60 min post-injection. These results demonstrate that acute activation of PI-linked D1 receptors induces long-term (3 h) elevations in locomotor activity, and that repeated (5 d) stimulation of these receptors produces neither tolerance nor sensitization to the locomotor-stimulating effect. Furthermore, these results indicate that repeated activation of PI-linked D1 receptor with SKF-83959 is sufficient to induce sensitization to the locomotor-stimulating effect of AMPH 7 d following the final injection. Collectively, these results suggest that the activation of PI-linked D1 receptors produce a long-term enhancement in dopamine synaptic efficacy. PI-linked D1 receptors may therefore represent a novel therapeutic target for the long-term modulation of dopamine synaptic plasticity. (Supported by NIDA DA16778-01A1 to N.M.R.)

88. Involvement of the Bed Nucleus of the Stria Terminalis (BNST) in the Expression of Conditioned Fear

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A major goal of psychiatric research has been to identify the neural substrates underlying the manifestation of fear and anxiety disorders (e.g. post-traumatic stress disorder [PTSD], generalized anxiety disorder). Much of this research has defined a critical role for the amygdala in the development and expression of fear-like and anxiety-like behaviors. Recently, focus has turned to structures of the extended amygdala, such as the bed nucleus of the stria terminalis (BNST), and the involvement of this brain area in fear and anxiety. Results from these studies suggest that the BNST may be differentially involved in anxiety-like behaviors produced by unconditioned aversive stimuli (e.g. bright-lights, predatory odors, stress-related stimuli) versus behaviors produced by explicit fear-conditioning. However, more studies are needed to fully establish the role of the BNST in the expression of fear-conditioned behaviors. In the present series of experiments, we used the fear-potentiated startle (FPS) paradigm, a form of Pavlovian conditioning often used as an animal model of fear and anxiety, to examine the involvement of the BNST in the expression of conditioned fear. First, we measured protein levels of the phosphorylated form of the transcription factor cAMP response element-binding protein (pCREB) to examine if physiological changes within the BNST correlate with levels of FPS expression. Male Sprague-Dawley rats were given two training days consisting of 10 presentations of a 3.7-sec light co-terminating with a 0.6-mA shock. The following day, the amplitude of the startle response was measured after presentation of startle-eliciting stimuli in the absence or presence of the light previously paired with shock. Because levels of FPS vary naturally between rats, we divided the animals into three groups based on their FPS response (difference between startle alone and light+startle trials): Low (0-50% FPS), Med (50-100% FPS) and High (100+% FPS). For comparison, a group of untrained rats were also included. Immediately after the test session, brains were rapidly removed and frozen. Western immunoblot quantification of pCREB showed that rats with higher levels of FPS tended to have lower levels of pCREB in the BNST (near-significant negative correlation), with a significant reduction seen in the High FPS group ($p < .05$). Based on these data, we hypothesized that the decrease in the activated form of CREB (i.e. pCREB) in the High FPS group might reflect inhibition occurring in the BNST that would predispose an animal to a higher level of FPS expression. To test this hypothesis, we next implanted rats with bilateral infusion cannula aimed at the BNST. One week

later, we divided the rats into two groups (n = 8/group) with equivalent baseline startle responses. The following day, rats were given a single training session consisting of 10 light+shock pairings. Twenty-four hours later, rats received intra-BNST infusions of either saline or the GABAA agonist muscimol (1 ng/side) and were immediately tested for FPS. Intra-BNST muscimol produced a dramatic increase in the average amount of FPS (76% vs. 215%; p = .0005) with no effect on startle alone (i.e. in the absence of the light). These data suggest that the BNST plays a key role in the expression of conditioned fear, and that GABA-mediated inhibition at this level may influence the magnitude of this expression. Further studies to determine if these effects can be considered anxiogenic (reflecting increased anxiety) or anxiolytic (reflecting decreases in anxiety that allow the animal to perform better in this amygdala-dependent cue-specific task) may provide new insights that help us better understand the role of the BNST in complex mood states.

89. Neuroendocrine, Behavioral and Synaptic Protein Changes in Rats Subjected to a Chronic, Variable Stress Paradigm for Two Weeks: A Model for Discovering Drugs for Stress-Related Disorders?

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Adaptation to repeated stressors is critical for survival. However, mal-adaptations to repeated stress exposure appear to underlie psychiatric diseases such as anxiety disorders, major depression and post-traumatic disorder. The present set of studies was carried out to develop a model of repeated stress-induced mal-adaptations in the rat to induce neuroendocrine, neuroanatomical and behavioral alterations associated with stress-induced psychiatric disorders.
Adult, male Sprague-Dawley rats were subjected to a single daily session of a specific stressor over a two-week period with stressors administered on days 1 to 5 and 8 to 11. The stressors included restraint (20-min), exposure to cold environment (5-10oC for up to 10 min), forced swim (5 min), tail pinch (5-10 min) or a combination thereof. The stress modality and the time of day when the rats were subjected to the stressor were changed daily. On day 12, rats were subjected to a 30-sec foot-shock session (0.5-1 mAmp for 0.2 sec, inter-shock duration of 1 sec) as a novel stressor. Plasma, adrenal glands and the pituitary gland were harvested 10 min after the foot-shock session to assess changes in the hypothalamic-pituitary-adrenal stress axis by examining alterations in corticosterone and adrenocorticotropin hormone (ACTH), adrenal gland hypertrophy and corticotropin releasing factor-1 (CRF-1) receptor binding. Data from chronically stressed animals were compared to two groups of control rats: (a) non-stressed rats, and (b) rats handled every day and subjected only to the final foot-shock stressor. Brains were collected to examine whether synaptic proteins associated with neuronal plasticity are altered in response to the chronic, variable stressors. Finally the behavior of animals was evaluated on day 11 to determine whether prior exposure to the chronic stress induces anxiety in the rats. The data indicate that rats subjected to chronic stress show an augmented neuroendocrine response to a novel stressor administered on day 12. Additionally, there was a significant increase in the weight of the adrenal glands confirming that the chronic stress paradigm had induced an adaptive change in the HPA axis responsive to and regulating stress systems. Rats subjected to the chronic stress also showed an augmented response to an audiogenic startle when tested on day 11 suggesting that the animals had developed an anxiety-related state as a result of the prior stress exposure. Finally, changes in synaptic proteins associated with neuronal dendritic spines were studied by western blots to determine the effects of the chronic stress on neuronal function. Overall, our results indicate that the stress paradigm used here induced neuroendocrine, behavioral and synaptic changes consistent with mal-adaptations to stress and may induce a state in the rat that predisposes it to anxiety and other stress-related disorders. The utility of such an animal model for discovery of novel drug for treatment of stress-related disorders will be discussed.

90. Visual Contexts Gate the Expression of Memory for Fear Extinction in Humans: A Psychophysiological Study

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Sponsor: Roger Pitman

Distinct memories are formed during fear conditioning and subsequent extinction. The expression of either memory is gated by the context. Extinction recall and its contextual modulation have been well studied in animals, however, little is known about these processes in humans. In the present study, healthy human volunteers underwent a differential fear conditioning and extinction protocol that specifically examined the recall of extinction memory. The experimental protocol was conducted in a mock scanner and was administered over two separate days. Pictures of two different virtual rooms served as the visual contexts, one of which served as the conditioning context (CTX+) and the other served as the extinction context (CTX-). The conditioned stimuli (CS) were virtual pictures of two different colors of lights. The unconditioned stimulus (US) was a 0.5 second electric shock delivered to the fingers of the participants. On day 1, participants were first exposed to the habituation phase. This phase consisted of 8 trials, in which CTX+ and CTX- were presented (4 trials each). The to-be CS+ and CS- were also presented in equal numbers (4 CS+ and 4 CS-). The conditioning phase consisted of 5 CS+/US pairings and 5 CS-/ no US trials, all presented within CTX+. The extinction phase consisted of 10 CS+ and CS- trials, all presented in CTX-. No shocks were delivered during the extinction training phase. On day 2, the extinction memory test was presented, which was identical to the extinction training phase on day 1. This was followed by the fear renewal test, in which 5 CS+ and 5 CS- were presented in CTX+ and no US was delivered. Reinstatement was the last phase and consisted of 2 trials in which CTX+ was presented without any CSs and the US was delivered at the offset of CTX+. Immediately after, 5 CS+ and 5 CS- trials were presented in CTX+, to test for the reinstatement of conditioned responding. Participants showed differential conditioning as evidenced by the significant increase in SC to the CS+ relative to the CS-. This conditioned response was fully extinguished on day 1. On day 2, during the recall of extinction memory in the safe context (CTX-), participants showed little response to the CS+, consistent with the recall of extinction memory. Conditioned responding was renewed when the subjects were exposed to the CS+ in the conditioning context (CTX+). ANOVA with repeated measures showed significant main effects of condition (CS+ vs. CS-) ($F(1,19) = 17.93$, $p < 0.001$) and phase ($F(6,114) = 5.28$, $p < 0.0001$) as well as a significant interaction ($F(6,114) = 5.13$, $p < 0.001$). Post-hoc analysis revealed that there was a significant increase in SC to the CS+ relative to CS- during conditioning ($p < 0.05$), and that SC response during extinction training on day 1 was significantly decreased when compared to the conditioning phase ($p < 0.001$). On day 2, post-hoc analysis showed that SC response to the CS+ was significantly increased during the renewal phase when compared to CS+ response during the extinction memory test ($p < 0.05$). These data provide clear evidence supporting the role of context in gating the expression of extinction memory. The interaction between the context and extinction memory is of clinical relevance to exposure therapies commonly used to treat anxiety disorders such as phobias and posttraumatic stress disorder. Therefore, these preliminary data provide a foundation for future planned experiments applying this protocol in conjunction with

fMRI to investigate the neural substrates of extinction recall and renewal in human subjects.

91. Once-Daily Bupropion XL for the Prevention of Seasonal Major Depressive Episodes

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Sponsor: Norman Rosenthal

Introduction: Seasonal affective disorder (SAD) is a common condition of recurrent episodes of autumn-winter depressions which can cause significant distress and functional impairment. Nonetheless, SAD often goes undiagnosed, largely due to failure to consider a potential seasonal pattern in patients who present with a history of depression. Although light therapy has been the mainstay of treatment for the past 20 years, it is not uniformly effective and many patients find the daily regimen to be cumbersome and inconvenient. Antidepressant medications have also been used to treat patients with SAD once the depressive episode is underway. No prior studies, however, have explored the possibility of preventing the onset of autumn-winter depression in patients with SAD by starting treatment with antidepressants early in the season while patients are still well. **Methods:** Three prospective, placebo-controlled parallel-group prevention trials with 1:1 randomization were conducted during the 2002-2003 and 2003-2004 seasons, consisting of a total 1042 ambulatory subjects with a history of SAD, who were enrolled in the fall prior to the onset of a seasonal depressive episode. Patients received bupropion XL, 150 mg (or matching placebo) p.o. q.a.m. for the first week, and 300 mg (or matching placebo) p.o. q.a.m. thereafter until the conclusion of the treatment phase of the study following the vernal equinox. The primary efficacy endpoints were depression-free rates at the end-of -treatment and time between randomization and onset of a seasonal major depressive episode. Onset of a depressive episode was defined by investigator judgment (DSM-IV criteria) or the occurrence of two consecutive scores > 20 on the SIGH-SAD, a 24-item HAM-D inventory that includes common symptoms of seasonal depressive episodes. **Results:** All three studies showed a significant reduction relative to placebo in the frequency of occurrence of seasonal major depressive episodes in patients taking bupropion XL ($p < .001$, .026, .049), for a pooled incidence of 15.7% for patients treated with bupropion XL versus 28% for placebo (relative risk 0.56). The survival analyses for onset of a seasonal depressive episode also favored bupropion XL over placebo across the three studies ($p < .001$, .081, .057). Bupropion XL was generally well tolerated with only dry mouth, nausea, constipation, and flatulence occurring in > 5% of subjects on drug and at a rate exceeding 1.5 times that of placebo. **Conclusions:** These studies are the first to demonstrate that it is possible to prevent depressive recurrence, and hence its potential complications, in patients with a history of SAD by beginning antidepressant treatment early in the season while patients are still well.

92. Neuroendocrine Response to Magnetic Seizure Therapy (MST) in Major Depression: Comparison with Electroconvulsive Therapy

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Seizure spread to the diencephalon during electroconvulsive therapy (ECT) causes a surge in prolactin (PRL). The magnitude of the PRL surge with ECT is related to electrode placement and dosage, but not to clinical efficacy. Magnetic Seizure Therapy (MST) uses magnetic fields to induce seizures from focal cortical regions with less spread to deeper structures. We previously reported that MST releases less PRL than electroconvulsive shock in the monkey. Now we provide the first description of PRL and cortisol surge following MST in patients with depression, and compare these with that seen in various forms of ECT. Following washout from psychotropic medications (except lorazepam up to 3 mg prn), twenty patients with major depression (age 47±10 yr, baseline 24-item HRSD=33±5, 40% female) received a course of MST 3 times a week in the context of a randomized, double masked controlled trial contrasting the antidepressant efficacy of 2 MST coils (double cone and cap). Seizure threshold (ST) was titrated at the first and last treatments, while the remaining treatments were given at maximal device output (50 Hz, 100% intensity, 8 s duration). Masked raters assessed antidepressant response and cognitive side effects. At the second, sixth and penultimate treatments, blood was drawn pre and at 5, 15 and 30 min post seizure. These data were compared with a separate but simultaneously conducted randomized, double-masked controlled trial of 4 forms of ECT (right unilateral (RUL) 0.3 ms pulse width (PW), RUL 1.5 ms PW, bilateral (BL) 0.3 ms PW, bilateral 1.5 ms PW). The RUL groups were at 6xST, while the BL groups were at 2.5xST. MST increased PRL by 261±306%, with a peak at 15 minutes ($p<0.0001$). Maximal PRL surge differed as a function of coil type (double cone>cap coil, $p<0.05$). The magnitude of this increase did not correlate with clinical outcome measures. ECT induced significantly more PRL than MST ($p<0.004$), however this effect was driven by the conventional PW group. MST did not differ from ultrabrief pulse ECT in PRL surge. There was no effect of MST on cortisol. MST did not increase cortisol, and the prolactin surge was less than that found with conventional PW ECT, consistent with the hypothesis that MST induced seizures have less impact on the diencephalon than conventional ECT. The finding that MST did not differ from ultrabrief PW ECT is of note because the PW of MST is in the ultrabrief range, and the seizures induced by these two modalities are less robust and carry fewer cognitive side effects than those induced by conventional ECT.

93. Time-Dependent Effects of Chronic DMI Treatment on Shock-Probe Defensive Burying in Rats

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Selective norepinephrine (NE) reuptake inhibitors (NRIs), such as desipramine (DMI), share many clinical features with other antidepressant drugs. For one thing, all antidepressants, including selective NRIs, alleviate the anxiety which is a prominent component of depression. This may seem somewhat paradoxical, however, as we have shown that stress-induced NE release in the limbic forebrain facilitates a variety of anxiety-like behavioral responses to acute stress. Second, a major shortcoming of many animal models that are used to study the behavioral effects of antidepressant drugs is that they fail to exhibit the time-dependency that is such a hallmark of clinical antidepressant treatment, the so-called therapeutic lag. Thus, in this study, we used the shock-probe defensive burying test (SPDB) to investigate the time course of behavioral and neurochemical changes that occur with chronic DMI treatment in rats. Defensive burying is an active behavioral response elicited by contact with an electrified probe. We first tested the modulatory influence of NE on the SPDB response using local administration of adrenergic antagonists into the lateral septum. Either α_1- or β-receptor antagonists attenuated the burying response ($p<0.05$), demonstrating that NE facilitates this anxiety-like behavior. We next determined whether the burying response is merely an index of the level of anxiety induced in the animal by contact with the probe, or if it instead represents an active, adaptive coping response that reduces anxiety. Plasma ACTH levels were measured in two groups of rats exposed to the probe in cages containing either sufficient bedding to allow burying, or minimal

bedding which did not allow burying. The initial ACTH response induced by contact with the probe was not different between groups, indicating that the encounter was equally stressful. However, ACTH levels returned toward baseline more quickly in the group that was allowed to bury, suggesting that the behavioral response had reduced anxiety in the continued presence of the probe. Thus, increasing the activity of a transmitter such as NE, which facilitates this coping response, could indeed serve to reduce anxiety. Finally, we tested the utility of the SPDB for investigating time-dependent regulatory mechanisms underlying the behavioral changes induced by chronic NE reuptake blockade. We tested separate groups of rats for SPDB after giving vehicle or DMI, either acutely (10 mg/kg, i.p.), or chronically (15 mg/kg/day) for 7, 14 or 21 days by minipump. Acute DMI had no affect on burying behavior compared to vehicle. However, there was a time-dependent decrease in burying behavior in DMI-treated rats over the course of 21 days relative to vehicle-treated controls ($p<0.05$). Thus, in sum, shock-probe defensive burying behavior is enhanced by NE release in the lateral septum; it represents an adaptive coping response to an anxiety-provoking stimulus; and it exhibits a time-dependent reduction with chronic DMI treatment. This test may thus be a useful model for elucidating time-dependent regulatory mechanisms that underly the beneficial behavioral effects of antidepressant drug treatment.

94. Quetiapine Has Placebo-Level Incidence of Akathisia in Bipolar Mania

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Objective: Extrapyramidal symptoms (EPS) have been a major problem in the use of typical or conventional antipsychotics in schizophrenia and bipolar disorder. Patients with bipolar disorder may be particularly sensitive to the development of EPS. Atypical antipsychotics may also be associated with varying degrees of EPS. Avoiding neurological movement disorders, such as akathisia, in patients treated with atypical antipsychotics is vital to ensure safety, tolerability, and good adherence to treatment. The incidence of akathisia in 4 placebo-controlled trials of quetiapine in bipolar mania was examined. **Methods:** Patients with bipolar I disorder (manic episode, DSM-IV) were randomized to quetiapine as monotherapy (up to 800 mg/d) for 12 weeks or in combination with lithium (0.7-1.0 mEq/L) or divalproex (50-100 mcg/mL) for 3 weeks in placebo-controlled, double-blind studies.(1,2) Assessments included the Simpson Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS) scores and adverse event reports. **Results:** The incidence of EPS-related adverse events (including akathisia) with quetiapine monotherapy (12.9%) and combination therapy (21.4%) was no different than placebo (13.1% vs 19.2%). The incidence of akathisia alone was lower in the quetiapine groups: 3.3% for monotherapy and 3.6% for quetiapine in combination with lithium/divalproex; and 6.1% for placebo alone and 4.9% for placebo plus lithium/divalproex. No statistically significant differences were observed between groups in the mean change from baseline to end of treatment in the SAS and BARS scores. Use of anticholinergics, a surrogate marker for EPS, was low and similar in both groups. In patients with bipolar mania, quetiapine monotherapy and combination therapy have a placebo-level incidence of akathisia. These results are consistent with those seen in controlled clinical studies in patients with schizophrenia.(3,4) References 1. Jones M, Huizar K. Quetiapine monotherapy for acute mania associated with bipolar disorder (STAMP 1 and STAMP 2). Bipolar Disord. 2003;5:57(Abstract P95). 2. Mullen J, Paulsson B. Quetiapine in combination with mood stabilizer for the treatment of acute mania associated with bipolar disorder. Bipolar Disord. 2003;5:70(Abstract P140). 3. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. Biol Psychiatry. 1997;42:233-246. 4. Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG. Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Seroquel Study Group. Arch Gen Psychiatry. 1997;54:549-557.

95. A Controlled Study of CSF Levels of Caspases 1, 3, 8 and 9 in Schizophrenia: Evidence of Apoptotic Overexpression

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Background: The pathophysiology of progressive brain tissue loss in schizophrenia remains unknown, but as with other neurodegenerative disorders, overexpression of cortical apoptotic pathways is a leading model. To test this hypothesis, we examined CSF concentrations of several caspases, a family of cysteine proteases that play central roles in apoptosis, in schizophrenia patients with good and poor response to antipsychotics as well as in healthy controls. **Methods:** The CSF of 63 drug-free relapsed patients with schizophrenia (mean age = 34.2 ± 8.9 years) and 13 healthy control subjects were assayed for the levels of caspases 1, 3, 8 and 9. The patients were classified into rapid responders, delayed responders and nonresponders based on 60% reduction in psychosis scores (SAPS) after 6 months. **Results:** ANOVA showed no significant differences between all schizophrenics and all controls. However, there were significant increases in caspase 3 ($p=.05$) and caspase 8 ($p=.05$) in nonresponders compared to rapid responders. There was no difference in caspase 9 but a significantly lower level of caspase 1 was found in rapid responders compared to healthy controls ($p=0.011$) and between healthy controls vs. delayed responders ($p=0.033$). **Discussion:** These data are consistent with increased cortical apoptosis in the schizophrenia group with non response to antipsychotic medications. The implications for further research into apoptotic mechanisms to elucidate the neurobiology of brain tissue loss in schizophrenia are discussed.

96. An Open-Label Trial of Escitalopram in Atypical Depression

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Sponsor: Stephen Strakowski

Background: Patients with major depression with atypical features, or atypical depression, respond better to monoamine oxidase inhibitors (MAOIs) than to tricyclic antidepressants (TCAs). Although serotonin reuptake inhibitors (SSRIs) are generally considered the first choice antidepressant for these patients, there are relatively few studies evaluating these agents in atypical depression. Available data regarding SSRIs in atypical depression have been mixed. Some studies have reported that SSRIs are as effective as MAOIs, while others suggest that they are less effective in atypical depression. Moreover, evidence suggests that SSRIs are less effective for maintenance treatment of patients with atypical depression than for patients who do not display prominent atypical features. This open-label, pilot study evaluated the effectiveness and tolerability of the SSRI escitalopram in the acute treatment of patients diagnosed with atypical depression. **Methods:** 20 patients who met Columbia criteria for a major depressive episode (unipolar) with atypical features participated in a twelve-week, open-label trial of escitalopram 10-20 mg/day. Psychiatric diagnoses were made using the Structured Clinical Interview for DSM-IV (SCID). The following rating scales were performed at each visit to evaluate clinical response: the Hamilton Rating Scale for Depression, 28-item version (Ham-D-28); a revised version of the Atypical Depression Diagnostic scale (ADDS); and the Clinical Global Impression Scale (CGI). **Results:** Twenty patients were evaluated after receiving at least 1 week of escitalopram. 17 pa-

tients completed all 12 weeks of the trial. Linear regression for repeated measures using LOCF showed a statistically significant change from baseline at all time points for the Ham-D-28 and ADDS. Mean change in score between baseline and week 12 was 14.6 for the Ham-D-28 ($p<0.0001$), 11.1 for the ADDS ($p<0.0001$), and 1.9 for the CGI ($p<0.0001$). Fourteen of the completers exhibited at least 50% improvement on the Ham-D-28 at week 12, while only 9 patients met this improvement criteria on the ADDS. Eleven patients met the criteria for full remission of the depressive episode (Ham-D-28 score ≤10) at week 12. Escitalopram was well tolerated overall. **Discussion:** The results of this trial suggest that escitalopram may be a safe and effective treatment for unipolar atypical depression. However, the open-label design and small number of patients limit the power of these findings. Larger double-blind, controlled trials of escitalopram monotherapy in atypical depression appear to be warranted. This study was funded in part by an unrestricted grant from Forest Pharmaceuticals.

97. Augmentation with Risperidone in Chronic Resistant Depression: A Double-Blind Placebo-Controlled Maintenance Trial

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Background: Although standard antidepressant therapies are effective for some patients with major depressive disorder, many patients fail to respond adequately to monotherapy with currently available antidepressants. This high prevalence and the associated poor outcome of nonresponders reflect a significant unmet medical need. ARISe-RD (Augmentation with Risperidone in Resistant Depression) is a large, multi-center international study that evaluated the efficacy, safety, and maintenance effect of risperidone augmentation in patients who are partially or fully nonresponsive to standard antidepressant therapy. **Methods:** Subjects were inpatients or outpatients aged 18 —85 years with a DSM-IV diagnosis of major depressive disorder and a score≥ 20 on the 17-item HAM-D at baseline. Each had failed to respond, in the current episode, to 1—3 antidepressant(s) other than citalopram or escitalopram, given at adequate doses for at least 6 weeks. During the open-label phase, patients received citalopram monotherapy for 4—6 weeks to confirm nonresponse (<50% reduction in HAM-D) or full resistance (<25% reduction in HAM-D) at endpoint. These patients were then eligible to enter a 4—6 week phase of risperidone augmentation of citalopram. Patients who experienced symptomatic remission (HAM-D score ≤7 or a CGI-severity score of 1 or 2) could enter the 24-week double-blind, placebo-controlled phase. Time to relapse in this phase (CGI-change score of 6 [much worse] or 7 [very much worse], HAM-D score ≥16, discontinuation due to lack of therapeutic effect, or deliberate self-injury or suicidal intent) was the primary outcome. **Results:** Of the 489 patients enrolled in the study, 89% were nonresponders to citalopram monotherapy; 69% were fully nonresponsive. 386 of these nonresponders entered the risperidone augmentation phase, of whom 63% achieved remission; 241 of these entered the double-blind trial during which 122 received risperidone augmentation and 119 received placebo augmentation. The 24-week trial was completed by 89% of risperidone patients and 91% of placebo patients. Among all 241 randomized patients, 53% of risperidone patients and 55% of placebo patients relapsed; median time to relapse was 102 and 85 days, respectively (NS). Among the 152 fully nonresponsive patients, 56% of risperidone patients and 64% of placebo patients relapsed; median time to relapse was 97 and 56 days, respectively (P=0.05). Risperidone augmentation was well tolerated, the most common adverse events being headache in 11%. **Conclusions:** Risperidone augmentation resulted in symptomatic remission in a substantial number of patients with chronic resistant depression who were nonresponsive to standard antidepressant therapy. Time to relapse in these remitted patients was similar with risperidone vs. placebo augmentation. In the population of fully nonresponsive patients, relapse was significantly delayed with risperidone augmentation. Supported by Janssen Medical Affairs, LLC

98. Potentiation of Antidepressants by Triiodothyronine: Role of 5-HT Autoreceptors

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Sponsor: Bernard Lerer

There is evidence from both human and animal studies linking thyroid hormones with effects on serotonergic transmission, and in particular suggesting that T3 may increase synaptic 5-HT levels by reducing the activities of the 5-HT1A and 5-HT1B autoreceptors which inhibit 5-HT release. In this work we have used in vivo microdialysis to determine the effects of fluoxetine and T3 alone and in combination on the activities of these receptors in rat brain, in an attempt to provide a scientific basis for the augmentation and acceleration effects seen clinically when T3 is given together with an SSRI. In male rats, a combination of T3 at 20 μg/kg and fluoxetine at 5 mg/kg given daily for 7 days induced desensitization of 5-HT1B autoreceptors in hypothalamus. while desensitization of 5-HT1A receptors as shown by the effect of the 5-HT1A receptor agonist 8-OH-DPAT to decrease 5-HT levels in cortex required either a higher dose (10 mg/kg) of fluoxetine or a longer period of administration (12 days). Measurement of mRNA levels for 5-HT1A and 5-HT1B autoreceptors in the raphe nuclei showed significant reductions after combined administration of T3 and fluoxetine but not after either of the treatments administered alone, suggesting that the functional changes may be due to alterations in gene expression. In female rats, neither fluoxetine nor T3 at doses up to 200 μg/kg nor a combination of these agents given daily for 7 days affected either 5-HT1A or 5-HT1B receptor activity in either frontal cortex or hypothalamus. The data presented represent the first attempt to provide a biochemical mechanism for the effects of T3 to augment and accelerate the clinical effects of antidepressant drugs. The differences observed between male and female rats are also of interest since some studies have indicated that T3 has a greater clinical potency in female subjects. The data to be presented were derived from protocols approved by our institutional review board (Hebrew University Authority for Animal facilities, Ethics committee research number MD 80.28-3 (NIH approval number OPRR-A01-5011) valid until December 2005).

99. Gene Expression Profiling in Postmortem Major Depressive Disorder Brain

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The use of postmortem brain tissue to perform microarray studies represents a powerful approach to understand disease mechanisms in neuropsychiatric disorders. However, postmortem gene profiling is accompanied by unique challenges not encountered in animal studies. Major factors include agonal state, tissue pH, postmortem interval, RNA integrity and use of appropriate control subjects. Altered profiles or knowledge of individual dysregulated genes could enhance our understanding of disease mechanism and also lead to the development of novel therapies. Mixed results have

been obtained from earlier gene array analysis of depressive disorder. In this context, we attempted to obtain better neurobiological resolution by utilizing samples that were pre-characterized for glial and neuronal abnormalities (Rajkowska et al., 1999). Precise punches were taken from cryocut sections of cortical area 9 of the dorsolateral prefrontal cortex. RNA was extracted using the RNAqueous (Ambion), non-phenolic RNA isolation kit. Average total RNA yield was 4 μg with OD 260/280 values above 1.7. RNA quality was further determined by Nanochip assay on the bioanalyzer (Agilent) and real time PCR. Only 2 μg of total RNA was reverse transcribed into cDNA for hybriridzation onto 16K human oligo chips (Agilent). A 2-step hybridization procedure was employed where the hybridized cDNA was indirectly post-labeled using fluorescent dendrimer molecules (Genisphere Inc). Gene profiles from 15 pairs of MDD and non-psychiatric controls, matched for age, gender, postmortem interval and race were analyzed using GeneSpring software (Silicon Genetics). Although Gene Ontology based clustering did not highlight any particular category of dysregulated genes, stringent statistical analysis revealed over 100 significantly regulated genes. A subset of regulated genes were confirmed by real-time PCR analysis.Supported by MH25642, MH45481, MH61578 and MH63187.

100. Behavioral Studies in Mice Lacking the clock Gene DBP: A Possible Animal Model of Anhedonia

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Sponsor: Ronald Kuczenski

Background: We have previously identified the clock gene D-box Binding Protein (DBP) as a candidate gene for bipolar and related disorders, using a Convergent Functional Genomics approach (Niculescu et al. 2000) cross-matching gene expression data from a methamphetamine treated rodent model with human linkage data. **Methods:** Mice with a homozygous deletion of DBP (Lopez-Molina et al. 1997) were challenged with methamphetamine (10mg/kg). Behavioral response was assessed by quantifying locomotor patterns in an open filed, using a video-tracking device. **Results:** Mice lacking DBP had a baseline lower locomotor activity, and blunted behavioral responses to acute metamphetamine stimulation. Moreover, they gained less weight over time compared to wild-type controls. **Conclusions:** We propose that mice lacking DBP may be useful as an animal model of anhedonia. Taken together with previous data showing that these mice have abnormal circadian and homeostatic aspects of sleep regulation. (Franken et al. 2000), our work suggests they reproduce phenotypic aspects of depression, consistent with the hypothesis that DBP is a candidate gene for bipolar (manic-depressive) disorder.

101. Predictors of Suicide Attempts in Bipolar Suicide Attempters: A Prospective Study

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Sponsor: J. John Mann

Bipolar disorder is associated with high rates of suicide attempt and completion. Over 50 studies have reviewed predictors for suicidal behavior in Major Affective Disorders and many have included subjects with Bipolar Disorder. However, there are no prospective studies of predictors of suicidal acts in exclusively bipolar samples. We studied bipolar suicide attempters (n=57) recruited while in a depressed or mixed phase, the types of episodes most associated with suicidal behavior. Patients were assessed for severity of depression, suicidal ideation, aggression and impulsivity at study entry and throughout the study period. Patients were followed for a maximum of 2.5 years and the outcome measure was suicide event defined as suicide completion, attempt or ideation with a plan requiring hospitalization or a change in medication. In this sample of 57 previous suicide attempters, there were a total of 29 suicide events during the study period occurring in 24 (42%) patients. Most of the events were in the first 6 months (21/29). Four patients had 2 events, one had 3. Of the 29 events, 13 were suicide attempts and the other 16 were severe suicidal planning requiring intervention. The attempts occurred among 10 patients. A Cox proportional hazards model identified baseline measures predicting time to first event or first attempt during the study period. Baseline depression was a significant predictor (HR=1.08, p=0.009) of time to first event. We detected trends for later age of onset to be protective (HR=.953, p=0.056) and for Barratt impulsivity (HR=1.03, p=0.065) and previous number of suicide attempts (HR=1.2, p=0.09) to be risk factors for suicide events. Likewise, for time to first attempt, we found that older age was protective (HR=.92, p=0.035) and that baseline number of suicide attempts (HR=1.5, p=0.019) and baseline suicidal ideation (HR=1.1, p=0.015) were risk factors. In terms of ongoing psychopathology, time to first event was significantly related to severity of ongoing depression (H.R.=1.09, robust s.e. 0.03, z=3.03, p=0.0024). Similarly, the risk of a suicidal event increased as ongoing suicidal ideation increased (H.R.=1.09, robust s.e.=0.03, z=1.92, p=0.054). While baseline aggression was not a predictor of time to event (HR=.97, p=0.36), follow-up aggression score tended to predict suicide events, even in this small sample (HR=1.2, p=0.12). For time to first attempt, a large hazard ratio for ongoing aggression was detected (HR=1.3, p=.095). In this group of 57 bipolar suicide attempters, baseline depression, suicidal ideation and impulsivity, but not aggression were predictors of future suicide events. The best predictor of suicide events was ongoing severity of depression. Moreover, in this sample, we found that aggressive behavior during the study period was predictive of suicide attempts. Thus, the predictors of suicidal behavior that we have reported in independent samples comprised mostly of unipolar depressed individuals, also predict suicidal acts in bipolar subjects. This is consistent with our stress-diathesis model for suicidal behavior.

102. Serotonin Transporter Occupancy in Rats Exposed to SSRIs in Utero or via Breast Milk

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Studies have begun to examine prenatal and/or post partum exposure of human infants to SSRIs. However, information regarding CNS effects such as neonatal CNS clearance post delivery or the impact of exposure via breast milk on CNS receptor occupancy is unknown. In many instances, SSRI concentrations in infants are below the limits of detection utilizing standard analytic techniques. Nevertheless, infants are exposed to trace concentrations of SSRIs which are hypothesized to partially inhibit the SERT. Rats were exposed to SSRIs in utero or postnatally via breast milk at doses that mimic serum concentrations observed in human investigations (median and ~85th percentile). Dam and pup serum drug concentrations were assayed by HPLC. Fresh frozen brains were sectioned and ex vivo autoradiography was performed using 125I-RTI55. E21 rat pups exposed to paroxetine or sertraline during the final 10 days of pregnancy exhibited ~80% or >95% occupancy, respectively, at delivery at both doses. By postnatal day 4, occupancy had significantly decreased. In a second

group of rats, naïve pups were exposed to paroxetine or sertraline via breast milk. Despite undetectable pup serum concentrations, the higher dose of both paroxetine and sertraline resulted in 30-50% SERT occupancy in 4 day old rat brains. Fine motor skills were assessed in adult rats exposed to an SSRI in utero using a beam traversing task for 5 consecutive days. Female rats exposed to an SSRI in utero performed worse than their vehicle control counterparts on day 5. In these preliminary studies, male rats also performed worse but less so than the females. SSRIs have proven extremely valuable in the treatment of pregnant and nursing women, nevertheless further modeling of drug exposure in infants combined with CNS measures will enhance guidelines which can be used to systematically minimize fetal and neonatal medication exposure.

103. Serotonin2c Receptors In The Postmortem Brain Of Depressed Suicide Victims

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Abnormalities in serotonergic mechanisms have been implicated in suicide and mood disorders. One of the major evidence to implicate suicidal behavior with serotonin was based on the observation that depressed suicidal patients had lower levels of 5HIAA in their CSF as compared to non-suicidal subjects. The levels of 5HT and 5HIAA in the CSF is regulated by the choroid plexus and presumably by $5HT_{2C}$ receptors, which are highly enriched in choroid plexus. Also, abnormalities of 5HT receptor subtypes such as $5HT_{2A}$ have been reported in the postmortem brain of depressed suicide victims. On the other hand, $5HT_{2C}$ receptor, which has been implicated in anxiety and suicidal behavior, has not been studied in the postmortem brain of suicide victims. One of the reasons may be that specific ligands for labeling the $5HT_{2C}$ receptors, i.e. [^{3}H]-mesulergine, which labels primarily 5HT2C receptors, has also been reported to label $5HT_{2A}$ receptors. In order to examine if abnormalities of $5HT_{2C}$ receptor are associated with suicidal behavior, we have determined the protein and mRNA expression of $5HT_{2C}$ receptors in the prefrontal cortex (PFC) obtained from 24 depressed suicide victims and 24 normal control subjects. Protein expression of $5HT_{2C}$ receptors was determined using specific antibodies to $5HT_{2C}$ receptors by Western blot technique. The mRNA expression was determined using quantitative RT-PCR technique. Postmortem brain samples were obtained from Lenhossek Human Brain Program, Semmelweiss University, Budapest, Hungary. Tissues were collected only after a family member gave informed consent. All tissues from control subjects and suicide victims were screened for evidence of neuropathology. The diagnosis was based on the Structured Clinical Interview for the DSM-IV (SCID). Two psychiatrists on the panel reviewed write up from this interview as well as the SCID. Immunolabeling of $5HT_{2C}$ receptors in the PFC (Brodmann Area 9) indicated that protein expression levels of $5HT_{2C}$ receptors were significantly increased in the postmortem brain of depressed suicide victims as compared to control subjects. However, in a small number of subjects there were no significant differences in the protein expression levels between depressed suicide victims (n = 7) and control subjects (n = 7) in the hippocampus. We are now determining the mRNA expression of $5HT_{2C}$ receptors in the PFC and hippocampus of depressed suicide victims and control subjects. We find mRNA expression levels of $5HT_{2C}$ receptors to be higher in hippocampus as compared to PFC. Earlier reports have indicated an increase in $5HT_{2A}$ receptors in the postmortem brain of suicide victims; however, this is the first report indicating an increase in $5HT_{2C}$ receptors in the postmortem brain of suicide victims. This work was supported in part by NIMH grant RO1-MH48153 to Dr. Pandey and NIHM grant KO1-MH01836 and RO1-MH068777 to Dr. Dwivedi.

104. Timing of Clinical Improvement and Symptom Resolution in the Treatment of Major Depressive Disorder

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Sponsor: Past Travel Awardee, GlaxoSmithKline, 2002

Objective: To assess for the relationship between the timing of clinical improvement with fluoxetine and the resolution of depressive symptoms in Major Depressive Disorder (MDD). **Method:** 182 MDD outpatients (mean age= 40.5 +/- 9.7 years; 53.8% female) who responded following an 8-week, 20mg, open trial of fluoxetine were included in the analysis. The symptoms questionnaire (SQ) and Beck hopelessness scale (BHS) were also administered to 83 and 153 of these patients, respectively. Onset of clinical response was defined as a 30% decrease in 17-item Hamilton depression scale (HAM-D-17) scores. Controlling for baseline symptom severity, we then assessed for the relationship between the timing of clinical improvement and depressive symptom at endpoint. **Results:** Earlier clinical improvement in responders predicted lower HAMD17, BHS, SQ-depression, SQ-anxiety, but not SQ-somatic symptom or SQ-anger/hostility scores at week 8. This was true regardless of whether improvement was defined as a continuous measure (a 30% or 50% decrease in symptom severity), as a dichotomous measure (clinical response occurring the first two weeks of treatment), and was also replicated in the subset of remitters (HAMD-17< 8). **Conclusions:** Earlier as well as early clinical improvement with fluoxetine treatment is predictive of greater symptom resolution at endpoint in responders as well as in remitters. Further studies exploring the impact of various treatment modalities as well as placebo on the timing of clinical improvement and symptom resolution in MDD are warranted.

105. Lower In Vivo Binding of [C-11]Mcn5652 to the Serotonin Transporter during a Major Depressive Episode

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Sponsor: Victoria Arango

Objective: Functional and structural imaging studies suggest an altered neural circuit in major depressive disorder (MDD). Cerebrospinal fluid analysis, neuroendocrine challenges, serotonin depletion, and treatment studies implicate the serotonergic system in the pathophysiology of MDD. Based on postmortem studies and functional and structural imaging studies, we hypothesized that MDD subjects in a major depressive episode (MDE) have fewer serotonin transporter (5-HTT) binding sites compared to healthy volunteers as assessed by positron emission tomography (PET). **Methods:** 5-HTT binding potential (BP = f1Bmax/KD) was determined using [C-11]McN5652 in 25 recent medication-free, DSM-IV diagnosed, MDD subjects during a MDE and in 43 healthy volunteers (controls). All subjects had arterial lines to determine metabolite corrected arterial input functions. **Results:** There was a significant brain region by MDD diagnosis interaction ($p = 0.016$). Post-hoc analysis revealed lower BP in MDD subjects compared to controls in the amygdala (AMY) ($p = 0.023$) and midbrain (MID) ($p = 0.027$). The lower BP in MDD subjects was more pronounced in antidepressant naive subjects. There was no correlation between MID BP and severity of depression or days off medication. There was no difference in BP between suicide attempters and non-attempters. **Conclusions:** MDD subjects in a MDE have lower 5-HTT BP in the AMY and MID compared to controls. These findings suggest focal serotonergic abnormalities in the neurocircuitry of MDD. Support Contributed By: NIMH and NARSAD.

106. Quetiapine Versus Haloperidol Decanoate for Long-term Treatment of Schizophrenia and Schizoaffective Disorder

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Objective: To compare the long-term efficacy and tolerability of oral quetiapine with that of intramuscular haloperidol. **Methods:** Patients with schizophrenia or schizoaffective disorder requiring long-term antipsychotic treatment were randomly assigned to open-label oral quetiapine or haloperidol decanoate for 48 weeks. Clinicians were instructed to target dosing at 500 mg/d of quetiapine or 200 mg of haloperidol decanoate every 4 weeks. The Positive and Negative Syndrome Scale was used to assess efficacy; the Simpson-Angus and Barnes Akathisia Scales were used to assess safety and tolerability. For statistical analyses, a general linear mixed-model repeated-measures analysis of covariance was used, with change scores for dependent variables computed with the baseline score as covariate. **Results:** Thirty-five patients were enrolled. Six patients refused to participate after being informed of their treatment assignment; 4 of the 6 refusals were for assignment to haloperidol decanoate. Mean dose at week 48 was 493 mg/d for quetiapine and 170 mg/28 d for haloperidol decanoate. In a survival analysis, we found no between-group differences in estimates of the number of patients remaining exacerbation-free over time. Both drugs were efficacious, but quetiapine was significantly superior to haloperidol decanoate in controlling negative symptoms ($P<0.05$). The incidence of extrapyramidal symptoms was low in both groups, but patients receiving quetiapine showed significantly greater improvement in rigidity and akathisia ($P<0.05$). **Conclusion:** Oral quetiapine was as efficacious as intramuscular haloperidol in preventing symptom exacerbation over 48 weeks in patients with schizophrenia or schizoaffective disorder, with fewer extrapyramidal symptoms, especially rigidity and akathisia. Quetiapine was more efficacious than haloperidol decanoate in treating negative symptoms.

107. Efficacy of Topiramate, Valproate and their Combination in Aggression/Agitation Behavior

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Sponsor: Guy Chouinard

Topiramate is an antiepileptic drug recently used also in the therapy of bipolar disorder and resistant schizophrenia. Since topiramate and valproate, which is currently used for aggressive behavior, share several pharmacological mechanism (positive modulatory effect on the GABA activity and negative modulatory effect on glutamatergic neurotransmission), the goal of the present study was to assess whether topiramate, valproate and their combination, could represent a valid approach for psychiatric patients showing marked aggression and agitation. A retrospective study in a sample of 48 inpatients, suffering from schizophrenia, schizoaffective and bipolar disorder, hospitalized in a maximum security Canadian psychiatry hospital was carried out. Overt Aggression Scale (OAS), Agitation-calmness evaluation scale (ACES), time spent in seclusion, isolation without seclusion, the number of PRN medication, time of restraints and the number of intervention of Security Team were used as parameters to measure any changes in aggression/agitation behavior over 12 weeks before and 12 weeks after the treatment. Preliminary results indicate that patients treated with topiramate show a decrease in the average score of OAS ($t=2.7$, $df=13$, $p=0.016$). This effect was similar to group treated with valproate ($t=2.3$, $df=12$, $p=0.04$) or with the combination valproate-topiramate ($t=2.5$, $df=11$, $p=0.026$). Moreover, valproate monotherapy, but not topiramate, decreased the intensity of agitation episodes ($p=0.001$) measured by ACES. These results suggest that topiramate could be a valid medicine in the control of aggression. Double-blind, randomized, placebo control studies need to further assess such possibility.

108. Regulation of Human Reelin Gene by Methylation: Implications for the Future Treatment of Schziophrenia

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Sponsor: Erminio Costa

RELN mRNA and protein levels are reduced by approximately 50% in various cortical structures of postmortem brain from patients diagnosed with schizophrenia and bipolar illness with mania. We have used ChIP assays to show that DNMT1, MeCP2 and MBD2 bind to the Reln promoter in NT2 and keep it in an inactive state. We have also shown that retinoic acid (RA) treatment of NT2 cells is accompanied by increased reelin mRNA expression and eventually induces the differentiation of these progenitors into neurons. This transition is associated with changes in the methylation status of the reelin promoter. Moreover, the binding of Dnmt1, MeCP2 and MBD2 are displaced within days of the retinoic acid treatment and prior to the appearance of the neuronal phenotype. The displacement of these negative regulatory factors may represent the initial event associated with the onset of transcriptional activation of the gene. On the 6th day after treatment, reelin expression was induced 130 fold by RA. A time course study showed that RA induces Pax6 mRNA expression some 48 hours before the onset of reelin mRNA expression. To demonstrate that Reln is directly regulated by Pax6, we introduced Pax6, along with Tbr1 and Sp1 expressing vectors, into NT2 cells. Our data show that the transfected reelin promoter was induced 80-fold by the factors and that the triple combination resulted in a synergistic action. The effect of these transiently introduced constructs on endogenous reelin mRNA expression was also apparent although the extent was less robust. A deletion study was performed to determine the sites of action of these factors. The results showed that these transcription factors lose activity when sequences between -155 and -140 are deleted. Also, reelin enhancer constructs cotransfected with Pax6, Tbr1 and Sp1 showed a 100 fold increase in reporter activity. Finally, gel shift analysis established that there is a Pax6 binding site within the reelin enhancer between -146 and -131 bp. The data suggest that transcription factors Pax6, Tbr1 and Sp1 play an important role in regulating reelin expression. As indicated above, the human Reln promoter is regulated by the methylation status of its associated CpG island. Moreover, we have recently shown that Dnmt1, the predominant CpG methylating enzyme, is more highly expressed in GABAergic neurons of schizophrenia patients. We have identified two sites within the Pax6 binding site that appear to be more heavily methylated in patients with schizophrenia. These studies provide a molecular mechanism by which reelin mRNA expression is down-regulated in the schizophrenia brain and suggests a new therapeutic target for alleviating the symptoms associated with this disease. Moreover, these studies suggest a potential common underlying problem that likely affects the expression of multiple genes expressed in GABAergic neurons. At the same time, it suggests that therapeutic agents that target this mechanism may prove beneficial in the restoration of multiple genes down regulated through this hypermethylating activity.

109. Symptom Response and Readiness for Discharge Among Inpatients with Schizophrenia: A Double-Blind Comparison of Risperidone, Quetiapine, and Placebo

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Sponsor: John Davis

Background: An important treatment goal for an inpatient with an acute exacerbation of schizophrenia or schizoaffective disorder is rapid symptom control and hospital discharge, thus permitting a return to family, society, and prior level of functioning. A 2-phase, 6-week, double-blind study assessed the efficacy/effectiveness of treatment on symptom response and readiness for hospital discharge in patients with schizophrenia experiencing a recent exacerbation of symptoms requiring hospitalization in the previous month. **Methods:** In a 2-week monotherapy phase, patients received risperidone (n = 153), quetiapine (n = 156), or placebo (n = 73). In the subsequent 4-week additive-therapy phase, investigators were permitted to prescribe additional psychiatric medications as necessary. A 7-item questionnaire that assessed readiness for discharge from the inpatient setting included items assessing the patient's psychopathology, the ability to execute activities of daily living, and overall clinical status. Clinically relevant improvement was defined as ≥30% improvement in PANSS total score and CGI-C score ≤2. **Results:** Mean (±SD) PANSS total scores in the three treatment groups at baseline ranged from 94.3±18.2 to 97.3±19.1. The 6-week study was completed by 82% of risperidone patients, 74% of quetiapine patients, and 62% of placebo patients. At monotherapy endpoint (LOCF), improvements in mean (±SE) PANSS total scores were significantly greater in patients receiving risperidone (-27.7±1.5) than quetiapine (-20.5±1.5; $P<0.001$) or placebo (-20.2±2.0; $P<0.001$). Clinically relevant improvement was achieved by significantly more patients receiving risperidone (45%) than quetiapine (28%; $P<0.001$) or placebo (24%; $P<0.01$). By day 14, significantly more risperidone patients were ready for discharge (56%) than those receiving quetiapine (38%; $P<0.001$) or placebo (32%; $P<0.001$). Differences between quetiapine and placebo were not significant. Mean doses at monotherapy endpoint were 4.7±0.9 mg/day of risperidone and 579.5±128.9 mg/day of quetiapine. During the additive-therapy phase, additional antipsychotics were received by 33% of risperidone patients, 53% of quetiapine patients ($P<0.001$ vs risperidone), and 57% of placebo patients. Reductions in PANSS total scores at the week-6 endpoint (LOCF) were -34.5±1.6 with risperidone, -30.9±1.6 with quetiapine, and -27.9±2.2 with placebo. The differences were significantly greater in patients receiving risperidone than placebo ($P=0.007$). Differences between quetiapine and risperidone or placebo were not significant. Both active treatments were generally well tolerated. There were more reports of movement disorders with risperidone and more reports of sedation/somnolence with quetiapine. Thyroid function tests showed reductions in total T_4 and total T_3 levels and greater increases in mean TSH levels in the quetiapine group. Effects with risperidone were comparable to placebo. Mean prolactin levels increased more in the risperidone group than the placebo group at endpoint and decreased in the quetiapine group. **Conclusion:** Prompt symptom control and readiness for hospital discharge were achieved by significantly more patients receiving risperidone than quetiapine. Greater symptom improvement was also seen with risperidone in the additive therapy phase during which significantly more quetiapine than risperidone patients received additive antipsychotics. Supported by Janssen Medical Affairs, L.L.C.

110. Neurocognitive Correlates of the Brain-derived Neurotrophic Factor Val66Met Polymorphism

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Background: Brain-derived neurotrophic factor (BDNF) not only plays an important role during neurodevelopment, it also has a pivotal function in activity-dependent synaptic plasticity. Valine to methionine substitution within the BDNF gene prodomain has been recently associated with impaired hippocampal function and memory performance. This variant $BDNF_{Met}$ affects intracellular distribution and activity-dependent secretion of the wild-type $BDNF_{Val}$, and may in turn, lead to hippocampal-related memory dysfunction. However, the cognitive correlates of this functional SNP have not been comprehensively studied. Its role in mediating cognitive impairment in schizophrenia also remains unclear. **Methods:** The relationships between BDNF val66met genotype and a comprehensive battery of standardized neuropsychological tests were studied in 157 healthy volunteers and 340 patients with DSM-IV schizophrenia. We examined the effects of genotype (Met/Met or Met/Val versus Val/Val) on five cognitive domains. Age, gender and full scale IQ were entered as covariates in these general linear models. **Results:** On verbal memory, there was a significant genotype effect but no genotype-by-diagnosis effect. Met allele was associated with poorer verbal memory performance in patients as well as in healthy volunteers. On visuospatial abilities, there were significant genotype as well as genotype-by-diagnosis effects. Impairment in visuospatial abilities associated with the Met allele was specific to schizophrenia patients, but not in healthy volunteers. No statistically significant genotype effects were observed with the remaining 3 cognitive domain scores (i.e. processing speed/attention, problem solving, language) or with full scale IQ. **Conclusions:** Besides replicating the recently reported association between BDNF val66met genotype and verbal memory performance, our findings also suggest that the variant $BDNF_{Met}$ may have a specific role in mediating visuospatial dysfunction in schizophrenia.

111. Is Cognitive Change with Atypical Antipsychotic Medications Pseudospecific? Assessing the Relationship with Dimensions of Change in Clinical Symptoms

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Background: Treatment of patients with schizophrenia using atypical antipsychotic medications has been shown to improve several aspects of schizophrenia, including psychosis, negative symptoms, cognition, and affective symptoms. Previous studies have examined changes in these predefined dimensions of symptoms and have not empirically identified the dimensions of change in symptoms after the initiation of treatment. **Methods:** 185 patients with schizophrenia were switched in an open-label manner from previous treatments with conventional medications, risperidone, or olanzapine to ziprasidone treatment due to lack of efficacy or tolerability. They were rated with the PANSS and assessed with a cognitive battery that examined aspects of cognitive functioning previously shown to be associated with functional outcome and improved by atypical antipsychotic medications. A composite cognitive performance score was created for the analyses in this study, by standardizing the scores at baseline and generating an average score. Patients were examined while on previous treatment, and again after 6 weeks and 6 months of continued treatment. **Results:** Change scores from baseline were examined with two-tailed t-tests. For the PANSS, 28/30 items improved significantly ($p<.05$) at 6 weeks, with this improvement sustained at 6 months. Improvements through week 6 constituted over 90% of the total clinical change. Cognitive performance improved significantly from baseline to both endpoints as well. Exploratory factor analyses (with orthogonal [varimax] rotation) of the PANSS change scores identified 4 factors with Eigenvalues over 1.0, with these dimensions

of change reflecting psychotic symptoms, negative symptoms, hostility/aggression, and anxiety-depression respectively. Interestingly, no PANSS cognitive factor emerged from these analyses. Correlational analyses relating changes in the cognition composite score and the clinical dimensions of change indicated that greater baseline impairment in cognition predicted slightly ($r=-.20$, $p<.05$) reduced response of negative symptoms from baseline to week 6. Changes in all four clinical factors from baseline to week 6 or endpoint were uncorrelated with cognitive changes occurring during this time period (all $r<.08$, all $p>.5$). **Discussion:** Empirically identified dimensions of clinical improvement associated with a switch to ziprasidone treatment include independent improvements in the major symptoms of schizophrenia, as well as hostility, affective symptoms, and performance-based measures of cognition. These improvements are detected at 6 weeks and sustained at 6 months, with most improvement in all dimensions occurring early in treatment. Change in performance-based measures of cognitive functioning was not found to be consequent to other clinical changes (i.e., pseudospecificity) and, in fact, the only significant relationships found suggested that cognitive impairments may constrain improvement in negative symptoms. These data are consistent with previous findings that cognitive change in schizophrenia is detectable and can be discriminated from other clinical changes associated with treatment. This research was funded by Pfizer, Inc.

112. Divalproex/Antipsychotic Combination Treatment of Schizophrenia: Effects on Adiposity and Lipid Metabolism

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Sponsor: Travel Awardee, BMS, 2004

Increased adiposity related to antipsychotic treatment can disturb lipid metabolism. While investigators have begun to examine the effects of antipsychotic monotherapy on lipid metabolism, few studies describe the effect of commonly used polypharmacies on lipid metabolism. This ongoing study seeks to use sensitive measures to observe changes in adiposity and lipid metabolism during combination therapy with divalproex and antipsychotics. Nondiabetic schizophrenia patients (n=23) underwent a 6-week baseline control period with a pre- and post-baseline assessment of metabolic endpoints to confirm stability of treatment endpoints prior to the experimental intervention. Subjects subsequently either initiated or discontinued adjunctive divalproex treatment, followed by repeat metabolic assessments 12 weeks after the experimental intervention. Metabolic assessments relevant to this analysis include dual energy x-ray abpsorptiometry (DEXA) and MRI scans, fasting plasma measurements, and Brief Psychiatric Rating Scale (BPRS) measures of clinical status. In this analysis of adiposity and lipid parameters, no significant changes occurred for either treatment group during the baseline test-retest period, indicating a stable baseline control condition. For all subsequent analyses, the two baseline assessments were averaged for all measures. For subjects starting adjunctive divalproex, a main effect of time (averaged baseline versus 12-week endpoint) was detected for DEXA total fat ($F[1,15]=10.56$, $p=.005$) and fasting triglycerides ($F[1,17]=4.54$, $p=.048$), indicating significant increases associated with initiation of divalproex treatment. A trend level increase in fasting total cholesterol was similarly observed. In the smaller sample of subjects discontinuing adjunctive divalproex, no significant changes in any metabolic endpoint were observed. For subjects going on or off divalproex, no significant changes in BPRS total scores were observed. These data do not support previous reports suggesting that divalproex therapy is associated with beneficial effects on plasma lipids. Additionally, the results suggest further evidence that psychiatric treatment conditions producing increases in fat mass can be associated with adverse effects on metabolic parameters. These results suggest the need for monitoring of adiposity and metabolic side effects during pharmacologic treatment of mental illness. Support Contributed By: NARSAD (Stephen and Connie Lieber), NIMH K23 MH 067795; NIH R01 63985, USPHS, #MOIRR00036, GCRC General Clinical Research Center Washington University, Clinical Nutrition Research Unit Center Grant P30 DK56341 and P60-DK20579

113. Relationship of Viral Infection to Progressive MRI and Neuropsychological Change in a 10 Year Follow-up Study of First Episode Schizophrenia

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Sponsor: Lynn DeLisi

There has been renewed interest in the potential role of viruses as possible etiological agents in the development of schizophrenia. In particular, herpesviruses have the capacity to infect the central nervous system with both acute and chronic effects. There also been interest in the capacity of viruses to moderate the course of illness. In a recent paper, Dickerson et al. (2003) found that serologic evidence of herpes simplex virus I was associated with the degree of cognitive dysfunction seen on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in patients with chronic schizophrenia. Given the lifetime presence of some viruses, we hypothesized that viral infection may be related to progressive brain structural and neuropsychological changes seen in patients with schizophrenia. Patients diagnosed with first episode schizophrenia (n=18) were evaluated at baseline, and after 5 and 10 years of illness using structured psychiatric interviews and symptom ratings, 1.5 Tesla MRI, and a large battery of neuropsychological tests. Serum assays were performed for the measurement of antibodies to members of the herpesvirus family (HSV-1, HSV-2, CMV, EBV, HHV-6, ZVZ, and HERVK) and toxoplasmosis. Slopes and percent change were calculated for MRI data, and differences scores were calculated for the neuropsychological data for baseline to year 5, baseline to year 10, and year 5 to year 10. Spearman correlations were used to assess the relationships between viral antibodies, baseline measurements, and change scores. Preliminary results indicated that higher levels of CMV antibodies were associated with decreased performance on baseline measures of verbal learning and memory whereas higher levels of HERVK were associated with a decline in both visual and verbal memory after 10 years of illness. There was a less consistent pattern of relationships between antibodies and longitudinal MRI and symptom change. Evaluating the influence of viral effects over the course of illness in larger samples of schizophrenia patients may be a useful tool in better understanding the pathophysiology of this illness. Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Ruslanova I, Yolken RH. Association of serum antibodies to herpes simplex virus 1 with cognitive deficits in individuals with schizophrenia. Arch Gen Psychiatry. 2003; 60: 466-472.

114. Deletion of the Glycine Transporter, GlyT1a, Enhances NMDA Glutamate Receptor Function In Vivo and Differentially Alters Amino Acid Levels in Forebrain, Brainstem and Cerebellum

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Sponsor: Kalpana Merchant

The hypoglutamatergic hypothesis of schizophrenia is based on the clinical observations that noncompetitive, use-dependent NMDA receptor antagonists induce psychotic symptoms and cognitive impairments in healthy individuals that are indistinguishable from

schizophrenia. Based on these observations, increased NMDA receptor activity may be efficacious in the treatment of schizophrenia. One strategy for the potentiation of NMDA receptor function is through increases in extracellular glycine, an obligatory NMDA receptor co-agonist that binds to the glycineB site of the NMDA receptor. In support of this therapeutic approach, glycine and other glycineB site agonists have improved cognitive deficits and negative symptoms in schizophrenics when combined with atypical antipsychotics. Re-uptake of glycine, mediated by glycine transporter 1 (GlyT1), is postulated to be important for modulating NMDA receptor activity. A single GlyT1 gene gives rise to 2 major isoforms, GlyT1a and GlyT1b. To further investigate the role of GlyT1a in modulating NMDA receptor function, GlyT1a-specific knockout mice were generated. Deletion of GlyT1a had no apparent effect in mice on viability, fertility, anatomy or morphology. Lack of GlyT1a expression was confirmed at the mRNA level by RT-PCR and at the protein level by radioligand binding and immunohistochemistry using both pan-GlyT1 and GlyT1a-specific antibodies. Levels of endogenous amino acids determined by in vivo microdialysis revealed a significant increase in extracellular glycine (190% of wildtype (WT)) in the prefrontal cortex, but no difference in other amino acids. In contrast, there was a significant decrease of tissue glycine levels in cortex, hippocampus, nucleus accumbens and hypothalamus. Surprisingly, glycine levels in brainstem and cerebellum were increased with significant increases in glutamate and alanine in the brainstem. In the cerebellum, glutamate, glutamine, threonine and taurine were also significantly increased relative to WT. Apparently, GlyT1b was not able to compensate for the absence of GlyT1a. Taken together, these data suggest that GlyT1a is a major determinant of extracellular glycine in the forebrain and hypothalamus and that glycine is tightly regulated, as expected for a neurotransmitter. Based on these results, NMDA receptor function was assessed by in vivo extracellular single-unit recordings in frontal cortical neurons in anesthetized mice. Small incremental iontophoretic applications of exogenous NMDA (range -1 to -22nA) induced a 2-fold greater increase in firing response in age-matched GlyT1a KO vs. WT mice. The threshold iontophoretic NMDA current required to excite GlyT1a KO neurons also appeared to be lower than in WT neurons. These data suggest elevated extracellular glycine levels in GlyT1a KO mice enhanced NMDA electrophysiological responses in the intact brain. Determination of electrical seizure thresholds were consistent with this enhanced NMDA receptor firing, revealing a small, but significant decrease in stimulus intensity required for maximal seizure threshold in GlyT1a KO compared to WT mice. However, no difference in kainate-induced seizures was observed between the two genotypes. Taken together, these functional data suggest that deletion of the GlyT1a enhances NMDA receptor function in vivo and provides further support for inhibition of GlyT1 as a therapeutic approach for schizophrenia.

115. Caspase-3 Activity is Increased by Antipsychotic Treatment in Rat Frontal Cortex

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Caspase-3 is a key downstream protein in the final common pathway of apoptotic activation. Recent data from our lab indicate that chronic treatment with typical and atypical antipsychotics increases activated caspase-3 levels in rat frontal cortex by 40-50% compared to saline-treated animals (German et al. 2004). However, the functional effects of higher caspase-3 levels remain uncertain. To explore this further, caspase-3 activity in cortex from rats treated with haloperidol, clozapine, quetiapine or saline i.p. daily for 4 weeks was measured using a colorimetric caspase-3 activity assay. ANOVA analysis demonstrated a significant effect of treatment at 1 hour ($F=7.32$, $df=3,45$, $p=0.0004$) and 2 hour timepoints ($F=4.62$, $df=3,45$, $p=0.0067$). Compared to saline control at 1 hour, post hoc Dunnett's showed 30% higher caspase-3 activity with haloperidol ($p<0.01$), 42% higher caspase-3 activity with clozapine ($p<0.01$), and 27% higher with quetiapine ($p<0.05$). At the 2 hour timepoint, only clozapine remained 26% higher ($p<0.05$) by post hoc testing compared to saline control. These data demonstrate that the antipsychotic-mediated increase in activated caspase-3 levels in rat frontal cortex is associated with greater functional activity of caspase-3. Although the consequence of elevated caspase-3 activity remains uncertain, it could suggest a role for caspase-3 in the antipsychotic mechanism of action given the similar effect on caspase-3 across typical and atypical agents. Studies on the association between activated caspase-3 and inhibitors of apoptosis proteins (IAPs) as well as rates of DNA fragmentation are ongoing and may provide further insight on this issue. Research supported by grants from NIMH MH-01752 (LFJ) and the Investigator Sponsored Trial Program of AstraZeneca (LFJ).

116. The Longitudinal Relationship of the Brief Assessment of Cognition in Schizophrenia (BACS) to Functional Capacity, Functional Outcome, and Cognitive Rating Scales

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Studies of the efficacy of pharmacologic compounds for improving cognition in schizophrenia will partially depend upon on the sensitivity, reliability, and validity of the instruments used to assess cognitive change. Clinical trials assessing the cognitive enhancing effect of new medications have used neurocognitive assessment batteries that often differ in content, length and administration procedures. Further, registration trials for potentially cognitive enhancing compounds may be required not only to assess efficacy with cognitive performance measures, but with co-primary measures of cognitive or functional change as well. These co-primary measures may include assessments of real-world functional outcome, performance-based functional capacity, or interview-based assessments of cognition. The Brief Assessment of Cognition in Schizophrenia (BACS) assesses the aspects of cognition found to be most impaired and most strongly correlated with outcome in patients with schizophrenia. The BACS requires less than 35 minutes to complete in patients with schizophrenia, yields a high completion rate in these patients, and has high reliability. In a comparison of 150 patients with schizophrenia and 50 healthy controls, the BACS was found to be as sensitive to cognitive impairment in patients with schizophrenia as a standard battery of tests that required over two hours to administer, and BACS composite scores were highly correlated with the standard battery composite scores in patients ($r=0.76$) and healthy controls ($r=.90$). The current study assessed 60 patients with schizophrenia over the course of six months while they were living in a rehabilitation setting. Cognitive functions were measured with the BACS. Functional capacity was measured with the UCSD Performance-based Skills Assessment (UPSA). Real-world functional outcome was measured with the Independent Living Skills Inventory (ILSI). The Schizophrenia Cognition Rating Scale (SCoRS) was used to interview patients and their caregivers about the patient's level of difficulty in seven cognitive domains. BACS composite scores were found to be correlated at baseline with performance-based functional capacity as measured by the UPSA ($r=.63$, $df=55$, $p<.001$), interview-based assessments of cognition as rated by the SCoRS ($r=-.54$, $df=56$, $p<.001$), and real-world functional outcome as assessed by the ILSI ($r=.37$, $df=56$, $p=.005$). Additional analyses will assess the longitudinal relationship of these factors. These data suggest that brief cognitive assessments such as the BACS will be able to assess aspects of cognition that are related to important functional measures in clinical trials of cognitive enhancement. They also suggest that the measures being considered as potential co-primary indicators of cognitive function for registration trials are strongly related to cognition as assessed by brief cognitive assessments.

117. PARS vs. Non-PARS Schizophrenia - A Comparison of Heart Rate Variability (HRV) and Symptoms

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Sponsor: Dolores Malaspina

Introduction: Paternal Age Related Schizophrenia (PARS; Malaspina et al., 2001) has been found to be a unique subtype of schizophrenia with distinct symptoms, cognition, and course patterns. Individuals with schizophrenia have been reported to present both over and under activation of their sympathetic and parasympathetic systems. Heart Rate Variability (HRV) reflects the interplay of the sympathetic and parasympathetic autonomic nervous system on the cardiac pacemaker and is used as a non-invasive measure of arousal. Our aim is to compare HRV in individuals with PARS and Non-PARS (NP), and assess its relationship to symptoms. **Method:** We compared HRV and symptom measures in 21 individuals with DSM-IV diagnosis of schizophrenia (5 with PARS, 16 with NP). Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). HRV was assessed over a 24-hour period using Holter electrocardiograms. Awake and sleep data were subjected to spectral analysis and were normalized for heart rate. Spectral powers were integrated in the Total range (0-.50 Hz), High Frequency (HF, .15-.50 Hz), Low Frequency (LF, .04-.15 Hz), Very Low Frequency (VLF, .0033-.04 Hz), and Ultra Low Frequency (ULF, 0-.0033 Hz). HF power is mediated by cardiac vagal function and LF power is dually mediated by sympathetic and vagal functions. The HRV data of the PARS and NP groups were compared for the entire 24-hour period, as well as during sleep and wakeful periods. **Results:** Analysis of variance using age as a covariate, PARS vs. NP as a grouping factor, and awake vs. sleep as a repeated measures showed that patients with PARS had decreased overall ULF power ($F=6.41$; $df=1,19$; $P=0.020$) and increased overall VLF ($F=5.89$; $df=1,19$; $P=0.025$) and LF power ($F=4.38$; $df=1,19$; $P=0.050$). The sleep period accounted for these groups differences with decreased sleep ULF power for PARS ($F=14.70$; $df=1,16$; $P=0.001$) and increased overall VLF power for NP ($F=8.72$; $df=1,16$; $P=0.009$). Additionally, each group HRV data displays unique relationship with symptoms. **Discussion:** The findings of significant PARS vs. NP group differences indicate distinct arousal patterns associated with each subtype. Specifically, patients with PARS displayed decreased HRV, in particular during sleep, indicating inadequate downward ANS regulation during rest states. These results are consistent with findings of higher sleep sympathetic activity in patients with panic disorder. The results suggest the presence of significant group differences in wake-sleep rhythms reflecting disturbances in the functions of thermoregulatory processes, peripheral vasomotor activity, and/or the Renin-Angiotensin system, as well as long-term regulatory mechanisms. The ULF data is particularly important considering its association with increased cardiac mortality in patients with cardiac disease. The findings also underscore the importance of using 24-hour records to quantify HRV. Our findings are also particularly significant given the fact that we assessed only five PARS subjects.

118. Improvement in Influences on Medication Adherence in Non-compliant Patients with Schizophrenia Treated with Orally Disintegrating Olanzapine

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Sponsor: Richard Mohs

Background: Rating of Medication Influences (ROMI)(1)scale was used to measure influences on medication compliance and non-compliance in 85 agitated, non-compliant schizophrenics treated with orally disintegrating olanzapine tablets (ODOT). **Methods:** In this post-hoc analysis of a 6-week study, we assessed mean change from baseline of ROMI items. We examined ROMI item correlations with Positive and Negative Syndrome Scale (PANSS) factors(2) using Pearson′s correlation coefficients. **Results:** Significant mean changes in ROMI-compliance (ROMI-C): 1 (perceived benefit), 2 (fear of relapse) and 3 (side effect relief), and ROMI-non-compliance (ROMI-NC): 10 (no benefit), 11 (unnecessary), 12 (never was ill), 13 (interferes with life goals), 14 (distressed by side effects), and 17 (outside opposition to taking medication) occurred by Week 1. Significant correlations between ROMI Items and PANSS factors at baseline ($p<.05$) included ROMI-C Items 1-3 and PANSS positive, negative, disorganized and hostile and, after Week 1, ROMI-C Items 1-4 (fulfillment of life goals) and PANSS positive, negative, disorganized and hostile and ROMI-NC Items 11, 12, and 16 (change in appearance) and PANSS positive, negative, and disorganized. **Conclusion:** Patients significantly increased ROMI-C item endorsement and decreased ROMI-NC item endorsement after 1 week ODOT. ROMI-C items correlated negatively and ROMI-NC items positively with PANSS factors. References: 1)Weiden P, Rapkin B, Mott T, Zygmunt A, Goldman D, Horvitz-Lennon M, Frances A.Rating of medication influences (ROMI) scale in schizophrenics. Schizophrenia Bulletin 1994;20:297-310; 2)Davis JM, Chen N. The effects of olanzapine on the 5 dimensions of schizophrenia derived by factor analysis:combined results of the North American and international trials.J Clin Psychiatry 2001;62(10):757-71.

119. Predominance of Psychiatric-Based Reasons for Antipsychotic Treatment Discontinuation

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Introduction: Antipsychotic treatment discontinuation in controlled, clinical trials was examined to provide insight into overall treatment effectiveness. **Methods:** A post hoc, pooled analysis of 4 randomized, double-blind clinical trials of 24-28 week duration included 822 olanzapine-treated and 805 risperidone-, quetiapine-, or ziprasidone-treated patients. **Results:** A majority of patients (53%; 866/1627) discontinued early from antipsychotic treatment with poor response/symptom worsening the most frequent reason for discontinuation (36%; 315/866). Patients who discontinued early appeared to have slower initial improvement compared to patients completing the study. Discontinuation due to poor response was overwhelmingly linked to patient preference as compared to physician preference alone (80% vs. 20%). Patient perception of poor response occurred sooner than physician perception alone. Additionally, 17% of discontinuations were due to worsening of the underlying psychiatric condition and 12% were due to medication intolerability. Patients discontinuing due to adverse events showed a response rate comparable to patients completing the study. **Conclusions:** Poor treatment response, underlying psychiatric symptom worsening, medication intolerability, and patients' perception of failure to improve contributed to treatment discontinuation, which can threaten patient well-being through illness exacerbation. A better understanding of causes for discontinuation may help improve patient engagement in long-term therapy and realization of treatment goals. References: 1.Santarlasci B, Messori A. Clinical Trial Response and Dropout Rates with Olanzapine Versus Risperidone. Ann Pharmacother 2003;37:(published online); 2.Perkins DO. Adherence to Antipsychotic Medications. J Clin Psychiatry 1999;60[suppl 21]:25-30.

120. 1-2 Year Outcome Associated with Naturalistic Treatment in First Episode Schizophrenia

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Sponsor: Ruben Gur

Background: Treatment of first episode schizophrenia patients (FE-SZP) presents as a challenging undertaking. Over the past 10-15 years, atypical antipsychotics have largely supplanted atypical antipsychotics as first line medications. Existing treatment studies have mostly focused on chronic schizophrenia patients and those who have focused on FE-SZP have shown high drop out rates and poor follow up rates. We examined the effects of antipsychotic treatment in a group of FE-SZP who underwent treatment as clinically indicated and were followed over a period of 1-2 years. **Methods:** At the Schizophrenia Research Center 63 FE-SZP (M:F=39:24, Caucasian: African-American=19:44), including 24 subjects with schizophreniform disorder who were subsequently diagnosed with schizophrenia, were evaluated between 1986-2004 and followed over a period of 1-2 years. According to published guidelines (Gur et al. 1991), subjects were diagnosed and assessed for positive, negative, overall psychiatric and depressive symptoms. Patients were treated with typical and atypical antipsychotics as clinically indicated. According to treatment for >80% of the follow up period, including >30 days prior to follow up evaluation, patients were grouped into adequate (AT) or inadequate (IT) treatment groups. The AT group was further separated into primary treatment with typical and atypical antipsychotics. The three groups were compared using nonparametric analyses, adjusting for symptom severity at intake. **Results:** AT and IT did not differ in distribution of gender, ethnicity, age at onset and status at intake (in- or outpatient). Duration of illness was higher in IT (p=.02). AT rated higher in thought disorder (p=.04). The group subsequently treated with atypicals had lower total negative (p=.04) and positive (p=.004) symptoms, lower hallucinations (p=.01), bizarre behavior (p=0.06) and cognitive symptoms of depression (p=.004). At follow up, AT (n=41) experienced lower ratings for total positive symptoms (p=.04) and delusions (p=.08), lower cognitive symptoms of depression (p=.07), and higher alogia (p=.06), when compared to IT (n=22). Comparing AT on typical (n=24) and atypical antipsychotics (n=17), the group on atypicals (average chlorpromazine equivalents/day=33, average olanzapine equivalents/day=14.5) experienced lower ratings on depression (p=.005) and alogia (p=.06). **Conclusions:** Patients who were adequately treated differed at intake in severity of thought disorder and duration of illness. Duration of illness may be a reflection of treatment noncompliance. Gender, ethnicity and hospitalization status at intake were not associated with treatment outcome. Patients subsequently treated with atypicals rated lower on several measures of positive, negative and depressive symptoms, perhaps indicating increasing awareness of symptoms and earlier treatment over the recent years.

121. DTI and MTR Abnormalities in Schizophrenia: Analysis of White Matter Integrity

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Sponsor: Travel Awardee, BMS, 2004

Background: Diffusion Tensor Imaging (DTI) and Magnetization Transfer Imaging (MTI) are new imaging techniques that may help to characterize white matter brain abnormalities in schizophrenia. To date, diffusion studies in schizophrenia show lower anisotropic diffusion within white matter, likely due to loss of coherence of white matter fiber tracts, to changes in the number and/or density of interconnecting fiber tracts, or to changes in myelination, although methodology as well as localization of such changes differs between studies. MTI, a technique sensitive to myelin and axonal alterations, and thus likely to increase specificity of DTI findings, has not been combined with DTI in the same study. **Objective:** The aim of this study is to localize and to specify further DTI abnormalities in schizophrenia, by combining DTI with MTI. **Methods:** 21 chronic schizophrenics and 26 controls were scanned using Line-Scan-Diffusion-Imaging and T1-weighted techniques with and without a saturation pulse (MT). Diffusion information was then used to normalize co-registered maps of Fractional Anisotropy (FA) and Magnetization Transfer Ratio (MTR) to a study specific template, using the daemon algorithm, an algorithm designed specifically to deal with multidirectional tensor information. FA and MTR maps were then subjected to voxel wise group comparisons. **Results:** Diffusion anisotropy was decreased in the schizophrenia compared to controls, bilaterally in the cingulum bundle, bilaterally in the superior occipito-frontal fasciculus, bilaterally in the internal capsule, in the fornix and the corpus callosum, also in the right inferior occipito-frontal fasciculus and left arcuate fasciculus. In contrast, MTR maps, similarly to the FA, demonstrated changes in the corpus callosum, fornix, right internal capsule and superior occipito-frontal fasciculus bilaterally, but not in the anterior cingulate fasciculus, left internal capsule, arcuate fasciculus or inferior occipito-frontal fasciculus. In addition, the right posterior cingulum bundle showed MTR but not FA changes in schizophrenia. **Conclusion:** These findings suggest that while some of diffusion abnormalities in schizophrenia are likely due to abnormal coherence, or organization of the fiber tracts, some of these abnormalities may, in fact, be attributed to, or coincide with, myelin/axonal disruption. In addition, few myelin/axonal alterations (i.e., right temporal cingulum bundle) occur without changes in DTI signal.

122. Early-Onset Schizophrenia: A Diffusion Tensor Imaging Study

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Sponsor: Past Travel Awardee, BMS, 2002

Purpose: To study white matter integrity of brain regions using diffusion tensor imaging and a voxel based approach for analysis in children with early onset of schizophrenia relative to healthy control subjects. **Materials and Methods:** Thirty-six patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and a mean age (+/- SD) of 15.59 (2.17) years were recruited from inpatient and outpatient facilities at the Zucker-Hillside Hospital. The normal control group consisted of thirty-four age (mean age 15.43 +/- 2.76 years) and gender-matched subjects who were obtained from advertisements and community centers. Normal controls were screened for any neurological and psychological impairment. In addition to routine clinical scans (T1, T2 and FLAIR) for clinical purposes, diffusion tensor images (DTI) with matching fast spin echo (FSE) double echo sequence for segmentation and 3D spoiled gradient recalled (SPGR) with inversion prep (IR-Prep) for registration were obtained. Twenty five gradient direction DTI slices were graphically prescribed parallel to the AC-PC. Double echo FSE sequence was obtained with matching slices to the DTI locations. Image analysis sections were comprised of intra and inter subject registrations. For the inter subject registration a brain extracted template image was selected from all the subjects and transferred into Talairach space using AFNI. Using a 3D warping technique all other images were registered to the template image. The warp field (W3D) of each individual subject was stored for the transformation of the FA map into the common Talairach

space. The intra subject registration was accomplished using a linear rigid-body transformation. The resultants rigid transformation matrix was stored for registering the FA maps of all subjects. Raw diffusion images were corrected for susceptibility induced spatial distortions using the T2 volume of each subject. The resultant warp field of each subject was stored for correction of FA maps for susceptibility distortion. The FA map of each subject was then transformed to the Talairach coordinates by combining all three transformations into a single transformation and applied it to the original FA map in one single interpolation step. Mann-Whitney and t tests were used for statistical analysis of FA maps. Voxels that had a t-statistic greater than 3.85 ($p < .001$; two-tailed) and were part of a spatially contiguous cluster size of 100 voxels or greater were considered to be significantly different between groups. **Results:** Compared to healthy volunteers, patients demonstrated lower FA in areas corresponding to the left superior fronto-occipital fasciculus and the left inferior front-occipital fasciculus using the fiber tract-based atlas of human white matter anatomy (Wakana et al., 2003). There were no areas of significantly higher FA in patients compared to healthy volunteers. **Conclusions:** The areas of lower FA possibly indicate a disruption of the structural integrity of visual pathways in adolescents with schizophrenia compared to healthy controls. Future studies will examine the functional correlates of decreased fractional anisotropy in these regions with measures of visual processing function and the development of these capacities in adolescents with schizophrenia and healthy comparison subjects.

123. Maintenance Therapy with Long-acting Risperidone: Functioning and Quality of Life in Patients with Schizophrenia or Schizoaffective Disorder

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Sponsor: David Feifel

Objective: Improvements in patient functioning and quality of life (QoL) are important goals of long-term treatment of psychotic illness. The objective of this analysis was to examine the impact of maintenance therapy with long-acting injectable risperidone on functioning and QoL in clinically stable patients with schizophrenia or schizoaffective disorder. **Method:** Data are from an ongoing, 52-week, prospective, randomized, double-blind, multicenter study in 324 patients with schizophrenia or schizoaffective disorder randomized to long-acting risperidone 25 or 50 mg every 2 weeks, previously taking oral antipsychotics. Patients were symptomatically stable, without signs of relapse during the 4 months prior to baseline (no psychiatric hospitalization due to worsening symptoms, no clinically significant self-injury, suicidal or homicidal ideation, or violent behavior), and taking stable doses of oral antipsychotic medication for 4 weeks prior to baseline. Functioning and QoL were assessed using the Strauss-Carpenter Level of Functioning Scale (LOF), the Personal and Social Performance Scale (PSP), and the Schizophrenia Quality of Life Scale (SQLS). **Results**: Results are reported here for the interim, 6-month endpoint. Seven of 9 items on the LOF improved: frequency of social contacts (≥1 per month) increased from 73.0% at baseline to 75.2%, and the percentage of at least moderately close relationships improved from 64.0% to 70.0%. The quality of useful work increased from 91.9% to 98.6%, and the percentage of patients with slight to no signs and symptoms improved from 63.4% to 66.4%. At baseline, 83.5% of patients reported they needed little to no help with basic needs; 85.8% reported this level of ability at the 6-month endpoint. The percentage of patients who reported a moderate to very full life increased from 58.3% to 61.6%, and, while 75.4% of patients had moderate to no impairment in function at baseline, 81.0% reported this level of function at the 6-month endpoint. The PSP score (mean±SD) improved statistically significantly, from 62.1±4.2 at baseline to 63.7±13.7 ($P<0.01$). The SQLS scores indicated that QoL was maintained, with no significant changes. **Conclusions:** Baseline measures of clinical status confirmed a symptomatically stable patient population. Even so, 6-month, interim data indicated improvements in measures of functioning and maintenance of QoL. Functional benefits, which are long-term outcomes of treatment, will be further explored when data with 52 weeks of long-acting risperidone treatment become available. Supported by Janssen Medical Affairs, L.L.C.

124. Enhancing the Clinical Relevance of PANSS Scores in Schizophrenia

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Introduction: The Positive and Negative Syndrome Scale (PANSS) is a well-validated 30-item clinical rating scale (score range: 30–210) commonly employed in experimental therapeutics in schizophrenia. Although valuable for research, changes in PANSS ratings are not readily translated to clinical status. Accordingly, we evaluated relationships of PANSS ratings to the Clinical Global Impression of Severity (CGI-S) scale, a validated 7-point scale (range: 1 = "not ill", to 7 = "extremely ill", so as to provide clinically meaningful ratings. **Methods:** Paired CGI-S and PANSS ratings from 3118 patients with schizophrenia or schizoaffective disorder (15,298 assessments) in 7 clinical trials were analyzed by linear regression modeling of the relationship between two ratings. PANSS-total scores were divided into 7 groups by a sensitivity analysis based on receiver-operating-characteristic (ROC) methods, and cut-off points were validated by kappa statistics. Proportional-odds analyses were used to build probability models for CGI-S predicted by either continuous or categorical PANSS-total measures. **Results:** With PANSS-total score as a continuous measure, a regression model [CGI = 0.899 +(0.040)(PANSS)] yielded $r^2 = 0.580$. We constructed a proportional-odds model: $\text{Logit}(g_i[\text{CGI}]) = y_i + k*(\text{PANSS total})$ with a common slope ($k = -0.104$), and y-intercept (y_i) values for CGI scores of 1-6: 1.713, 4.282, 6.599, 9.427, 11.78, and 14.87. For example, a PANSS-total score of 100 corresponded to CGI-S scores with probabilities of: 0.02% (CGI=1), 0.20% (CGI=2), 2.0% (CGI=3), 25% (CGI=4), 52% (CGI=5), 19% (CGI=6), and 1.1% (CGI=7), or most closely to CGI=5 ("markedly ill"). We used PANSS-total score as a categorical variable to generate cut-off points based on the condition, sensitivity = [1 —specificity]. Corresponding to CGI-S scores of 1-6, we determined PANSS cut-off points of: 57, 57, 66, 78, 86, and 105. Kappa testing showed high agreement of CGI and categorized PANSS scores. A proportional-odds model for CGI scores using a categorical PANSS scale was constructed as $\text{Logit}(g_i[\text{CGI}]) = y_i + k_j*(\delta\_\text{PANSS total})$ used the following coefficients (y_i) for PANSS-total scores at CGI-S scores of 1—6:—6.030,—3.645, —1.453, 1.296, 3.521, and 6.496, with kj of: 1.618, 0.665, —0.453, —1.483, and —3.459, respectively. In this model, PANSS scores of 86-104 corresponded to CGI-S scores of 1-7 at probabilities of: 0.05%, 0.50%, 4.0%, 40%, 43%, 11%, and 0.70%, indicating maximum correspondence to a CGI rating of 4 or 5 ("moderately" or "markedly ill"). **Conclusions:** Statistical analyses based on continuous or categorized PANSS-total scores yielded similar predictions of corresponding CGI-S ratings. With categorical methods, a patient with a PANSS-total score of 30-65 is most likely to be considered "mildly ill" (CGI=3); scores of 66-85 correspond most closely to "moderately ill" (CGI=4), and PANSS-total ≥86 indicates "markedly ill" (CGI≥5). PANSS reductions within the defined categories indicate corresponding CGI-S global improvement scores. For example, a patient with a PANSS score of 60 has only 11% chance of being "not ill" (CGI=1) or "minimally ill"(CGI=2), whereas one rated

50 has a 37% chance of achieving such a low CGI score. These findings indicate the feasibility of simple translations of PANSS scores into clinically readily appreciated outcomes. Supported in part by Janssen Medical Affairs, L.L.C. (BC, YZ, RL, CS), and a grant from the Bruce J. Anderson Foundation and the McLean Private Donors Fund for Psychopharmacology Research (RJB).

125. Neurons in the Medial Prefrontal Cortex Receiving Monosynaptic Inputs from the Basolateral Amygdala Encode Learned Emotional Associations through Burst and Frequency Codes

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Sponsor: Travel Awardee, BMS, 2004

Neurons in the medial prefrontal cortex (mPFC) are involved importantly in the processing of emotionally salient sensory information and are functionally and anatomically linked to the basolateral amygdala (BLA). We have reported previously that neurons in the BLA encode emotional learned associations. An important question concerns whether neurons encoding emotional learning are localized to circumscribed neural regions or are arranged in a distributed pathway among other projection areas of the amygdalar network. Using single-unit extracellular recordings of rat mPFC neurons, we isolated mPFC neurons that responded monosynaptically and orthodromically to electrical BLA stimulation (200-800 ?A) and paired a specific odor with either footshock (CS+) or no footshock (CS-). Post-conditioning, mPFC neurons displayed significantly greater firing frequency rates relative to baseline in response to presentations of CS+ odors but displayed baseline or lower activity levels when presented with the CS- odor. In contrast, neither non-BLA responsive mPFC neurons nor mPFC neurons antidromically activated from the BLA displayed any associative learning. In addition, both the level of burst firing and number of spikes per burst event were significantly increased in BLA-responsive mPFC neurons in response to CS+ presentations. We examined the possible role of dopamine D4 receptors in the encoding of emotional memory formation in the mPFC. Systemic administration of a competitive and specific antagonist of the D4 receptor subtype (L,741-741; 0.8mg/ml) blocked emotional learning in neurons of the mPFC as demonstrated by blockade of both firing frequency and burst activity increases in the presence of the CS+. Our findings demonstrate that neurons in mPFC that receive BLA input display emotional associative learning to classically conditioned odors and this information may be represented by burst and frequency codes dependent upon signaling through dopamine D4 receptors at the level of single mPFC neurons.

126. The 5-HT2A/2C receptor dysfunction in male patients with schizophrenia and its interaction with BMI

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Serotonin (5-HT)2A/2C receptor mechanisms have been suggested to be involved in pathophysiology of schizophrenia (SCH), as well as in obesity. Thus, we have examined 5-HT2A/2C receptor function and its interaction with body weight in male patients meeting DSM-III-R criteria for schizophrenia (SCH) or schizoaffective disorder (n=94) and in male normal controls (NC) (n=38) by using MK-212 (6-chlor-2[1-piperazinyl]-pyrazine) (20 mg p.o.), a 5-HT2A/2C receptor agonist, as a probe. Plasma cortisol, prolactin and oral body temperature were measured for a 3-hr period after the baseline blood sampling followed by the MK-212 or placebo administration, single blindly in random order. Each group was divided by body mass index (BMI) following the conventional classification of over weight (BMI < 25 vs ≧25). Group differences, as well as group and BMI interactions on cortisol, prolactin and temperature responses to MK-212 were examined by applying the univariate analysis of covariance. The SCH showed a significantly blunted temperature response to MK-212 compared to NC ($p=0.04$). There was no significant group differences for plasma cortisol or prolactin responses to MK-212. Only plasma cortisol responses to MK-212 showed a significant diagnosis and BMI interaction ($p=0.009$), which was due to an opposite direction of interaction between groups; in NC, the over weight NC had a significantly greater cortisol responses to MK-212 compared to the normal weight NC ($p=0.04$). However, in SCH, the over weight SCH had a trend of lower cortisol responses to MK-212 compared to the normal weight SCH ($p=0.08$). Similarly, the cortisol response to MK-212 showed a significant positive correlation with BMI in NC ($p=0.02$), but a negative correlation in SCH ($p=0.01$). The cortisol response to MK-212 has been suggested to be mediate via 5-HT2A receptor mechanisms, and the temperature response to MK-212 via 5-HT2A/2C receptor mechanisms. The results of this study suggest that SCH has subsensitive 5-HT2A/2C functions and/or down-regulated 5-HT2A/2C receptors. The 5-HT2A receptor function appears to be related with obesity in both NC and SCH, as well as with pathophysiology of SCH. The reason for an opposite direction of interaction of the cortisol response to MK-212 with BMI in SCH compared to NC merits further study.

127. Mismatch Negativity Deficits and their Relationship to Functional Impairments are Stable in Chronic Schizophrenia Patients

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Objectives: Mismatch negativity (MMN) is a preattentive, auditory event-related potential component that is automatically elicited when oddball stimuli occur in the context of large numbers of standard stimuli. Previous studies have demonstrated that MMN deficits are associated with neurodegenerative changes in first episode schizophrenia patients and with poor everyday functioning in chronic schizophrenia patients. If these deficits are stable in chronically impaired schizophrenia patients, then MMN may show promise for characterizing schizophrenia patients in longitudinal treatment-outcome studies. The aims of the present study were to: 1) assess the long-term stability and/or progression of MMN deficits; and 2) examine the longitudinal stability of the previously reported MMN/functional status relationship. **Methods:** Chronic schizophrenia patients (n=10) underwent repeated testing over a 1-2 year period (average retest interval=578 ±39.3 days) and were compared with age-matched normal subjects (n=10). **Results:** Schizophrenia patients had significantly reduced MMNs ($t=-3.56$, $p<0.01$) that were highly stable over time ($r=0.79$, $p<0.01$ at Fz). Group means in the schizophrenia patients were stable across the retest interval (Fz: session 1: -2.23; session 2: -2.07; $p>0.50$). MMN deficits were also significantly associated with poor functional status at both session 1 ($r=-0.63$, $p<0.05$) and session 2 ($r=-0.68$, $p<0.05$) in the schizophrenia patients. **Conclusion:** MMN deficits and their relationship to poor functional status are stable in chronic schizophrenia patients. The high stability of MMN deficits in chronic schizophrenia patients raises the possibility that MMN may be useful for assessing changes in preattentive sensory processing in longitudinal psychopharmacological treatment studies. Future studies will clarify the time course of the emergence and progression of these deficits across the course of the illness.

128. An Item Response Analysis of the Positive and Negative Syndrome Scale (PANSS)

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Sponsor: Robert Smith

Background/Objectives: The Positive and Negative Syndrome Scale (PANSS) is the most widely used measure of symptom severity in schizophrenia. This 30-item scale has demonstrable high internal reliability and construct validity, and has undergone factor analyses in different patient populations to identify its underlying factor structure. Despite extensive research, it is unclear how the PANSS individual items differ in their usefulness in assessing the severity of schizophrenia. The objective of this study was to use Item Response Theory, a statistical approach that can provide information regarding the degree of usefulness of each PANSS item in the assessment of the overall severity of schizophrenia. **Method:** Data included baseline PANSS item scores of patients with schizophrenia or schizoaffective disorder who have been enrolled in a large naturalistic observational study or in one of 12 randomized double blind clinical trials comparing olanzapine to other antipsychotic drugs. These studies were conducted between 1995 and 2003. Using a nonparametric item response model, option characteristic curves were produced to examine how the probability of endorsing a particular option (each PANSS item has 7 options corresponding to the 7 levels of severity) changes with increasing overall severity of illness, as measured by the PANSS total score. Ideal items are those for which increased illness severity corresponds to increased responses on that item across the entire range of illness severity. Illness severity was also defined as the score on the PANSS subscales (Positive, Negative, and General Psychopathology), and option characteristic curves were generated to examine the ability of each of these PANSS subscales to discriminate among individual differences in illness severity. **Results:** PANSS data were available for 9205 individuals, primarily male (65%) inpatients or outpatients, with an average age of 39.0 (SD=11.5), whose average PANSS total score was 81.9 (SD=22.0), ranging broadly from 30 to 177. Option characteristic curves identified 9 PANSS items that performed very well (e.g., P1, delusions; P6, suspiciousness; N1, blunted affect; N4, passive/apathetic social withdrawal; P2, conceptual disorganization), 7 items that were good (e.g., P5, grandiosity; P4, excitement; G4, tension; G11, poor attention) and 14 items that performed less well (e.g., G1, somatic concerns; G6, depression; G10, disorientation). Among the PANSS subscales, the Positive and the Negative subscales were more discriminating than the General Psychopathology subscale score or the PANSS total score, suggesting that use of individual scales may be more sensitive to change than use of the scale total score. **Conclusions:** This first item response analysis of the PANSS supported its sound psychometric properties and demonstrated that most of its items were very good or good at assessing the overall severity the illness. Results did show where a number of items and options, primarily on the General Psychopathology subscale, might be improved. Further, because the Positive and the Negative subscales may be more sensitive to change than the PANSS total score, these subscales may constitute a "mini PANSS" that may be more reliable, require shorter administration and training time, and may possibly reduce the sample size needed for future research studies.

129. Expression of Disc1 in Development and in Schizophrenia

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DISC1 was identified in chromosome 1q42.1 based on a balanced translocation (chr 1;11), which segregated with major mental illness in an extended Scottish family (Millar et al. 2000). Single nucleotide polymorphisms in exon 11 and around are associated with schizophrenia and various intermediate phenotypes, including hippocampal function/structure (Callicott et al., in press). In humans, DISC1 is transcribed as at least two major splice variants (L and Lv). Evidence for additional alternative splicing (S, Es) in humans has also been reported. In the present study, we characterized a developmental profile of DISC1 expression by in situ hybridization from neonatal age through late adulthood using slices from the human hippocampus (n=39) and measured expression of DISC1 mRNA by RT-PCR in the postmortem hippocampal samples from controls and schizophrenic patients (total n=122). The expression of DISC1 using a riboprobe (1172 bp fragment of human Disc1, nucleotides 915-2087, exons 2-10, Austin et al. Neuroreport 14, 2003), was markedly increased in the infant hippocampus as compared with neonates (by 104%), teens (85%), adolescents (103%), adults (146%) and aged adults (202%), $p<0.01$. In RT-PCR analysis using probes designed for Es and S variants, we did not obtain any amplification of cDNA from the adult human hippocampal tissue, in contrast to an L and Lv probe. This was confirmed by in situ hybridization analysis of the hippocampal slices using a riboprobe recognizing L and Lv transcripts, which revealed an abundant signal in the adult dentate gyrus but no signal with E or S probes. We found that combined L and Lv expression in the hippocampus measured by RT-PCR tended to be increased in schizophrenics, $p=0.057$. There was no effect of any of the high risk SNP alleles identified in our clinical datasets on DISC1 expression in the hippocampus of normal controls or all subjects, though ethnic background is not the same in the brains and clinical samples. Our preliminary results suggest that DISC1 mRNA may be upregulated in the hippocampi of schizophrenics, but more research is needed to rule out secondary effects and to relate expression to genetic susceptibility.

130. Schizophrenia Subgroups: Carving Nature at its Joints

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Introduction: Schizophrenia is frequently studied and discussed as if it were a unitary condition, although it is actually a syndrome comprised of different variants, yet to be clearly demarcated. Recent epidemiology studies consistently show advancing paternal age as an independent risk factor for schizophrenia, explaining up to 25% of all cases. Translational research studies show complementary findings; including a significant association of late paternal age with neurobehavioral deficits in inbred 129S6/SvEv mice and with lower mean IQ and social capacity in a cohort of human adolescents. We brought this burgeoning epidemiology and animal data to the clinical interface. **Method:** We characterized 265 schizophrenia patients as to demographics, symptoms, cognition (WAIS-R, Wechsler Scales), and studied subsets in imaging and physiology protocols. Paternal age related schizophrenia (PARS) was defined as family history negative (sporadic) cases with paternal age >33 yrs. We first compared PARS to familial cases using multivariate analyses. Next, we used K-means clustering techniques that included paternal age and family history as clustering variables to identify latent classes amongst the entire sample. **Results:** PARS cases had superior WAIS-R IQ scores, greater medication free positive symptoms, and less deficit syndrome schizophrenia than familial cases. A group by sex interaction showed that PARS females were significantly more cognitively impaired than PARS males, with the converse being true in other cases. On neuroimaging, PARS had resting hypofrontality, whereas familial cases had left lateralized hypoperfusion. The K-means clustering yielded 5 clusters and strengthened the evidence that PARS was a specific variant. There were 3 sporadic (S1, S2, S3) and 2 familial (F1, F2) clusters. (S1): "PARS" N=55, included 78% of the cases we defined as PARS. It had the largest Verbal IQ vs. Performance IQ difference (V IQ, P IQ: 94;

84.1); 13.8 yrs education, with onset at= 20.4 (5.1) yrs. (S2): N=103, was a cognitively intact group (108.7, 105.5), with 14.4 yrs education; onset =26.7 (7.0) yrs. (S3): N=75, was more impaired (73.8, 70.4) with 9.7 yrs education; onset =17.9 (5.1) yrs. The familial clusters were (F1): N=37, a late onset (28.7) more educated (14.4 yrs) group with normal IQ (98.8, 91.2), and (F2) N=84, an impaired (78.6, 71.2) group with onset at 18.6 (4.6) yrs and less education (10.4 yrs). The five clusters showed differences in positive and negative symptoms and their responsiveness to antipsychotic medications. They also showed differed in attention, Wechsler memory scales, deficit syndrome, and in psychophysiological measures. **Conclusion:** These findings demonstrates that paternal age related schizophrenia (PARS) may be a specific variant of schizophrenia and that segregating it from other forms of the disease can significantly reduced the remaining unexplained variance in the schizophrenia syndrome. Altogether, we identified five subtypes of schizophrenia. These results may provide methods to distinguish disease variants in early illness for targeted treatment studies, to trace pathophysiological pathways to disease, and to clarify phenotypes for genetic studies.

131. Efficacy and Safety of Donepezil in Patients with Schizophrenia or Schizoaffective Disorder: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial

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Sponsor: Lisa Gold

Background: Schizophrenia is a neuropsychiatric disorder characterized by positive symptoms, negative symptoms, and prominent cognitive deficits. Cognitive impairment is often present at or before the first onset of psychosis and continues throughout the course of the disorder, affecting memory, attention, and executive function. Atypical antipsychotic medications have been shown to partially ameliorate cognitive deficits. Despite these modest improvements, substantial cognitive impairment remains and contributes to the longer term morbidity associated with schizophrenia. Treatment with cholinesterase inhibitors has been shown to improve cognition, function, and the behavioral symptoms associated with Alzheimer disease. Pilot studies of donepezil used adjunctively with commonly prescribed antipsychotic medications in patients with schizophrenia have demonstrated benefits in cognition, with no reported safety issues. **Objective:** To evaluate the efficacy and safety of donepezil as cotreatment in improving cognition in patients with schizophrenia or schizoaffective disorder receiving atypical antipsychotic medications. **Methods:** This 12-week, multicenter, double-blind, placebo-controlled trial was conducted at 35 North American sites and randomized 251 patients (aged 18-55 years) with a clinical diagnosis of schizophrenia or schizoaffective disorder to receive either placebo or donepezil (5 mg/d for 6 weeks followed by 10 mg/d for 6 weeks). Patients were stabilized on an optimal dose of atypical antipsychotic medication (risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole alone or in combination) for at least 3 months prior to study. The primary efficacy measure was a composite score based on the NIMH Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Neuropsychological Battery, a comprehensive assessment of cognition developed for use in multicenter trials. Secondary efficacy measures included the Clinical Global Impression, Role Functioning Scale, assessments of psychiatric symptoms, and a patient self-rating of cognition. Safety was monitored by physical examination, electrocardiogram, clinical laboratory tests, and incidence of adverse events. Patients were evaluated for efficacy and safety at baseline and Weeks 3, 6, 9, and 12. **Results:** Preliminary data analyses from this clinical trial are now under way. Data from the cognitive end points will be presented to assess the efficacy of donepezil treatment across a number of cognitive domains that are often impaired in patients with schizophrenia. Moreover, we will present data on the effects of donepezil on the behavioral and functional end points. Research supported by Pfizer Inc, New York, NY, and Eisai Inc., Teaneck, NJ.

132. Combined α2- and D2 Receptor Blockage Enhances Cortical Glutamatergic Transmission and Reverses Cognitive Impairment Induced by MK-801 in the Rat

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Sponsor: Past Travel Awardee, ECNP-ACNP, 2003

The atypical antipsychotic drug (APD) clozapine (CLOZ) shows superior clinical efficacy compared with conventional APDs, including an advantageous effect on cognitive and negative symptoms, in spite of a much lower dopamine D2 receptor occupancy in brain. In contrast to most other APDs, CLOZ possesses a high affinity for α2 adrenoceptors, and adjunctive treatment with the selective α2 adrenoceptor antagonist idazoxan (IDA) enhances the efficacy of typical D2 antagonists in treatment-resistant schizophrenia. Adding IDA has also been shown to dramatically enhance the antipsychotic-like effect of low doses of the selective D2/3 antagonist raclopride (RAC, 0.05 mg/kg) in the rat. CLOZ, but not typical APDs, as well as the combination of RAC and IDA, have also been found to produce a marked increase in dopamine release in the medial prefrontal cortex (mPFC), which is of major interest because of the role of prefrontal dopamine in cognitive functioning. In addition, CLOZ has been shown to potentiate postsynaptically expressed N-Methyl-D-Aspartate (NMDA) receptors in the mPFC via a dopamine-mediated activation of D1 receptors. Thus, facilitation of both dopamine- and glutamate-mediated transmission in the PFC may contribute to the advantageous clinical profile of CLOZ. By using intracellular recording we have investigated the effects of RAC, IDA and a combination of RAC and IDA, as well as CLOZ, on electrically evoked excitatory postsynaptic potentials and currents (EPSPs and EPSCs) in pyramidal cells of the rat mPFC. Neither RAC (1 μM) nor IDA (1 μM) alone caused any significant potentiation. In contrast, the combination of RAC and IDA completely mimicked the potentiation by CLOZ. This effect could be abolished by previous monoamine depletion (reserpine 5 mg/kg, -20h and α-methyl-p-tyrosine 200 mg/kg, -1h), showing that the effect is indeed mediated via presynaptic α2 adrenoceptors, as well as blocked by a selective D1 antagonist (SCH 23390, 1 μM) confirming the D1 receptor mediation. Using the 8-arm radial maze test as a behavioral correlate, we have also studied the effects of CLOZ (5 mg/kg), a low dose of RAC (0.05 mg/kg), IDA (1.5 mg/kg), and the combination of IDA and RAC, on the impairment of cognitive function in the rat induced by the selective NMDA receptor antagonist MK-801 (0.1 mg/kg). Both CLOZ and a combination of RAC and IDA completely restored cognitive functioning, whereas neither RAC nor IDA alone had any significant effect. Consequently, adding α2 adrenoceptor blockage to a D2 antagonist not only augments dopaminergic, but also glutamatergic neurotransmission in the PFC, and concomitantly improves cognitive dysfunction, in complete analogy with the effects of CLOZ. Our results indicate that presynaptic α2 adrenoceptor blockage has a major role in the advantageous effects of CLOZ on cognitive dysfunction and negative symptoms in schizophrenia. Moreover, our data provide experimental support for the adjunctive use of IDA with typical APDs as an effective and rational means to enhance the efficacy of APDs that lack appreciable α2 receptor antagonistic action. Adding IDA may alternatively allow for substantial reduction in APD dosage with maintained clinical efficacy. Since major side effects of APDs, such as extrapyramidal side effects, increased prolactin secretion, weight gain and sedation are in all

probability related to pharmacological properties other than α2 blockage, the adjunctive use of IDA may allow for a reduction of such side effects simply by reduction in dosage.

133. DTI Measures Are Insensitive to the Effect of Neuroleptics

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Background: Little information is currently available on the reproducibility of diffusion tensor imaging (DTI) in clinical populations where motion artifacts and other variables such as pharmacological manipulations could affect the basic measures of water diffusion in brain tissue. We studied a group of patients with schizophrenia or schizoaffective disorder (SCZ) before, during and after a period of withdrawal from neuroleptic treatment. We derived measures of reproducibility from the scans obtained before and after the withdrawal and evaluated the effect of neuroleptics on DTI measures by comparing the scans on and off drug. **Methods:** 16 SCZ (mean age 25.3+4.8 SD) were scanned at least twice while on neuroleptics with a single shot cardiac gated EPI sequence (8 mm3 resolution). 13 patients had three scans, two on and one off neuroleptics with an average interval from first to last scan of 3.77 months. The medication-free interval was about 3 weeks. Fractional anisotropy (FA) and Trace images were computed for each subject and normalized to a FA template. ROIs were sampled on the normalized images. Intra-class correlation coefficients (ICCs) were computed on the mean ROI values for two repeated scans on medications. A repeated measures ANOVA was used on mean ROI values for three on-off-on scans. Statistical non-parametric mapping (SnPM) using a permutation test was conducted on 13 on-off scans. **Results:** ICCs for the centrum semiovale, corpus callosum and peduncles exceeded 0.80 for Trace and FA. Gray matter structures such as cerebellar and frontal cortex, insula and putamen had ICCs ranging from 0.18 to 0.65 for FA and from 0.58 to 0.75 for Trace. Repeated measures ANOVA and SnPM analysis did not show any significant differences between on and off scans. **Conclusions:** The ICCs found in the patients with schizophrenia scanned twice while on neuroleptics were similar to those found in matched normal controls scanned at the same intervals and indicated good reproducibility of the technique in this clinical population for FA measurements in white matter and Trace in most brain regions. This limited period of neuroleptic withdrawal of about 3 weeks did not seem to have any detectable effect on DTI measures. We conclude that DTI measures are stable over periods of months in patients with schizophrenia and they are unaffected by medication status.

134. WAY-163909, A Novel Selective, 5-HT_{2C} Receptor Agonist, Exhibits an Atypical Antipsychotic-like Profile: Behavioral, Neurochemical and Electrophysiological Evidence

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Sponsor: Fridolin Sulser

5-HT_{2C} receptor agonists represent a unique therapeutic approach toward the treatment of schizophrenia. 5-HT_{2C} agonists selectively decrease mesolimbic dopamine without affecting nigrostriatal dopamine, suggesting that 5-HT_{2C} agonists will have limbic selectivity and will be less likely to produce the extrapyramidal side effects associated with typical antipsychotics. WAY-163909, a selective 5-HT_{2C} agonist, was tested in several models that are predictive of antipsychotic activity. In behavioral assays, WAY-163909 antagonized apomorphine-induced climbing in mice with an ID_{50} of 10.7 mg/kg while this same dose had no effect on apomorphine-induced stereotypy. At doses up to 30 mg/kg, WAY-163909 showed no significant mouse cataleptogenic potential. In the rat conditioned avoidance model, WAY-163909 significantly reduced avoidance responses with an ID_{50} of 1.3 mg/kg, an effect antagonized by the 5-HT_{2C} antagonist SB-206553. WAY-163909 significantly and preferentially reduced PCP induced hyperactivity with an MED of 0.1 mg/kg, while the MED for a reduction in spontaneous and d-amphetamine locomotor activity was 30 fold higher. WAY-163909 was also tested against disruptions of prepulse inhibition (PPI). WAY-163909 significantly attenuated the NMDA antagonist MK-801 and 5-HT_{2A} agonist DOI induced disruptions in sensorimotor gating (MED = 5.4 mg/kg versus both of these disruptive agents), but did not reverse PPI disrupted with d-amphetamine. In addition, WAY-163909 enhanced PPI in DBA2 mice. Neurochemical studies confirmed a selective decrease in dopamine levels in the nucleus accumbens (*vs* striatum) of rats treated with WAY-163909, whilst producing limited effect on dopamine but an increase in extracellular acetylcholine level in the medial prefrontal cortex. In addition, in vivo electrophysiology studies indicated selective inhibition of dopamine neuronal firing in the ventral tegmentum relative to substantia nigra following acute and chronic treatment with WAY-163909 (1-10 mg/kg). Taken as a whole, these data suggest that WAY-163909 shows a rapid onset atypical antipsychotic-like profile.

135. Neuroactive Steroid Alterations in Schizophrenia and Bipolar Disorder: A Negative Ion Chemical Ionization Gas Chromatography/Mass Spectrometry Investigation in Posterior Cingulate

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Sponsor: Past Travel Awardee, BMS, 2000

BACKGROUND: Neuroactive steroids may be candidate modulators of schizophrenia pathophysiology and contribute to antipsychotic efficacy. We have determined previously that dehydroepiandrosterone (DHEA) plasma levels were elevated in first-episode schizophrenia patients at baseline compared to carefully matched control subjects, and that DHEA levels were negatively correlated with SANS scores (Scale for the Assessment of Negative Symptoms). Similarly, pregnenolone levels were also negatively correlated with SANS scores. The second generation antipsychotics clozapine and olanzapine dose-dependently elevate the GABAergic neuroactive steroid allopregnanolone in rat cerebral cortex (Marx et al 2003), and may contribute to the anxiolytic, antidepressant, and antipsychotic actions of these compounds. Olanzapine also elevates pregnenolone levels in rodent hippocampus (Marx et al 2004). We therefore investigated neuroactive steroid levels in postmortem brain tissue (posterior cingulate) from the Stanley Foundation in subjects with schizophrenia, bipolar disorder, depression, and non-psychiatric control subjects. **METHODS:** Frozen posterior cingulate tissue from the Stanley Foundation Neuropathology Consortium was analyzed for neuroactive steroids by negative ion chemical ionization gas chromatography / mass spectrometry, preceded by high performance liquid chromatography. Levels of the neuroactive steroids DHEA, pregnenolone, and allopregnanolone were determined in posterior cingulate from 59 subjects (15 with schizophrenia, 15 with bipolar disorder, 14 with depression, and 15 non-psychiatric control subjects). Posterior cingulate tissue was unavailable for one subject with depression, and therefore 14 specimens were analyzed in this group. Subjects were group matched for age, sex, ethnicity, brain pH, and postmortem interval. Statistical analyses were performed by ANOVA with post-hoc Dunnett tests on log-transformed neuroactive steroid levels. **RESULTS:** Levels of the neuroactive steroid DHEA were signif-

icantly higher in posterior cingulate tissue from subjects with schizophrenia and bipolar disorder compared to non-psychiatric control subjects (ANOVA p=0.0015; df 3,55; F=5.84; post-hoc Dunnett p<0.01 for both schizophrenia and bipolar disorder groups; p>0.05 for depression group). Pregnenolone levels were also significantly higher in both schizophrenia and bipolar disorder subjects, but not in depression subjects (ANOVA p=0.0017; df 3,55; F=5.73; post-hoc Dunnett p<0.01 for both schizophrenia and bipolar disorder groups; p>0.05 for depression group). Allopregnanolone levels were not significantly different in any psychiatric group compared to non-psychiatric control subjects. **CONCLUSIONS:** DHEA and pregnenolone levels in posterior cingulate were significantly higher in both schizophrenia and bipolar subjects compared to non-psychiatric control subjects. DHEA is neuroprotective in a number of rodent models (Marx et al 2000), and DHEA augmentation decreases negative, depression, and anxiety symptoms in schizophrenia patients (Strous et al 2003). Pregnenolone and its sulfate enhance learning and memory in preclinical studies (Flood et al 1992, Akwa et al 2001, Vallee et al 2001). DHEA and pregnenolone elevations may therefore represent potential compensatory mechanisms in schizophrenia and bipolar disorder. It is also possible that alterations are related to antipsychotic treatment. Neuroactive steroids may represent novel treatment strategies for future interventions.

136. The Neuroactive Steroid Dehydroepiandrosterone Sulfate (DHEAS) Predicts Nicotine Dependence Severity

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Sponsor: Cynthia Kuhn

BACKGROUND: Nicotine dependence is an addiction with major health sequelae affecting over 40 million persons in the United States. Although progress has been made in the area of smoking cessation, current treatment strategies have high failure rates and more effective approaches are needed. Nicotine administration alters a number of neuroactive steroids in rodent brain (Porcu et al 2003), and these molecules may play a role in tobacco addiction. We therefore investigated levels of the neuroactive steroid dehydroepiandrosterone sulfate (DHEAS) in smokers at baseline to investigate potential links to nicotine dependence rating scales and other symptom severity measures. **METHODS:** DHEAS levels were determined by radioimmunoassay at baseline in 27 male smokers preceding randomization to specific smoking cessation treatment arms. Partial correlations controlling for age were performed to determine potential associations with rating measures, including: The Fagerstrom Test for Nicotine Dependence (FTND), the craving item on the Reasons to Smoke (RTS) questionnaire (1-7 scale), and the addiction subscale of the Ikard Smoking Motivation Questionnaire (ISMQ). **RESULTS:** Baseline DHEAS levels were negatively correlated with FTND scores (r= -0.399, p=0.05) and the RTS craving item (r= -0.425, p=0.03). DHEAS levels also tended to be negatively correlated with the ISMQ addiction subscale (r= -0.379, p=0.06). **CONCLUSIONS:** DHEAS levels appear to predict nicotine dependence severity in male smokers. Since DHEAS levels are negatively correlated with craving measures in this study, we hypothesize that DHEA administration may hold promise as a novel smoking cessation agent. Investigations are currently underway to test this possibility.

137. Disrupted Functional Connectivity During Speech in Schizophrenia

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Background: Abnormal left fronto-temporal circuitry subserving language and auditory processing have been implicated in the pathophysiology of schizophrenia and may underlie positive symptoms. Previous studies support the operation of a "forward model" during the auditory processing of self-generated speech. This forward model is posited to involve the transmission of an "efference copy" of the speech command to the auditory cortex where it produces a "corollary discharge" representing the expected auditory consequences of the speech. The result is a dampened auditory cortical response to self-generated speech sounds, perhaps via "subtraction" of the expected sound (corollary discharge) from the actual sound (reafference). This putative forward model system appears to be disrupted in schizophrenia: Patients do not show normal auditory cortical dampening (modulation of N100 amplitude) or normal fronto-temporal EEG coherence during speech production (Ford and Mathalon, 2004). In order to identify brain regions that normally communicate with auditory cortex during self-generated speech, contributing to dampening of the auditory cortical response, as well as to identify regional abnormalities in this communication in schizophrenia, we conducted a functional MRI study (fMRI) of self-generated speech and applied a functional connectivity analysis known as psychophysiological interaction (PPI). **Methods**: FMRI data were collected while 16 schizophrenic patients (DSM-IV) and 16 age- and gender-matched healthy adults uttered the syllable [a] aloud and then listened to the recorded sound played back through headphones. Both talking and listening were timed to occur only during the silent periods of a clustered acquisition MRI sequence. In one run, blocks of talking alternated with blocks of rest. In the second run, blocks of listening alternated with blocks of rest. Data were analyzed using SPM2. PPI analyses were conducted on the time-series for the Talk/Rest and Listen/Rest sessions separately for each subject. In the PPI analysis, the (deconvolved) time series of the left auditory cortex was correlated with the time series of each voxel in the brain during two different task conditions (Talk vs. Rest; Listen vs. Rest). The PPI term in the model indicates the voxels whose correlations with the left auditory cortex are significantly different during Talk (or Listen) than during Rest. PPI maps from each subject were subjected to second-level random effects analysis to detect condition effects (Talk vs. Listen) and group effects. **Results**: In healthy subjects, brain regions involved in speech production/vocalization, including motor speech areas, supplementary motor areas, insula, inferior frontal gyrus, basal ganglia, middle and inferior temporal gyri, as well as anterior cingulate and dorsolateral prefrontal cortex, showed more negative correlations with left auditory cortex during Talking than during Rest (but not during Listening relative to Rest). Schizophrenic patients did not show this normal pattern of functional connectivity with left auditory cortex for many brain regions involved in speech production/vocalization, particularly left fronto-temporal regions. **Conclusion**: The observed negative correlations of frontal-temporal-limbic regions with auditory cortical activity during speech production is consistent with forward model theories positing efference copy/corollary discharge signals that dampen auditory cortical responsiveness during self-produced speech. The failure to observe these negative correlations in schizophrenic patients is consistent with fronto-temporal disconnectivity underlying the failure to modulate auditory cortical responsiveness during speech in schizophrenia.

138. Aripiprazole Versus Olanzapine in Schizophrenia: A 52-Week, Open-Label Extension Study

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Sponsor: Frank Yocca

Objective: To compare long-term efficacy, safety, and metabolic profile of aripiprazole in comparison to olanzapine in patients with either acute relapsing or chronic stable schizophrenia. **Methods:** This was a 52-week, open-label extension to a 26-week, randomized,

double-blind, placebo-controlled trial in stabilized patients (n=310) with chronic schizophrenia (Pigott et al., 2003). Patients who completed the 26-week treatment phase (chronic stable patients: baseline PANSS Total = 66) or who met the protocol definition of relapse after at least 2 weeks of double-blind treatment (acutely relapsing patients: baseline PANSS Total = 99) were eligible for a randomized, open-label extension trial of aripiprazole (15–30 mg/day, n=104) vs olanzapine (10–20 mg/day, n=110) for up to 52 weeks. **Results:** Overall, 69% of the patients completed the 52-week study. At week 52, mean doses for aripiprazole and olanzapine were 22 mg and 14 mg, respectively. Among patients with acute relapse of symptoms, similar symptom improvement was seen in those treated with aripiprazole or olanzapine. At week 52, mean change in PANSS Total score was –21.8 for aripiprazole and –23.8 with olanzapine (LOCF analysis). For patients who completed the 52-week trial, the magnitude of improvement was greater, and comparable for the two agents (mean change in PANSS total score (OC at week 52): aripiprazole = –31.2, olanzapine = –29.6). In stable chronic patients, improvement of symptoms was observed in those treated with aripiprazole or olanzapine (mean change in PANSS Total (LOCF): aripiprazole, –4.6; olanzapine –5.5); for patients who completed the 52-week trial, improvement was also comparable for the two agents (mean change in PANSS Total (OC at week 52): aripiprazole = –7.9, olanzapine = –7.4). Magnitude of improvement across all psychiatric scales was comparable with aripiprazole and olanzapine and was not significantly different. Olanzapine led to significantly greater weight gain at all time points in comparison to aripiprazole (week 52 (LOCF): 2.54 kg vs 0.04 kg; $p<0.001$). Changes in fasting glucose and fasting lipid levels at endpoint favored aripiprazole over olanzapine, with significant differences observed for total cholesterol (aripiprazole, 1.6 mg/dL; olanzapine, 17.2 mg/dL; $p=0.009$), LDL (aripiprazole, –1.5 mg/dL; olanzapine, 13.9 mg/dL; $p=0.006$) and HDL (aripiprazole, +1.1 mg/dL; olanzapine, –2.7 mg/dL; $p=0.026$). Similar differences were observed for changes in fasting glucose (aripiprazole, –1.4 mg/dL; olanzapine, 12.0 mg/dL) and triglycerides (aripiprazole, 4.9 mg/dL; olanzapine, 24.8 mg/dL) which did not meet statistical criteria. Incidence of EPS and akathisia was comparable for aripiprazole- and olanzapine-treated patients and no significant differences were seen between the two drugs in EPS rating scales at study endpoint. **Conclusion:** In both acutely relapsing and stable, chronic patients treated for up to 52 weeks, comparable symptom improvement was observed with both aripiprazole and olanzapine. With regard to weight and metabolic factors, aripiprazole was consistently superior to olanzapine.

139. Expression of NMDA Receptor Subunits and Associated Intracellular Interacting Proteins in Prefrontal Cortex in Schizophrenia

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Schizophrenia has been associated with dysfunction of glutamatergic neurotransmission, particularly abnormalities of the NMDA subtype of glutamate receptor. Recent data suggest involvement of the NMDA receptor-signaling complex, which includes NMDA receptor subunits as well as associated interacting proteins that are critical for normal NMDA receptor assembly, trafficking, insertion in the plasma membrane, and activation. The interacting proteins are selective for NMDA receptor subunits, the most well characterized being PSD-93, PDS-95, SAP102, CIPP, NF-L and yotiao. Previously, studies from our lab have detailed changes in glutamate receptor subunit transcript expression in schizophrenia in postmortem brain tissue. In the present work, we have expanded the scope of our studies to include examination of protein expression by western blot analysis. In prefrontal cortical tissue homogenates from the same cohort of elderly schizophrenics and control subjects that we have used in our earlier in situ hybridization studies, we have assayed expression of two isoforms of the NR1, as well as NR2A-2D, NMDA subunit proteins, as well as the intracellular associated proteins PSD-93, PDS-95, SAP102, and NF-L. While the NR2 subunits were unchanged in schizophrenia, there was significantly less expression of one of the C-terminal splice variants of the NR1 subunit in schizophrenia. Interestingly, this is the region of the NR1 protein where NR1-specific intracellular interacting proteins bind. Accordingly, we are now in the process of examining the expression of the protein levels of these intracellular proteins in these same subjects. PSD-95 protein expression is decreased in these same subjects with schizophrenia. We propose that schizophrenia has a glutamatergic component involving alterations in the NMDA receptor signaling complex including the intracellular machinery that is coupled to the NMDA receptor subunits. These data suggest that schizophrenia is associated with abnormal intracellular signaling, and points to novel targets for innovative drug discovery.

140. A Double-Blind Controlled Study Of Adjunctive Treatment with Risperidone in Schizophrenic Patients Partially Responsive to Clozapine

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Combinations of antipsychotic drugs, a common form of polypharmacy, has seldom been tested in controlled studies. Open trials tend to report positive results for improvement in psychopathology. Evidence to support or refute the safety and efficacy of combined treatments is urgently needed. We have carried out a double blind, placebo-controlled. 6 week study of the addition of risperidone to clozapine in 30 stable patients with treatment-resistant schizophrenia who had had a partial response to clozapine during approximately two years of treatment. The primary outcome measure was improvement in the PANSS Positive symptom subscale. The mean dose of risperidone was 5.1 mg/day. Significant improvement was noted in both the placebo-and risperidone-treated groups in a variety of measures of psychopathology, including PANSS Total, Negative, General, Calgary Depression Scale and CGI-S but there was significantly greater improvement in the placebo-treated patients in the primary outcome measure. Significantly greater improvement in the Stroop Test, Trial 1 and the Controlled Word Association Test, two measures of executive function, were noted in the placebo-treated group, while the risperidone-treated group showed greater improvement in the Reys Auditory Verbal Learning test, a test of secondary long term memory. There were no significant differences between the treatment groups with regard to EPS or weight gain. Taken together, these results suggest that addition of risperidone to clozapine may diminish rather than enhance the ongoing benefits of clozapine, possibly due to excessive dopamine receptor blockade. It is unlikely that these results are unique to the combination of clozapine and risperidone. The results support the need for controlled studies of the effect of polypharmacy on psychopathology as open studies tend to indicate the opposite of what was observed in this study.

141. The Metabolic Syndrome in Patients with Schizophrenia

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Sponsor: Henry Nasrallah

Numerous studies indicate that a major contributor to the excess mortality in patients with schizophrenia is cardiovascular dis-

ease. Risk factors for cardiovascular disease include the cluster of clinical abnormalities (in glucose, triglycerides, high density lipoproteins, blood pressure, and waist circumference) that defines the metabolic syndrome (MS). The syndrome has been identified in 22% of US adults. Limited data exist on the prevalence of MS among patients with schizophrenia, or the impact of antipsychotic medication. **Methods:** This analysis assessed the prevalence of MS (using National Cholesterol Education Program diagnostic criteria of 3 or more of the following: abdominal obesity, fasting glucose ≥ 110 mg/dL, triglycerides ≥ 150 mg/dL, low HDL, bp ≥ 130/85 mm Hg) and measures on related parameters in obese patients with schizophrenia or schizoaffective disorder who were intolerant of, or poorly responding to ≥30 days' treatment with olanzapine, and who subsequently enrolled in a two-phase, 20-week, open-label, rater-blinded risperidone switch study. During phase 1, olanzapine was withdrawn and risperidone was started at 2-4 mg/day for 1 week followed by flexible doses for a further 5 weeks. In phase 2, patients with a BMI >26 kg/m^2 and motivation to lose weight entered a 14-week period during which they received a mean risperidone dose of 4.5 mg/day. **Results:** Baseline assessments of MS parameters were available for 121 of the 123 patients enrolled in the study. MS was identified in 63 (52.1%) of these patients at study entry. Baseline and 20-week endpoint (LOCF) assessments were available for 71 patients. In these patients, the prevalence of MS was reduced from 38 (53.5%) patients at baseline to 26 (36.6%) at endpoint (McNemar's χ^2=8.0, p=.0047). In addition, mean anthropometric and metabolic measures (weight, BMI, waist circumference, HDL cholesterol, triglycerides, fasting glucose, and systolic blood pressure) were reduced at endpoint, with clinical improvements as measured by mean PANSS and CGI-S ratings. **Conclusions:** It is concluded that the metabolic syndrome was highly prevalent in these obese patients. Switching to risperidone was associated with a reduction in the prevalence of MS and improvements in clinical status.

142. Switching Schizophrenia Patients Previously Stable on Chronic Conventional Antipsychotic Therapy to Risperidone versus Olanzapine

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Objective: Schizophrenia patients who have been chronically and successfully maintained on treatment with conventional antipsychotics represent a unique population of individuals who may exhibit a differential response profile to atypical antipsychotic medications. **Method:** In order to further examine treatment responses to atypical antipsychotics in such patients, 36 subjects (17 male, 19 female, mean age = 46.8 years) diagnosed with a schizophrenia spectrum disorder according to DSM-IV criteria, who had been stable on treatment with conventional antipsychotics for at least 2 years, were randomly assigned in double-blind fashion to switch to risperidone versus olanzapine. During the first 10 weeks of the study, atypical agents were titrated up to 3 pills per day (6mg risperidone, 15mg olanzapine), while conventional medications were tapered and discontinued. Atypical agents were then administered alone for 12 weeks. The Positive and Negative Symptom Scale (PANSS) was used to assess clinical status at regular intervals throughout the study. Data was assessed using an intent-to-treat analysis, and the last visit carried forward method was employed. **Results:** In both treatment groups, significant improvement from baseline to week 22 was seen in the total PANSS score [risperidone: baseline = 59.3 (SE 3.1), 22 weeks = 44.3 (SE 2.3) (p<0.001); olanzapine: baseline = 55.9 (SE 3.3), 22 weeks = 46.9 (SE 3.2) (p<0.001). Risperidone-treated patients also exhibited significant reductions in all five PANSS factor scores including positive and negative symptoms, disorganized thoughts, hostility, and anxiety and depression (p<0.001). In contrast, patients randomized to olanzapine had significant PANSS score reductions from baseline in positive and negative symptoms (p<0.05 and p<0.001, respectively) and disorganized thoughts (p<0.001), but not in hostility or anxiety and depression (p=0.59 and p=0.14, respectively). **Conclusions:** The results indicate that atypical antipsychotic medications further improve a broad range of behavioral symptoms in schizophrenia patients who have been chronically stable on conventional agents. In addition, there may be some advantage of risperidone in treating certain symptom clusters in these patients, including hostility, depression and anxiety.

143. Polymorphisms of the Genes that Code for the 5-HT2C Receptor, Weight Gain, and Clinical Response During Clozapine Treatment

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Sponsor: Raymond Crowe

BACKGROUND: Several investigators have reported an association between the -759C/T polymorphism of the 5-HT2C receptor and weight gain related to clozapine and other atypical antipsychotics. Clozapine-induced weight gain has also been reported to be related to clinical response. **AIM:** To determine the relationship between changes in body weight and clinical response, and the -759C/T and Cys23Ser polymorphisms of the genes that code for the 5-HT2C receptor during clozapine treatment. **METHODS:** This study included 56 subjects with treatment-refractory schizophrenia (DSM-IV) who were followed prospectively during treatment with clozapine. Ratings of psychopathology, weight, and height measurements were obtained prior to starting clozapine and throughout six months of treatment. Clozapine doses were based on plasma concentration determinations and clinical response. Genomic DNA was isolated from a whole blood sample and analyzed for the -759C/T and Cys23sSer polymorphisms of the genes that code for the 5-HT2C receptor. **RESULTS:** Increases in BMI were associated to the -759C/T polymorphism; the end point BMI was significantly predicted by the presence or absence of a T allele and the baseline BMI. Increases in BMI were not related to the Cys23Ser polymorphism. There was no relationship between increases in BMI and improvement in psychopathology, or between improvement in psychopathology and -759C/T or Cys23sSer polymorphisms of the 5-HT2C receptor. **CONCLUSIONS:** The T allele from the -759C/T polymorphism of the 5-HT2C receptor appears to have a protective function in preventing significant clozapine-induced weight gain. We did not find a relationship between clozapine-induced weight gain and improvement in psychopathology, or between improvement in psychopathology and two polymorphisms of the genes that code for the 5-HT2C receptor.

144. Improving Decisional Capacity in Schizophrenia Research

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Sponsor: Travel Awardee, Memorial, 2004

Background: A growing body of literature has shown that most individuals with schizophrenia possess adequate decisional capacity to provide informed consent for research participation. Additionally, it has been demonstrated that those individuals with schizophrenia who lack the ability to provide consent can benefit significantly from

interventions aimed at enhancing this capacity. Typically, however, these interventions have been rather prolonged, sometimes taking place over several days. The current study was conducted to determine whether a much briefer intervention could yield beneficial effects on decisional capacity. **Methods:** Participants included 30 individuals with schizophrenia and 30 healthy controls of similar age and educational level. All participants were asked to pretend they were being considered for a medication trial (no deception was involved) and then, with the examiner, read through a detailed consent form for a hypothetical, randomized, double-blind, placebo-controlled trial of a cognition-enhancing agent. Decisional capacity was then assessed with the MacCAT-CR, a semi-structured interview that assesses Understanding, Appreciation, Reasoning, and Ability to Express a Choice within the context of research participation. Participants with schizophrenia then received a brief semi-customized intervention, which consisted of a PowerPoint slideshow reiterating the key elements of the hypothetical study, followed by discussion of all MacCAT-CR items on which s/he earned less than the maximum score. Decisional capacity was then re-assessed with the MacCAT-CR, and participants were also administered the much briefer Evaluation to Sign Consent, another capacity instrument that assesses basic understanding of study procedures, risks and benefits. A neuropsychological battery and psychiatric rating scales were also administered. **Results:** At baseline, the schizophrenia group earned significantly lower scores than controls on two aspects of decisional capacity [Understanding: t (58) = -2.68, p = .009; Appreciation: t (58) = -2.45, p = .017]. At follow-up, the schizophrenia group had improved significantly on the Understanding score relative to baseline [t (29) = -2.85; p = .008] and were no longer significantly different from controls on any of the four dimensions of decisional capacity. Furthermore, all participants demonstrated adequate understanding of the hypothetical study, as measured by the Evaluation to Sign Consent. Participants with schizophrenia earned significantly lower scores than controls with regard to global neuropsychological functioning and across multiple cognitive domains. **Discussion:** These findings suggest that even a brief intervention can improve decisional capacity in individuals with schizophrenia, despite the fact that this illness often involves significant cognitive dysfunction. Magnitude of improvement was relatively small, primarily due to ceiling effects, as many individuals with schizophrenia earned high MacCAT-CR scores even prior to the intervention. This study and others continue to indicate that the large majority of individuals with schizophrenia can make independent and informed decisions regarding research participation. This study and presentation were supported by a grant from the Nellie Ball Research Trust.

145. Is the Therapeutic Effect of Celecoxib in Schizophrenia Depending from Duration of Disease?

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Sponsor: Mansfred Ackenheil

A beneficial therapeutic effect of the COX-2 inhibitor celecoxib in schizophrenia was observed(1). In this 5-week study the largest improvement in the celecoxib group was seen between week 2 and 4, while the difference between celecoxib and placebo became smaller at the end of the study suggesting a possible exhaustion effect. We performed an 8 weeks study using the same design. The study was performed prospective, double-blind, and randomized. The dose of risperidone was flexible and ranged from 2-6mg/day. 40 patients were included into the study, 24 males and 16 females. The mean age was 33 years. Psychopathology was assessed PANSS. The analysis was performed according to the criterion last observation carried foreward. Regarding the general psychopathology, the mean value was 53 at baseline and 38 at the end of the study. In the celecoxib group, the mean value was 52 at baseline and 35 at the end of the study. In the placebo group, the mean value of the total scale was 108 at baseline, 75 at the end of the study. In the celecoxib group, the mean value of the total scale was 102 at baseline and 68 at the end of the study. We observed a significant decrease of the total scale and all subscales in both groups, but no influence of the treatment group. A further explorative analysis showed that there might be an influence of the duration of the disease to the differences in the outcome of celecoxib therapy. In patients with a short duration of disease (≤2 y.) a 35% decrease of the symptoms in the total scale was observed in the celecoxib group, while the improvement was 22% in the placebo group. In patients with a longer duration of disease (>2 y.) the improvement was 24% in the celecoxib group and 27% in the pacebo group. A comparison with the first study showed, that the advantage of the celecoxib group was due to the patients with a short duration of disease, too (≤2 y.). These patients showed an improvement of 24% in the total scale, while the improvement was 13% in the placebo group. The improvement was makedly smaller in patients with a duration of disease >2 y. We could not replicate an advantage of the celecoxib treatment in the total group of schizophrenics. A re-analysis of the data of our first study showed, that the advantage of the celecoxib group was due to patients with a short duration of disease. Much more patients with a short duration were included into the sample of our first study. Using duration of disease ≤2 y., 32.5% of the patients had a short duration of disease in the actual study and 44% in the first study. In the celecoxib groups, twice as much patients (24%) had a short duration of disease in the first study compared to the actual study (12.5%). This difference in the sample-characteristics might contribute to the negative outcome of the actual study. From an immunological point of view, it can be expected that a short-term process responds better to anti-inflammatory treatment than chronic inflammation. In a chronic inflammatory process, cell destruction, apoptotic and degenerative processes take place. Although neuroprotective properties of COX-2 inhibitors are described, they might not be able to reverse a chronic process (at least in short-term studies). In parallel, it is known that anti-inflammatory treatment reduces the risk for Alzheimers Disease, a disorder presenting first symptoms a long time after neuropathological changes took place, but clinical studies failed to show therapeutic effects. COX-2 inhibitors show therapeutic effects in early stages of schizophrenia, but not in later stages. Further work has to identify a cut-off point or marker predicting response.

(1) Mueller N, et al (2002) Am J Psychiatry 159:1029-1034.

146. PKA Anchoring is Required for the Maintenance of Long-Term Hippocampal Synaptic Plasticity

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Cyclic AMP-dependent protein kinase (PKA) is often found anchored to subcellular compartments via interactions with A-kinase anchoring proteins (AKAPs). Binding to AKAPs brings PKA into macromolecular signaling complexes that include PKA substrates such as NMDA receptors as well as phosphates. Pharmacological disruption of PKA anchoring using a peptide inhibitor of PKA anchoring Ht31 has been found to mimic treatment with a PKA inhibitor in cell culture systems. Because PKA is known to play a critical role in memory storage and hippocampal synaptic plasticity, we chose to test the hypothesis that disruption of PKA anchoring in a genetically modified mouse would impair PKA-dependent forms of hippocampal synaptic plasticity. We have generated mice that inducibly express a truncated form of Ht31, an AKAP cloned from human thyroid tissue, in forebrain neurons under the control of the tetracycline transactivator system. We have demonstrated that expression of Ht31 in one line of mice disrupts AKAP complexes that contain PKA and

PP1. These animals also display alterations in hippocampal function as assessed by behavioral characterization in the spatial version of the Morris Water Maze and fear conditioning. In the present study, we find that although measures of basal synaptic transmission are normal in these animals, expression of Ht31 results in impairments in PKA-dependent forms of hippocampal L-LTP, and that suppression of Ht31 expression by treatment with doxycycline (200 mg/kg in the diet) reverses this impairment. These results are mimicked by treatment with the peptide form of Ht31 (10 μM), whereas Ht31P (10 μM) does not impair PKA-dependent forms of hippocampal L-LTP. Synaptic potentiation induced by the adenylyl cyclase agonist forskolin (50 μM) was not impaired in Ht31 transgenic mice, and the peptide form of Ht31 did not impair synaptic potentiation induced by treatment with forskolin (50 μM) and the phosphodiesterase inhibitor IBMX (30 μM). We therefore conclude that PKA-anchoring via AKAPs is necessary to support the function of PKA in some but not all forms of hippocampal synaptic plasticity. Supported by: Merck Foundation, NIH, the Packard Foundation, the University of Pennsylvania Research Foundation and the Whitehall Foundation. 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.

147. Dopamine-Mediated Plasticity: Distinct Roles for the Scaffolding Proteins, Spinophilin and Neurabin

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Sponsor: Travel Awardee, Memorial, 2004

Coordination of the activity of signaling enzymes at synapses requires both spatial and temporal regulation. Protein phosphatase 1 (PP1) plays a major role in the governance of excitatory synaptic activity, and is subject to control via the neuromodulatory actions of dopamine. The mechanisms involved in regulating PP1 activity include interactions with the cytoskeletal elements spinophilin and neurabin. These scaffolding proteins are highly enriched in dendritic spines and bind filamentous actin. The requirement for spinophilin and neurabin in dopamine neuromodulation was tested using knockout mice. In brain slices, LTP at cortico-striatal synapses was normal in the spinophilin KO but was deficient in the neurabin KO. This deficit was rescued by application of a D1 receptor agonist. In contrast, LTD was normal in the neurabin KO but was deficient in the spinophilin KO; in this case the deficit was rescued by D2 receptor activation. Spontaneous EPSC frequency was increased specifically in neurabin KO mice and was modulated by D2 receptor agonism. Place preference for cocaine was enhanced in spinophilin KO mice but was decreased in neurabin KO mice. Furthermore, divergent responses in the two KO strains were detected in neurochemical measures of immediate early gene induction and DARPP-32 phosphorylation. Therefore, despite their high degree of structural relatedness, spinophilin and neurabin appear to play specific but highly distinct roles in dopaminergic signal transduction.

148. Hippocampal 5-HT_{1A} Receptors Couple to Activation of Akt and Inhibition of GSK3β

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5-HT_{1A} receptors have been hypothesized to mediate some of the actions of serotonin selective reuptake inhibitors. Such actions include stimulation of hippocampal neurogenesis. Although the cellular signaling pathways required for antidepressant-induced neuronal plasticity have not been determined, roles for the anti-apoptotic ERK MAP kinase and Akt pathways have been suggested. It has therefore been somewhat surprising that coupling of 5-HT_{1A} receptors to activation of ERK has so far not been identified in hippocampal neurons. In the current studies we have utilized cultured rat hippocampal (E18) neurons to determine whether 5-HT_{1A} receptors couple to activation of Akt. We found that hippocampal neurons exhibit an approximately 2-fold activation of Akt when exposed to nanomolar concentrations of 5-HT. The 5-$HT_{1/7}$ receptor-selective agonist 5-carboxamidotryptamine maleate (5-CT) and the 5-$HT_{1A/7}$ receptor-selective agonist 8-hydroxy-N,N-dipropyl-aminotetralin (8-OH-DPAT) maleate were found to activate Akt with equal efficacy, and similar potency, to 5-HT. p-MPPI and WAY-100635, antagonists selective for 5-HT_{1A} receptors, completely inhibited 5-CT- stimulated Akt activation. In contrast, the 5-HT_7 selective antagonist, SB269970, caused no inhibition. Activation of Akt was inhibited by pretreatment with pertussis toxin as well as the phosphatidylinositol 3-kinase inhibitors, wortmannin and LY294002. Activated Akt is known to phosphorylate glycogen synthase kinase (GSK)3, resulting in inhibition of the pro-apoptotic protein. We found that in addition to activating Akt, 5-CT stimulated an inhibitory inhibition of GSK3β at Ser 9. These findings may be relevant to understanding the mechanisms by which serotonergic antidepressants induce neuroprotective changes in the hippocampus.

149. A Regulated Association of the LIM Domain Protein Hic-5 with the Antidepressant-Sensitive Serotonin Transporter (SERT) in Native Tissues

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Sponsor: Travel Awardee, NIMH, 2004

In the central nervous system, presynaptic SERT proteins constitute the major mode of inactivation of serotonin (5-HT) following transmitter release. SERTs are also expressed by several nonneuronal cell populations including colonic epithelial cells, pulmonary smooth muscle cells and platelets. SERT activity and/or surface trafficking are subject to rapid regulation following kinase activation/phosphatase inhibition, though precise mechanisms remain ill defined. One possibility includes the alteration of physical associations between transporters and interacting proteins through either direct phosphorylation of SERT and/or the modulation of transporter-linked scaffolding systems. In an effort to identify and characterize SERT-interacting partners subject to kinase regulation, we have investigated the interactions of the native SERT with the multiple LIM domain protein Hic-5, previously established to interact with SERT proteins through yeast 2-hybrid studies (Carneiro et al., 2002). Using platelet extracts, we observe that SERT specific antisera co-immunoprecipitate SERT and Hic-5, interactions not evident using nonimmune serum. Further studies of the platelet SERT:Hic-5 complex reveal both phorbol ester and psychostimulants modulated associations. PKC activation seems to stabilize the SERT:Hic-5 interaction in a time-dependent manner. On the other hand, the exposure of platelets to MDMA seems to disrupt this interaction, indicating that independent mechanisms are involved in SERT modulation by phorbol esters and psychostimulants. Studies are underway to map sites of SERT:Hic-5 interactions, to define mechanisms by which signaling pathways psychostimulants influence complex stability, and to define additional partners whose localization to SERTs could be Hic-5 dependent. Clarifying these transporter protein associations may provide insights into pathways altered in mood disorders and offer new targets for therapeutics.

150. Alterations In Brain Protein Kinase A Activity And Reversal Of Morphine Tolerance By Two Fragments Of Native Protein Kinase A Inhibitor Peptide (PKI)

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Sponsor: William L. Dewey

Morphine and other clinically relevant opioids act mainly at the mu opioid receptor to produce analgesia and rewarding effects. However, chronic treatment with opioid agonists, such as morphine, has also been shown to produce problematic side effects which inlcude tolerance and dependence. The cellular mechanisms underlying opioid antinociceptive tolerance have been studied for decades. Low intrinsic efficacy agonists, such as morphine, appear to produce tolerance through downstream cellular signalling pathways, such as the adenylate cyclase/Protein Kinase A (PKA) cascade. For instance, studies have demonstrated that morphine antinociceptive tolerance is reversed by the PKA inhibitor KT-5720 in mice. In the present study, we developed a model to determine the effectiveness of two synthetic peptide fragments of native PKA inhibitor (PKI), PKI-(6-22)-amide and PKI-(Myr-14-22)-amide, to reverse a low-level of morphine antinociceptive tolerance. In addition, the *in vitro* and *in vivo* inhibition of PKA activity by both drugs was measured in specific brain regions (thalamus, periaqueductal gray (PAG), and medulla) and lumbar spinal cord (LSC) which previous studies have shown play a role in morphine-induced analgesia and opioid antinociceptive tolerance. The *in vitro* inhibition of PKA activity was measured in homogenates taken from drug naive mice, while the *in vivo* inhibition of PKA activity was measured following i.c.v. injections of each drug. In addition, PKA activity was quantified and compared between each region. Finally, PKA activity was measured in each region in morphine-tolerant mice to determine the effect of morphine antinociceptive tolerance on enzyme activity. Results from this study demonstrated that PKI-(6-22)-amide and PKI-(Myr-14-22)-amide significantly reversed morphine antinociceptive tolerance in mice. In drug naive animals, cytosolic PKA activity was greater than particulate PKA activity in each region, while cytosolic and particulate PKA activity was greater in thalamus and PAG compared to medulla and LSC. The addition of both peptides to homogenates from each region completely abolished cytosolic and particulate PKA activity. Following injection into the lateral ventricle of the brain, both peptides inhibited PKA activity in the cytosolic, but not the particulate fractions of thalamus and LSC. In addition, PKA activity was not affected in the medulla, while the effects of both peptides were less consistent in the PAG. Finally, the direct measurement and kinetic analyis of PKA activity in each region revealed that PKA activity was significantly increased only in LSC of morphine-tolerant mice that received morphine pellets for 15 days. Thus, the present study provides evidence that PKA plays a role in morphine antinociceptive tolerance. These studies were supported by NIDA grants DA-01647, T32-DA-07027, K05-DA-00480.

151. Evidence that Adenosine Receptor-Linked Protein Kinase G and p38MAPK Acutely Regulate the Serotonin Transporter *In Vivo*

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Sponsor: Randy Blakely

The 5-hydroxytryptamine (serotonin, 5-HT) transporter (5-HTT) is important in terminating serotonergic neurotransmission and is a primary target for many psychotherapeutic drugs. Determining how activity and expression of the 5-HTT is regulated is therefore of fundamental importance. Recent *in vitro* studies using RBL-2H3 cells transfected with the 5-HTT and adenosine receptor (AR) revealed two protein kinase G (PKG)-dependent pathways that support rapid regulation of the 5-HTT by A_3 ARs. One leads to increased expression of the 5-HTT in the plasma membrane and the other, a p38 mitogen activated protein kinase (MAPK)-dependent process that augments the intrinsic activity of the 5-HTT (Zhu et al., 2004, Mol Pharmacol. 65:1462). Because identification of pathways that regulate the 5-HTT has important implications for the development of improved therapeutics for numerous psychiatric disorders it was critical to determine if such regulation of the transporter also occurs in the whole animal, *in vivo*. In hippocampus ARs have been found to exert complex actions on extracellular 5-HT but the impact on 5-HTT-mediated clearance has not been established. Here we use high-speed chronoamperometry to measure clearance of exogenously applied 5-HT from the CA3 region of hippocampus of anesthetized rats. Local application of the non-selective AR agonist, 5′-N-ethylcarboxyamidoadensoine (NECA) increased the rate at which 5-HT was cleared and consistent with *in vitro* studies, enhancement of clearance was confined to a narrow dose-range. The PKG inhibitor N-[2-(methylamino)ethyl]-5-isoquinoline-sulfonamide (H8), dose-dependently inhibited 5-HT clearance and when locally applied at a dose that did not by itself alter 5-HT clearance, blocked the NECA-stimulated increase in 5-HT clearance. Local application of the MAPK activator, anisomycin (55 pmol), prolonged 5-HT clearance while there was no effect of the MAPK inhibitor, SB203580. These data are consistent with PKG- and MAPK-dependent pathways mediating AR regulation of 5-HTT activity *in vivo* and underline sites along these pathways as potential targets for the development of improved therapeutics for psychiatric disorders such as depression and anxiety.

152. Rapid Signaling Effects of Estrogen in the Brain: Roles of ER α and βin Neurons and Glia

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CNS effects of estrogen have been reported to include prevention of postmenopausal symptoms, enhanced cognition, neuroprotection, and reduced risk for Alzheimer's Disease. Use of Estrogen in hormone replacement therapy (HRT) has recently been called into question by results of the Women's Health Initiative Study. While these results are still being evaluated, it is clear that more selective, mechanism specific, estrogenic agents will be required to separate positive from adverse effects, many of which are the result of nuclear effects of the hormone. This and other laboratories have shown that the same estrogen receptors (ER's) that mediate nuclear effects, ER α and β, also transduce rapid, membrane-initiated effects of the hormone. Transfection of these receptors into either HT22 immortalized murine hippocampal neurons, or C6 astrocytic gliocytoma cells promotes rapid responses to estrogen exposure not seen in untransfected cells. In HT22 cells, MAP kinase activation is noted within minutes after treatment with 10nM estrogen. This activation leads to subsequent phosphorylation events including that of CREB. In ER β expressing cells, movement of receptor from the cytoplasmic compartment to the neuronal membrane is observed using either immunostaining techniques, or GFP-tagged ER β. This occurs within 5 min after estrogen exposure. In C6 glioma cells, transfection of ER α confers sensitivity to estrogen's rapid effects as well, but in this case appears to involve coupling to Gi-related effects, promoting a reduction in forskolin-stimulated cAMP accumulation. Thus, the rapid effects of estrogen may differ in neurons and glia. These rapid, membrane-initiated effects observed in in vitro cell systems also appear to occur in the brain in vivo. In ovariectomized rats, a single injection of 15ug of 17 β estradiol (but not its 17 α isomer) promotes MAP kinase phosphorylation within 20 min as measured by Western blot of ex-

tracts from microdissected brain tissue. These effects are region specific in that they occur only in a subset of areas known to express either ER. Thus, the combination of these in vitro and in vivo systems should allow molecular, pharmacologic, and functional characterization of this particular aspect of estrogens effects in the brain. This work was supported by NIH Grant NS-20311 and the University of Washington Alzheimer's Center AG 05136-18.

153. Altered Expression of Rap1 in Postmortem Brain of Suicide Victims

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Sponsor: Past Travel Awardee, Memorial, 2003

Accumulating evidence from our group and others indicates that abnormalities in signal transduction mechanisms may play an important role in the pathophysiology of depression and suicide. Rap1 is a member of the Ras family of small guanine nucleotide triphosphates bearing the highest homology to Ras and is highly expressed in the CNS. Rap1 has been shown to be activated through the stimulation of various transmembrane receptors, including receptor tyrosine kinases, G protein-coupled receptors, cytokine receptors, and cell-adhesion molecules. Common second messengers such as cyclicAMP, diacylglycerol and Ca^{2+} are involved in transducing the extracellular signals to Rap1. A number of studies suggest that Rap1 is activated directly by protein kinase A (PKA) or indirectly by cyclicAMP through Epac and thereby modulates various pathways including those involved in cell survival, such as extracellular signal-regulated kinases (ERK) and phosphatidyl inositol 3-kinase pathways, and a number of transcription factors. This leads to the modulation of physiological functions such as cell proliferation, differentiation, adhesion, and neurite outgrowth. Interestingly, we have shown that catalytic activity of PKA and that cyclicAMP binding to regulatory subunits of PKA are significantly decreased in postmortem brain of suicide victims. We have also shown that activation of ERK-1 and ERK-2 is decreased in postmortem brain of depressed suicide victims. In light of these observations, the present study was undertaken to examine whether expression of Rap1 is altered in postmortem brain of suicide victims. This study was performed in prefrontal cortex and hippocampus of suicide victims (n = 25) and nonpsychiatric controls (n = 25). Postmortem brain samples from suicide and nonpsychiatric controls were obtained from Maryland Psychiatric Research Center in collaboration with the Medical Examiner's Office of the State of Maryland. The psychiatric evaluation was performed using Diagnostic Evaluation After Death and Clinical Interviews for the DSM-IV. mRNA levels of Rap1 and cyclophilin (a housekeeping protein) were determined by quantitative RT-PCR, and protein levels of Rap1 and beta-actin were determined by Western blot. We observed that the level of Rap1 was greater in prefrontal cortex than in hippocampus. Comparison of mRNA levels of Rap1 between nonpsychiatric controls and suicide victims showed that the mRNA level of Rap1, whether determined independently or as a ratio to cyclophilin, was significantly decreased in prefrontal cortex and hippocampus of suicide victims. The magnitude of decrease in prefrontal cortex was slightly greater than in hippocampus. A similar pattern of decrease in protein level of Rap1 was observed (independent or as ratio to beta actin) in prefrontal cortex and hippocampus of suicide victims. These decreases were not related to age, PMI, gender, pH of the brain, or drug toxicity. Given that a number of signals and pathways funnel into Rap1 and that Rap1 modulates the functions of a number of effectors, including those involved in cell survival and proliferation, and also that recent studies demonstrate structural abnormalities in the brain of mood disorders patients and suicide victims, abnormalities in Rap1 expression may be of critical importance in the pathophysiology of depression and suicide. Funded by RO1 MH068777 and K01MH 01836 to Dr. Yogesh Dwivedi.

154. Does Dopamine Neurotransmission Occur in the Cerebellar Vermis?

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Sponsor: F. Xavier Castellanos

Children with ADHD have been shown to have smaller cerebellar volumes, particularly in the posterior-inferior cerebellar vermis (lobules VIII-X). Activation of the cerebellar vermis following stimulant administration has been demonstrated by multiple groups using neuroimaging. There is no well characterized dopaminergic pathway that projects to the posterior-inferior cerebellar vermis, although there are immunohistochemical reports of dopamine transporter (DAT) and tyrosine hydroxylase (TH) localization in the posterior-inferior vermis in the non-human primate. We hypothesized that DA neurotransmission does not occur in the cerebellar vermis and that TH and DAT are found in the vermis to facilitate NE neurotransmission and its regulation. To investigate this hypothesis, cerebellar tissue was obtained from rats and non-human primates. Monoamines were extracted and analyzed using HPLC with coulometric detection. A regional gradient of NE and DA was found with NE levels always higher than DA in both rats and monkeys. In addition, in vivo microdialysis studies were performed in the rat posterior-inferior cerebellar vermis in anesthetized animals. Significant NE overflow was observed over baseline ($0.19 \pm .04$ nmoles/l) following reverse microdialysis induced activation from both potassium ($0.82 \pm .10$ nmoles/l, $p<0.01$) and d-amphetamine ($1.3 \pm .2$ nmoles/l, $p<0.001$, n=7). DA overflow was not observed over baseline ($0.29 \pm .08$ nmoles/l) for potassium stimulation ($0.44 \pm .15$ nmoles/l), but was significant for d-amphetamine stimulation ($0.83 \pm .15$ nmoles/l, $p<0.001$). These studies support the hypothesis that DA neurotransmission does not normally occur in the rat cerebellar vermis. Further studies are needed to assess the function of DAT in the cerebellar vermis. Supported by USPHS grants MH70840, MH01245, DA14944, NS39787, and MH066393.

155. Effects of Antidepressant Treatment with Electroacupuncture and Fluoxetine on Interleukins and Signal Transduction Aspects

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Background: There are multiple theories concerning the pathobiology of depression as well as the target actions of antidepressants. Two promising interventions are modification of immune parameters and signal transduction processes- assuming that they are abnormal in depressed patients and "normalize" following treatment. We tested that assumption with a double-blind placebo controlled trial of Electroacupuncture (EA) and Fluoxetine. We previously demonstrated that clinical response rate to EA was slightly higher than fluoxetine and both were better than placebo. Biological parameters determined- pro-inflammatory and anti-inflammatory cytokines, G proteins, platelets membranes and cytosolic PKC's and cytosolic ERK- in depressed (N= 95) and healthy controls (N= 30). **Main results:** In untreated depressed patients there was an increase in IL-1β and IL-4 and decrease in TNFα and IL-10, suggesting an imbalance between pro-inflammatory and anti-inflammatory cytokines (IL 1β and IL-10) and between Th1 and Th2 cytokines (TNFα and IL-4). Both fluoxetine and EA reduced levels of pro-inflammatory cytokines, EA but not fluoxetine also modulated Th-2 cytokines and restored balance between pro- and anti-inflammatory cytokines. Untreated depressed patients had increased expressions of Gi and Gq

proteins but not Gαs proteins, as compared to healthy controls. They showed decreased platelets membrane PKCα, PKCβII and PKCξ but no significant change in PKCα1. Only cytosolic PKCΘ was decreased but not other cytosolic PKC's. There was no difference in ERK1 and ERK2. Both fluoxetine and EA as well as placebo did not cause any significant change in any of the G proteins nor was there any difference between responders and non responders to any of the treatments. EA treatment was associated with significant increase in platelet membrane PKCα and increased cytosolic PKCα, PKCβI, PKCβII as well as decreased PKC?. Fluoxetine was associated with increase in membrane PKCα and increase in cytosolic PKCα. There were no pre-post treatment changes in cytosolic ERK 1 and 2. It is of note that responders differ from non responders only in membrane PKCβI (for fluoxetine and placebo) and cytosolic PKCξ (for EA). **Suggestions:** a) Different antidepressant treatments may be associated with different biological processes. b) EA may be associated with specific biological changes. c) Though some signal transduction processes have been suggested to be abnormal in depressed patients, they are not necessarily associated with treatment response to SSRI nor to EA.

156. Regulation of Intracellular Calcium Signaling by Vesl/Homer Proteins

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Sponsor: Past Travel Awardee, Memorial, 2003

The Vesl/Homer family of proteins comprises cytosolic scaffold proteins that have been implicated in the clustering of neurotransmitter receptors, memory formation and axon path finding. We hypothesized that binding of Vesl/Homer proteins to intracellular calcium channels changes their activity and contribution to intracellular calcium signaling. The activity of intracellular calcium channels was determined in the presence and absence of Vesl-1/Homer 1 isoforms using single channel electrophysiology and fluorimetric calcium measurements. Binding of Vesl-1L/Homer-1c to the ryanodine receptor or inositol-1,4,5-trisphosphate receptor significantly modulated channel activity independent of the mode of activation. Crucial biophysical parameters of the intracellular calcium channels, including channel current amplitude, single channel conductance and dependence on cytosolic free calcium, were preserved after Vesl-1L/Homer-1c binding. However, both the mean open time and the channel opening frequency of the ryanodine receptor and inositol-1,4,5-trisphosphate receptor were altered by binding to Vesl-1L/Homer 1c, leading to significant changes in the open probability. Vesl-1S/Homer 1a, a neuronal immediate early gene that is upregulated during seizure, long-term potentiation and synaptogenesis, bound to intracellular calcium channel isoforms, but unlike the long isoform of Vesl-1/Homer 1 did not change their activity. Spectrofluorimetric measurements of calcium release from intracellular stores corroborated these results at the subcellular level. Our results indicate that binding of Vesl/Homer proteins to intracellular calcium channels provides a novel modulatory mechanism for the regulation of intracellular calcium signaling. We propose that this mechanism can be utilized to control cellular degeneration and cell death induced by elevated cytosolic calcium levels.

157. Electrophysiological "signature" of Psychedelic Hallucinogens is Mediated Selectively by NR2B-containing NMDA Glutamate Receptors

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Sponsor: Past Travel Awardee BMS, 2002

Hyperglutamatergic states are thought to play a role in schizophrenia, particularly during early stages of pathogenesis. This suggests that treatments which limit or suppress glutamatergic transmission may be therapeutic or prophylactic in the illness, especially manipulations which are specific for certain pathways or receptor subtypes. In prefrontal cortical slice from adolescent and adult rats, psychedelic hallucinogens induce a delayed wave of asynchronous glutamate release (late EPSC) following the fast component of evoked release (fast EPSC). Unlike the precisely-timed, fast EPSC, the hallucinogen-enhanced late EPSC can occur at variable intervals after the stimulus and persist for several seconds. In the present study we show that this electrophysiological "signature" of hallucinogens, like LSD (D-lysergic acid diethylamide) and DOI (2,5-dimethoxy-4-iodophenyl-2-aminopropane hydrochloride), is dependent on NR2B-containing NMDA receptors. Ifenprodil (300 nM), a selective NR2B antagonist, markedly suppresses the characteristic DOI-enhanced late EPSC without altering the normal fast EPSC. It is known that high concentrations of haloperidol (3-10 microM), higher than those needed to block dopamine D2 receptors, selectively block NR2B-containing NMDA receptors which do not also contain NR2A. Haloperidol at this high concentration blocks the DOI-enhanced late EPSC, suggesting that the NMDA receptors involved are either NR1/NR2B dyads or possibly NR1/NR2B/NR2D triads. NR2B receptors have an extrasynaptic location in adult and have been shown to mediate "cross talk" (glutamate spillover) between neighboring pathways. Imaging studies will be needed to define the pattern of cross talk. We hypothesize that a pathologically-elevated level of cross talk is responsible for the disruptive effects of hallucinogens on cortical function. Selective NR2B antagonists are currently in clinical trials for the treatment of stroke or cerebral trauma. These clinical studies have revealed that selective NR2B antagonists, unlike broad-spectrum NMDA antagonists, are not psychotomimetic. Our work suggests that NR2B antagonists may have potential as novel therapeutic agents for psychosis.

158. 5-HT_{1E}: A Forgotten Serotonin Receptor

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Sponsor: David Leander

Serotonin (5-hydroxytryptamine, 5-HT) is a major mammalian neurotransmitter, and serotonergic neurons and receptors have proven utility as targets for drugs used to treat a variety of human diseases. The flurry of cloning during the last decade that revealed as many as fourteen distinct mammalian 5-HT receptors provided the possibility of adding a number of additional therapeutic targets. However, a number of the 5-HT receptors remain poorly characterized, and for some little has been learned about them since their initial cloning more than a decade ago. The 5-HT_{1E} receptor is one of these. It was originally proposed to exist based on radioligand binding in human brain tissue in 1989 (Leonhardt et al., J. Neurochem. 1989, 53: 465-71) and then later cloned from human tissue in 1992. Since that time only minimal work has been reported on this receptor and no characterization has been described in common laboratory animals. A characterization of the coding region for this receptor in samples from 157 unrelated humans identified only a single silent mutation and led the authors to conclude that there appears to be high evolutionary conservation of this receptor (Shimron-Abarbanell et al. Brain Res Mol Brain Res. 1995, 29:387-390). Given the potential interest in this receptor, we set out to determine if a suitable laboratory species could be identified for the study of the 5-HT_{1E} receptor (Bai et al., Eur. J. Pharmacol. 2004, 484:127-39). PCR analysis using degenerate oligonucleotide primers based on N- and C-terminal sequences of the human 5-HT_{1E} receptor gene was performed to probe for the presence of the 5-HT_{1E} receptor gene in genomic DNA samples from several different species. A genomic fragment of approxi-

mately 1.1 kb was identified in samples from human, monkey, pig, rabbit, and guinea pig. However, no amplification product was seen in the rodent samples, which included rat, mouse, gerbil or hamster. Also, no signal was detected in dog or chicken. Given the absence of any PCR product in rodents, the mouse genome database was searched using the guinea pig and human protein sequences for the query. The most significant match in the mouse genome was the 5-HT_{1F} receptor, indicating that no mouse ortholog exists for the 5-HT_{1E} receptor. The close structural homology between the 5-HT_{1E} and 5-HT_{1F} receptors and the presence of the 5-HT_{1F} receptor in all mammalian species studied so far has led to a hypothesis that the 5-HT_{1E} receptor may have arisen from the 5-HT_{1F} receptor via a gene duplication event. Extensive characterization of the guinea pig 5-HT_{1E} receptor showed that this receptor has high structural homology to the human receptor (95% amino acid homology) and very similar pharmacology. The absence of the 5-HT_{1E} receptor in rats and mice and the lack of selective pharmacologic tools will make the study of this receptor's physiologic roles a challenge. However, the finding of this receptor in laboratory animals like the guinea pig and rabbit may provide a path forward for studying this receptor *in vivo*.

159. Chronic Ithium Treatment of Rats Reduces Brain Nmda-Initiated Arachidonic Acid Signaling by Downregulating Ca2 -Dependent Cytosolic Phospholipid A2

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Glutamate, and particularly N-methyl-D-aspartate (NMDA), are reported to activate NMDA receptors to allow extracellular Ca2+into the cell. Increased intracellular Ca2+ can activate many Ca2+ -dependent enzymes, one of which is Ca2+ -dependent cytosolic phospholipase A2 (cPLA2). This enzyme selectively releases the second messenger, arachidonic acid (AA, 20:4 n-6), from the stereospecifically numbered (sn)-2 position of phospholipids. cPLA2 has been localized to excitatory post-synaptic dendritic and other membrane sites in brain (1), and its inhibition by bilobalide has been related to bilobalide's ability to protect against NMDA-induced excitotoxicity (2). Also, we reported that chronic LiCl feeding to rats, to produce a therapeutically equivalent brain Li concentration, reduced brain mRNA and activity levels of cPLA2, without affecting brain expression of Ca2+ -independent iPLA2 or Ca2+ -dependent secretory sPLA2 (3). In the present study, we hypothesized that chronic LiCl feeding to rats would reduce brain cPLA2 activation, imaged as an AA signal by a method that we have developed (4), in response to NMDA by reducing the cPLA2 response to Ca2+. To test this, we administered an acute sub-convulsant dose of NMDA to unanesthetized rats, and used quantitative autoradiography to measure regional brain incorporation coefficients k* of AA as a marker of PLA2 activation. In control rats, NMDA (25 or 50 mg/kg i.p.) compared with saline increased k* significantly in 49 and 67 of 83 brain regions examined, respectively. These regions, having high densities of NMDA receptors, included the cortex, hippocampus, caudate putamen and thalamus. The increases were entirely blocked by acute pretreatment with the non-competitive NMDA antagonist MK-801 (0.3 mg/kg i.p.), as well as by feeding LiCl to the rats for 6 weeks. The reduction by lithium of post-synaptic NMDA-mediated signaling involving Ca2+ -induced cPLA2 activation to release AA is consistent with glutamatergic hypotheses for both lithium's antimanic and neuroprotective actions (5), and with our hypothesis that lithium and certain anticonvulsants are therapeutic in mania by targeting cPLA2 to downregulate brain AA metabolism (6). Ref: 1. Ong et al. J Hirnforsch 39, 391, 1999 2. Weichel et al. Naunyn Schmied Arch Pharmacol 360, 609, 1999 3. Rintala et al. Neuroreport 10, 3887, 1999 4. Rapoport J Mol Neurocsci 16, 243, 2001 5. Bauer et al. Pharmacopsychiatry 36 Suppl 3:S250, 2002 6. Rapoport & Bosetti Arch Gen Psychiatry 59, 492, 2002.

160. Identification of D1 Dopamine Receptor Interacting Proteins using Co-immunoprecipitation-based Proteomics

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It is becoming increasingly apparent that dopamine receptors (DARs) do not exist as singular independent units within the synaptic membrane, but rather are part of a large macromolecular complex of interacting proteins. The protein constituents of this complex (signalplex) may be quite dynamic with respect to space and time. These interacting proteins may serve to influence the receptor in a variety of ways including subcellular localization, receptor trafficking, and functional characteristics. Our current studies employ a co-immunoprecipitation assay for D1 DARs (from mouse brain and transfected cell lines), coupled with mass spectrometry (MS) sequencing to identify interacting partners. Immunoprecipitation was verified via western blot and MS, both of which were able to positively identify the D1 DAR. To limit false positive identification of interacting proteins, negative controls were used including species and class matched non-immunized antibodies, mock transfected cells, and D1 DAR knockout animals. Following immunoprecipitation of the D1 DAR from transiently transfected human embryonic kidney HEK293T cells, the complex was separated using one dimensional SDS-PAGE and stained. Sixteen independent bands were excised, de-stained, trypsinized, and subjected to MS-based peptide sequencing. Peptides were matched to parent proteins by searching against a non-redundant protein database. Peptides were observed for approximately 46 proteins in addition to the D1 DAR. Approximately 10 of these proteins were also found in immunoprecipitates from mock-transfected controls and therefore identified as non-specific. The remaining 36 proteins were specifically associated with the D1 DAR. These findings demonstrate that the D1 DAR is expressed as part of a protein complex that is capable of being selectively isolated via co-immunoprecipitation assays. Studies are currently in progress to identify D1 DAR interacting proteins in neuronal systems (cell lines and brain) and characterize the effects of these proteins on the D1 DAR.

161. Catechol-O-Methyltransferase (COMT) Polymorphism and Anxiety Susceptibility in Persons with Schizophrenia and Normal Controls

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Sponsor: ACNP Secretariat

The val allele of the Val158Met polymorphism in the COMT gene appears to exert a deleterious effect on cognition and increases risk for schizophrenia. In contrast, the Met allele has been linked to anxiety states (1978; Matthew et al, 1980a; and Matthew et al. 1980b). We examined the effect of val158met on the four subscales related to anxiety from the TPQ (Cloninger, 1978) in 280 patients with schizophrenia and 366 normal controls. Patients with Schizophrenia included 72 female and 208 males while the normal controls consisted of 201 females and 165 males. The mean ages were 36.5 for patients with schizophrenia and 33.8 for normal controls. No significant effect of genotype was observed for shyness (p=.99), fear of uncertainty (p=.50) or fatigability (p=.30). A weak main effect was evident in the worry scale (p=.08) and post hoc comparisons showed that val/met subjects with schizophrenia had increased anxiety levels compared to the val/val subjects. This was not evident for their normal control counterparts. . While a significant main effect for gender was observed, there were no significant interactions between gender and genotype on any anxiety score. These results suggest that COMT genotype may exert a slight effect on anxiety in patients with schizophrenia.

162. Pregabalin Reduces Synaptic Vesicle Release in Cultured Rat Neurons

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Sponsor: Karl Rickels

Pregabalin is a novel anxiolytic drug, effective in clinical trials of generalized anxiety disorder and in anxiolytic models, such as the Vogel test in rats. Its mechanism is distinct from benzodiazepines or serotonin-reuptake inhibitors. It is a high-affinity ligand at alpha$_2$-delta (α_2-δ) protein (Gee et al., 1996) from brain tissues. This protein is a membrane-bound auxiliary subunit of voltage-gated calcium channels. Previous studies showed that binding of pregabalin at α_2-δ is required for anxiolytic-like and analgesic actions in animal models. The present study was performed to explore details of pregabalin's action to reduce neurotransmitter release (e.g., Dooley et al., 2002; Maneuf et al., 2001) that has been associated with its anxiolytic-like and analgesic effects. Cultures of rat hippocampal neurons were grown by standard methods. Release of synaptic vesicles was measured by scanning laser fluorescence microscopy with the lipophilic dye, FM4-64. This agent is retained by lipids, such as plasma membrane, but does not diffuse across lipid bilayers. Exposure of neurons to FM4-64 during repetitive stimulation traps fluorescent dye within synaptic vesicles, where it remains until released by exocytosis (10 Hz electrical stimulation). Thus, FM4-64 destaining is a relatively direct measurement of synaptic vesicle release with high resolution in time and space. Pregabalin (100 μM) reduced the rate and amount of FM4-64 destaining from synaptic terminals, and this effect was observed regardless of whether the terminal was co-labeled by the GABA presynaptic marker, glutamic acid decarboxylase (unlabeled terminals were assumed to contain glutamate). The initial speed of dye unloading was reduced 28% at GABA synapses and 24% at nonGABA synapses, and the amount of releasable dye was decreased by 13% at GABA synapses and 12% at nonGABA synapses. In addition, release triggered by application of hypertonic sucrose in zero calcium solution was reduced by pregabalin treatment (32% reduction). Interestingly, if neurons were electrically stimulated immediately after exposure to hypertonic sucrose, pregabalin had no effect on subsequent release. These findings suggest that synaptic vesicle release is reduced by pregabalin regardless of the transmitter substance involved (glutamate or GABA). Vesicle release from a pathway independent of calcium influx, involving presynaptic proteins (e.g., synaptotagmin, syntaxin, VAMP) also is sensitive to reduction by pregabalin. Pregabalin may preferentially reduce release from the readily-releasable vesicle pool. These findings suggest that pregabalin binding alters the action of presynaptic proteins through protein-protein interactions with α_2-δ or, alternatively, through another, unknown mechanism. References Gee NS, Brown JP, Dissanayake VU, et al. J Biol Chem. 1996;271:5768-5776. Dooley DJ, Donovan DM, Meder WP, Whetzel SZ. Synapse. 2002;45:171-190. Maneuf YP, Hughes J, McKnight AT. Pain. 2001;93:191-196.