266. TREATMENT WITH THE PRESYNAPTIC 5-HT1A-ANTAGONIST PINDOLOL IN PATIENTS WITH PANIC DISORDER

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SSRIs like paroxetine play an important role in the treatment of patients with panic disorder. It is striking to observe that at the beginning of the treatment an exacerbation of the symptoms occurs, usually in the form of an increase in the number of spontaneous attacks. It is known that at the beginning of the treatment with SSRIs the activity of serotoninergic neurons in the nucleus raphe dorsalis (DRN) is suppressed via 5-HT1A autoreceptors, therefore inhibiting serotonin (5HT) tone in projection areas (Romero et al., 1996). As locus coeruleus (LC) neurons are suppressed by 5-HT from the DRN and their activation accompanies anxiety, the increase in anxiety in panic disorder could be mediated via the inhibition of DRN-neurons. We therefore studied the effect of the presynaptic 5-HT1A/B-adrenergic antagonist pindolol on the clinical response in 3 inpatients (2 male, 1 female) with spontaneous panic attacks. All were diagnosed as suffering from panic disorder according to the DSM-IV criteria. It was ensured that these patients did not have a history of asthma or low blood pressure. We gave pindolol, 2.5mg three times daily in combination with an SSRI (10 mg paroxetine or citalopram at the beginning). The patients took the pindolol and SSRI regimen without reporting untoward side effects. An increase of spontaneous panic attacks was not found. All patients had a marked improvement of panic symptoms and remitted quickly. Our results indicate that pindolol addition to SSRIs is highly effective in reducing panic symptomatology.

267. rTMS TREATMENT OF PTSD AND MAJOR DEPRESSION

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Repetitive transcranial magnetic stimulation (rTMS) is a new modality with potential for treating mood disorders. Antidepressant treatment of depressive and post-trauma symptoms in post-traumatic stress disorder (PTSD) gives mixed results, and in clinical practice there are many non-responders.

We administered rTMS as an open-label adjunctive treatment to antidepressant medication to 7 patients with PTSD and major depression diagnosed on Structured Clinical Interview for diagnosis. rTMS was administered at 90% of motor threshold at either 1 Hz or 5 Hz daily for 10 days. 40 stimuli/minute were administered for 15 minutes daily, for a total of 6000 stimuli per patient. Outcome measures included Hamilton Depression Rating Scale (HAM-D), Mississippi Scale of Combat Severity, Profile of Mood States (POMS), and University of Southern California Repeatable Episodic Memory Test (USC-REMT). Statistical significance was assessed with repeated-measures ANOVA.

All 7 patients tolerated rTMS well with no EEG changes or side effects except transient headache. Mean HAM-D scores decreased from 27.9 to 13.6 two months after rTMS (p = .000) while sleep scores trended toward improvement. POMS subscales Tension-Anxiety, Depression-Dejection, Anger-Hostility, and Vigor-Activity showed significant improvement (p < .05). Mississippi score decreased from 124 to 111 two months following rTMS (p < .05). USC-REMT scores were unchanged.

Depressive symptoms improved robustly after rTMS treatment in an open-label study of 7 patients with PTSD and major depression, while sleep and trauma symptoms decreased to a lesser extent. rTMS may be a promising new treatment for depression in PTSD.

268. SIMULTANEOUS CATECHOLAMINE AND INDOLEAMINE DEPLETION IN UNMEDITATED DEPRESSED SUBJECTS

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Although significant evidence suggests that alterations in monoamine systems are associated with clinical depression, catecholamine or indoleamine depletion alone has not been associated with significant mood changes in unmedicated depressed subjects, a finding that complicates the classic monoamine hypotheses on the neurobiology of depression. As one possible explanation, dysfunction in one monoamine system may be balanced by intact function in another. To test this hypothesis, unmedicated depressed subjects underwent a 2-week, double-blind, random-ordered crossover study consisting of the following active and control conditions respectively: indoleamine (via tryptophan depletion) plus catecholamine (via alpha-methyl-paratyrosine administration) depletion and, separately, indoleamine plus sham (via diphenhydramine administration) depletion and, separately, indoleamine plus sham (via diphenhydramine administration) catecholamine depletion. Ten subjects completed both conditions; 2 subjects were withdrawn after active testing and one after control testing. Time (F 7.1, df 4, 36, p = 0.0003) but not time-by-condition or condition effects were statistically significant. Mean HDRS scores decreased progressively throughout the study days (baseline 26.7 points ± 1.4 SEM; termination 21.3 ± 1.7). Response (i.e., >50% HDRS decrease and maximum score <15 points) rates were 3 [25%] of 12 subjects undergoing active testing and 4 [36%] of 11 undergoing control testing, inclusive of follow-up day ratings. Overall, results suggest that simultaneous disruptions of indoleamine and catecholamine function do not exacerbate symptoms in unmedicated depressed subjects, thus lending further support to the notion that monoamines regulate mood in actively depressed patients via indirect mechanisms.

269. CHANGES IN ANXIETY AFTER PREFRONTAL rTMS IN PATIENTS WITH GAD

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While prefrontal repetitive Transcranial Magnetic Stimulation (rTMS) is being widely investigated for treating depression, the use of rTMS in anxiety disorders has not been extensively studied and use in Generalized
Anxiety Disorder (GAD) is limited to a single case report. Here, we administered lateral orbitofrontal rTMS to 7 subjects with GAD. On separate days, subjects received right or left high frequency, right or left low frequency, or placebo rTMS in a counterbalanced, single blind, randomized order. Serial self-rated visual analogue scales measuring anxiety and mood were performed. We hypothesized that right high frequency rTMS would increase anxiety whereas right low frequency rTMS would decrease anxiety based on: (1) data suggesting that the orbitofrontal cortex is important in anticipatory anxiety; (2) studies of healthy volunteers and depressed patients as well as a single case report in a GAD patient suggesting that high frequency prefrontal rTMS temporarily increases anxiety, and (3) the theory that high and low frequency rTMS may have opposite effects on brain function. Preliminary analysis reveals that placebo stimulation significantly decreased anxiety during the hour after stimulation. Also, relative to placebo stimulation, a trend exists suggesting that all the active stimulation types were anxiogenic. There did not appear to be a significant difference in anxiety ratings between the active stimulation cells. These results do not support our hypothesis. In fact, they suggest that single session lateral orbitofrontal stimulation may be anxiogenic, regardless of hemisphere or frequency. Pain with the active stimulation cells may have confounded our results.

270. DONEPEZIL AUGMENTATION FOR COGNITIVE IMPAIRMENT IN EUTHYMIC BIPOLAR PATIENTS

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Memory is an important area of neuropsychological research. Cognition in Bipolar Affective Disorder (BPAD) has been an under-researched field. Psychiatric patients with impaired cognition, have a worse prognosis than those who do not. Cognitive impairment, even in euthymic BPAD, particularly in the domain of declarative memory has been reported. Sachs and colleagues have reported donepezil augmentation of typical and atypical antipsychotics in a previously randomized, cross-over, double-blind, placebo controlled study in patients with schizophrenia (data abstracted). Furthermore, those subjects who showed cognitive improvement also displayed activation on fMRI in the dorsolateral prefrontal cortex and anterior cingulate gyrus. These findings hold promise for those patients suffering from psychiatric illnesses which impair memory.

Sachs and colleagues have reported donepezil to be helpful for treatment resistant BPAD. We are currently conducting a randomized cross-over double-blind, placebo controlled study in BPAD with donepezil augmentation. It is our hypothesis that donepezil augmentation will enhance mood stability and cognition (in a similar manner to that seen in our ongoing studies of donepezil augmentation of neuroleptics in schizophrenia). The results of our ongoing studies of donepezil augmentation in BPAD as it effects mood and cognition will be reported.

271. DEPRESSION IN ASTHMA PATIENTS: PRELIMINARY FINDINGS

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Data suggest that asthma and asthma-related deaths have increased in recent years. Depressive symptoms are reportedly associated with non-compliance and even sudden death in asthma patients. However, minimal data are available which correlate depressive symptoms or the presence of a mood disorder with subjective and objective measures of asthma severity. Preliminary data from two studies are reported. In the first study, forty-five consecutive asthma patients (9 males, 36 females, mean age = 51.2, SD = 13.2) were given the mood disorders component of the SCID-I-V. Out of 6 patients with current major depressive disorder only one received an antidepressant. Surprisingly, patients with a mood disorder had significantly (p = 0.04) less severe airway obstruction (mean FEV₁ = 73%) than those without a mood disorder (mean FEV₁ = 61%). In the second study, twenty-six asthma patients (4 males, 22 females, mean age = 50, SD = 12.9) were given the Inventory of Depressive Symptomatology-Self Report (IDS-SR) and the SF-12 consisting of two self-reported subscales which measure mental and physical functioning. A significant relationship was found between higher IDS-SR scores and lower scores on both of the SF-12 subscales measuring mental (p = .02) and physical (p = .03) functioning. These results suggest that depression is associated with greater subjective but less objective ratings of medical disability. In addition, these data suggest that while mood disorders may be common in this population, asthma patients may be infrequently treated for depressive symptomology. The implications of these findings and directions for future research are discussed.

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272. ANTIDEPRESSANT RESPONSE AND REGIONAL CEREBRAL BLOOD FLOW

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Despite advances in the pharmacological armamentarium for depressive illness, treatment response variability remains unpredictable and poorly understood. In order to evaluate the functional neuroanatomical correlates of antidepressant treatment response variability, we employed serial positron emission tomography (PET) in a double-blind randomized antidepressant trial of monotherapy with venlafaxine or bupropion among never-hospitalized patients with unipolar depression. Oxygen-15 PET was performed at baseline and then after at least 6 weeks of venlafaxine or bupropion monotherapy. Non-responders to the first antidepressant were crossed over to the second antidepressant and after