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Dopamine D3 Receptor Gene and Olanzapine Response in Schizophrenia

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Introduction: Several single nucleotide polymorphisms (SNPs) for dopamine D3 receptor gene (DRD-3) have been associated with differential anti-psychotic response, including ser-9-gly (rs6280).

Methods: We assessed response in 82 patients with schizophrenia retrospectively genotyped for SNPs of neuroreceptor genes associated with olanzapine activity. Baseline-to-endpoint reduction in Positive and Negative Syndrome Scale (PANSS)-positive sub-scores over 6 weeks of olanzapine treatment was assessed by repeated measures ANOVA. Categorical response was an endpoint rating of mild or minimal or less on each PANSS-positive item.

Results: PANSS-positive reduction for 3 DRD-3 SNPs differed significantly by allelic and genotypic analyses respectively at chromosome 3 positions rs1800828 ($p = 0.238$ and 0.0130), rs6280 ($p = 0.022$ and 0.0045), and rs3732790 (dbSNP) ($p = 0.0006$ and 0.0130). For each SNP, one homozygous genotype was associated with greatest response ($N = 10$, 24, and 42, respectively) compared with the rest of the 82 patients. Of patients homozygous for the more responsive ser-9-gly SNP vs. others, 45.8% vs. 17.24% ($p = 0.0116$) had at most minimal PANSS-positive symptoms, and 79.2% vs. 58.6% ($p = 0.127$) had at most mild PANSS-positive symptoms at endpoint.

Conclusions: DRD-3 receptor gene SNPs predicted statistically and clinically significant acute positive symptom reduction with olanzapine in substantial subsets of patients with schizophrenia.

Differential Rates of Clinical Trial Discontinuation as a Measure of Treatment Effectiveness among Antipsychotic Medications

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Objective: Antipsychotic treatment discontinuation may be used to measure overall treatment effectiveness. Few studies systematically assess early treatment discontinuation differences among antipsychotics. We investigate olanzapine discontinuation compared to other atypical antipsychotics.

Methods: A post hoc, pooled analysis of 4 randomized, 24–28 week, double-blind clinical trials included 822 olanzapine-treated and 805 risperidone-, quetiapine-, or ziprasidone-treated patients. Discontinuation rates and the probability of staying in treatment were compared between olanzapine and the other atypicals combined.

Results: Poor response/symptom worsening was the primary reason for discontinuation regardless of medication. There was a significant treatment difference in the rate of discontinuation due to poor response/symptom worsening (olanzapine 14.23% vs. other atypicals 24.60%, $p < 0.001$). There was no treatment difference in the rate of discontinuation due to medication intolerability (olanzapine 5.60% vs. other atypicals 7.45%, $p = 0.13$). Olanzapine-treated patients were significantly more likely to complete treatment (53.9% vs. 39.3%, $p < 0.001$) and stayed in treatment longer (19.1 vs. 16.1 weeks, $p < 0.001$) than other atypical-treated patients.

Conclusions: The predominant reason for difference in early discontinuation between olanzapine and other antipsychotics was higher dropouts due to poor response/symptom worsening with other antipsychotics. Treatment discontinuation may be an important gauge of relative treatment effectiveness among antipsychotics.

Oral Olanzapine Transition Dose Following Intramuscular Olanzapine Treatment

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Background: Intramuscular (IM) antipsychotics are first line treatment for acute agitation in patients with schizophrenia. After stabilization, patients are transitioned to oral medication.

Methods: This was a post-hoc analysis of transitional oral antipsychotic dose per IM group in a double-blind, randomized study. Over 24 hours, agitated inpatients received 1, 2, or 3 injections of IM olanzapine (OLZ) 10 mg ($n = 92$, 26, 3, respectively), haloperidol (HAL) 7.5 mg ($n = 82$, 32, 1, respectively), or placebo (PBO, $n = 24$, 21, 2, respectively) followed by 4 days of oral treatment with 5–20 mg/d OLZ for IM OLZ and PBO groups and 5–20 mg/d HAL for IM HAL group. Agitation was assessed by the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC).

Results: Median/means of mean oral doses in patients receiving 1, 2, and 3 injections, respectively, were 10.0/12.0 mg, 13.8/13.8 mg, and 20.0/18.3 mg OLZ for OLZ IM group; 10.0/9.9 mg, 11.3/11.8 mg, and 10.0/10.0 mg HAL for HAL IM group; and 10.0/10.6 mg, 11.3/12.5 mg, and 8.8/8.8 mg OLZ for PBO IM group. Reduction in agitation continued during transition to oral antipsychotic for HAL and PBO groups and for OLZ patients who received 1 IM dose. Reduction in agitation was maintained during transition for patients who received multiple OLZ IM doses.

Conclusions: Reduction in agitation was maintained following transition from IM to oral therapy. Transitional oral doses increased with the number of OLZ injections.

Topiramate Modulates Neuronal Excitability in the Basolateral Amygdala by Selectively Inhibiting GluR5 Kainate Receptors and Acting as a Positive Modulator of $GABA_A$ Receptors

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Topiramate is a novel antiepileptic drug that has also shown promise in the treatment of certain psychiatric illnesses. The

mechanisms underlying the clinical therapeutic effects of topiramate are poorly understood. Recently, we reported that topiramate inhibits postsynaptic GluR5 kainate receptor-mediated responses in basolateral amygdala (BLA) principal neurons, suggesting that a reduction of GluR5 receptor-mediated excitation of pyramidal neurons is one mechanism responsible for the antiepileptic properties of topiramate. Since GABAergic inhibition plays a primary role in neuronal excitability, in the present study we examined whether topiramate 1) also inhibits GluR5 receptors on GABAergic interneurons in the BLA, and 2) directly influences GABAergic synaptic transmission. We have previously demonstrated that GluR5 receptors are present on both somatodendritic and presynaptic sites of BLA interneurons. Activation of these receptors enhances GABA release. However, when extracellular glutamate concentrations are high (as during epileptic seizures), activation of interneuronal, presynaptic GluR5 receptors inhibits GABAergic transmission, further contributing to hyperexcitability. Using whole-cell recordings in rat amygdala slices, we found that topiramate, in a dose-dependent manner (1–10 μM), 1) suppressed excitatory postsynaptic currents (EPSCs) evoked in BLA interneurons by the selective GluR5 agonist, ATPA (10 μM), 2) suppressed the ATPA-induced enhancement of spontaneous inhibitory postsynaptic currents (sIPSCs) recorded from pyramidal cells, and 3) prevented the ATPA-induced reduction of IPSCs evoked in pyramidal cells. Thus, by an effect on interneuronal GluR5 receptors, topiramate can suppress spontaneous release of GABA, but promote evoked GABA release during intense activation of GluR5 receptors. In addition, we found that topiramate enhances inhibitory transmission by a direct effect on postsynaptic $GABA_A$ receptors. Thus, topiramate increased the amplitude of evoked, spontaneous, and miniature IPSCs recorded from BLA pyramidal cells. These results indicate that topiramate, at clinically relevant concentrations, selectively inhibits GluR5 receptor-mediated responses of interneurons, and acts as a positive modulator of $GABA_A$ receptors.

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Duloxetine at Doses of 60 mg QD and 60 mg BID is Effective in Treatment of Diabetic Neuropathic Pain (DNP)

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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 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.

The Safety of Duloxetine in the Long-Term Treatment of Diabetic Neuropathic Pain

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Background: Duloxetine, a balanced and potent dual reuptake inhibitor of serotonin and norepinephrine, was found to be safe and effective in the acute treatment of pain associated with diabetic neuropathy (Goldstein et al., 2003). The objective of the study's extension phase was to examine the safety of up to 52 weeks' exposure to duloxetine in comparison to routine care, and to compare the effect of these treatments on progression of diabetic complications.

Methods: This was a 52-week, multicenter, open-label study extension of an acute placebo-controlled study, in which 337 patients with diabetic neuropathic pain were re-randomized to either duloxetine 60 mg BID or routine care. Diabetic complications were measured using the physical examination portion of the Michigan Neuropathy Screening Instrument (MNSI; neuropathy progression), microalbumin/creatinine ratio (nephropathy progression), and ophthalmologic examination with fundus photograph (retinopathy progression). Treatment effects on QOL were compared using the Short Form-36 and EQ-5D version of the EuroQoL instrument.

Results: There were no significant differences between treatment groups regarding neuropathy, nephropathy or retinopathy progression. Discontinuation rates due to adverse events (AEs) were 9.6% and 14.0% for routine care and duloxetine, respectively. Serious adverse events (SAEs) were reported by 19.1% of routine care patients and 14.4% of duloxetine patients. Duloxetine was not significantly greater than routine care regarding the occurrence of SAEs or AEs. There were no significant differences in the number of hypoglycemic events or treatment-emergent abnormal HbA1c or lipids. Duloxetine was significantly better than routine care on the bodily pain subscale of the Short Form 36 Health Survey and the EQ-5D Index.

Conclusion: In this study, duloxetine 120 mg/day was safe and well-tolerated in the long-term treatment of diabetic neuropathic pain. Duloxetine was superior to routine care on several measures of quality of life.

Venlafaxine vs. Placebo: A Subgroup Analysis of Efficacy in Patients with Moderate or Severe Major Depression

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Objective: To compare treatment response with venlafaxine and placebo in patients with moderate or severe major depression.

Methods: Data were pooled from 19 multicenter, randomized, double-blind, placebo-controlled venlafaxine studies for the treatment of patients with major depressive disorder (MDD). Symptoms were assessed with the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$), and patients separated into 2 groups via a median split in their pretreatment $HAM\text{-}D_{17}$ scores. The primary endpoint was remission of symptoms ($HAM\text{-}D_{17}$ score of 7 or less). Remission analysis was based on the Fisher Exact Test on an intent-to-treat (ITT) sample consisting of all patients who had at least 1 dose of study medication and at least 1 postbaseline efficacy evaluation.

Results: The median split occurred at the score of 23 on the $HAM\text{-}D_{17}$ scale. Patients received venlafaxine (n = 2803) or placebo (n = 1626). At endpoint (week 8), for patients with moderate depression (baseline $HAM\text{-}D_{17}$ scores of 23 or less), remission rates for venlafaxine versus placebo were 37% and 24%, respectively ($P < 0.001$, LOCF). For patients with severe depression (baseline $HAM\text{-}D_{17}$ score of greater than 23) remission rates for venlafaxine versus placebo were 28% and 17% respectively ($P < 0.001$, LOCF). This was consistent with observed cases (OC) data where remission rates for patients with moderate depression were 44% for venlafaxine and 28% for placebo ($P < 0.001$) versus 36% for venlafaxine and 25% for placebo ($P < 0.001$) for patients with severe depression. Beginning at week 3, for patients with both types of depression, venlafaxine showed statistically significant differences in remission rates versus placebo for both LOCF and OC cases.

Conclusion: Venlafaxine achieved significantly higher remission rates than placebo, starting at week 3, for patients with either moderate or severe depression as defined by a post-hoc analysis of $HAM\text{-}D_{17}$.

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Cluster Analysis—Typology of Patients with Psychotic Disorders Who Achieve Distinct Functional and Symptom Outcomes

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Purpose: To enrich the characterization of patients' medication response in schizophrenia by exploring a typology relying not only on post-treatment disease state symptoms, but also social and occupational functioning.

Methods: A hierarchical cluster analysis (based on Ward's minimum-variance method) was used to define groups of patients based on endpoint values for psychiatric symptoms, social functioning, and useful work. Patients (n = 1499) from 6 randomized, active-control studies who had received an antipsychotic drug for at least 10 weeks were included. Residual psychiatric symptoms were assessed with Positive and Negative Syndrome Scale (PANSS) 5 factors, functioning was assessed by Quality of Life (QLS) *Interpersonal Relations* and *Instrumental Role Functioning* subscales, and a separate questionnaire assessed amount of useful work. A recursive partitioning regression tree algorithm was used to generate parsimonious descriptors for each cluster.

Results: Five distinct clusters of patients were identified at endpoint: *Cluster A* (25.6%): no or minimal residual symptoms and mild functional impairment; *Cluster B* (29.1%): minimal residual symptoms but moderate-to-severe functional impairment; *Cluster C* (16.2%): mild symptoms and mild-to-moderate functional impairment; *Cluster D* (14.3%): moderate negative symptoms and disorganization, mild positive and depressive symptoms and hostility, and severe functional deficit; and *Cluster E* (14.8%): moderate-to-severe symptoms across all factors and severe functional deficit.

Conclusion: Although psychiatric symptoms alone have been used to define the outcome of treatment with antipsychotic drugs, functional outcomes provide an essential and complementary dimension of the patients' overall clinical status.

Cell Cycle Inhibition Provides Neuroprotection and Reduces Glial Scarring after Traumatic Brain Injury

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Traumatic brain injury (TBI) causes neuronal apoptosis, inflammation, and reactive astrogliosis, which contribute to secondary tissue loss, impaired regeneration, and associated functional disabilities. Here we show that up-regulation of cell cycle components are associated with caspase mediated neuronal apoptosis and glial proliferation after TBI in rats. In primary neuronal and astrocytes cultures, cell cycle inhibition—including the CDK inhibitors flavopiridol, roscovitine and oloumucine— reduced up-regulation of cell cycle proteins limited neuronal cell death following etoposide-induced DNA damage, and attenuated astrocyte proliferation. After fluid percussion induced TBI in rats, flavopiridol treatment after injury reduced cyclin D1 expression in neurons and glia in ipsilateral cortex and hippocampus. Treatment also resulted in decreased neuronal cell death and lesion volume, reduced astroglial scar formation, and significantly improved motor and cognitive recovery. The ability of cell cycle inhibition to decrease both neuronal cell death and reactive gliosis after experimental TBI suggests that this treatment approach may be useful for clinical brain trauma.

Flavopiridol Decreases Lesion Volume and Improves Functional Recovery after Acute Spinal Cord Injury

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Spinal cord injury (SCI) induces delayed biochemical changes that contribute to tissue damage and neurological dysfunction. Implicated secondary injury mechanisms include neuronal and oligodendroglial apoptosis, leading to neuronal loss and demyelination, as well as micoglial related inflammation and formation of a glial scar. Flavopiridol, a cyclin dependent kinase (cdk) inhibitor known to block cell cycle progression, is under active investigation as an anti-tumor therapy. We have shown that SCI causes upregulation of cell cycle proteins associated with neuronal apoptosis, and that inhibition of cell cycle pathways by cdk inhibitors reduces neuronal apoptosis *in vitro* and limits glial proliferation. The present study evaluated the effect of intrathecal administration of flavopiridol on lesion volume and functional recovery following contusive spinal cord injuries. Adult male Sprague-Dawley rats were subjected to moderate or severe spinal cord contusion at T9, using a weight drop method. Thirty minutes after injury rats received an intrathecal injection of 5 μl of 250 μM flavopiridol. Prior to injury and at days 3, 7, 14, 21, and 28 post-injury, neurological

function was assessed using footprint analysis, Basso-Beattie-Bresnehan motor scores and a modified Tavlov motor score. Additionally, gadolinium contrast enhanced MRI images were obtained at day 28 post-injury. A significant improvement in function, as demonstrated by a return of toe spread measurements to normal values, and a significant reduction in lesion volumes as assessed by MRI imaging was found at day 28 post-injury in the flavopiridol treated moderate injury group in comparison to the vehicle treated group. A non-significant trend toward reduction in lesion volume and improved function after treatment was found in the severe injury group Thus, flavopiridol treatment improves outcome following mild-moderate spinal cord injury. It is likely that protective effects are multifactorial, reflecting reduction of neuronal cell loss, demyelination, microglial activation and formation of the glial scar. Such mechanism studies are in process.

Phase I Investigation of the Novel Antioxidant-Neuroprotectant R(+)Pramipexole in Amyotrophic Lateral Sclerosis

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R(+) pramipexole (R(+) PPX) is the dopamine receptor-inactive stereoisomer of the potent D2R dopamine agonist S(−) pramipexole that is used to treat symptoms of Parkinson's disease. PPX is a lipophilic divalent cation that possesses redox properties suggesting that it can scavenge reactive oxygen species (ROS) and be concentrated into mitochondria. Subsequent experiments showed that radiolabeled PPX is accumulated into mitochondria, and both R(+) and S(−) scavenge ROS. R(+) and S(−) PPX are approximately equally neuroprotective in neural cell culture death models based on oxidative stress. Based on these positive results in preclinical studies, and negative short-term (8-week) toxicology up to 100 mg/kg/day, in December 2000 an IND was filed for treating ALS patients with R(+) PPX; Phase I dosing began in April 2004. The underlying rationale for this study was that much higher doses of R(+) PPX should be tolerated, compared to S(−) PPX, and that substantial evidence exists for ROS-mediated damage to ALS brain and spinal cord tissues. The purpose of the initial Phase I evaluation was to assess safety and tolerability of increasing daily intake of R(+) PPX in the target population. 18 participants (16 ALS, 2 normal volunteer spouses) progressed through weekly dosage escalations from 1.5 mg/day to 30 mg/day over 7 weeks. No adverse events or toxicities were observed. Following a 4-week washout, the 16 ALS participants entered an 8-week continuous daily dosing of 30 mg/day. One adverse event was recorded that was not related to experimental medication (mild peritonitis following PEG tube reinsertion). In this chronic dosing phase, 8 out of 16 ALS participants spontaneously reported mild motor improvements that positively altered their ADLs. No negative effects were reported, and in particular there were no behavioral effects to suggest D2R activity. R(+) PPX is well tolerated at doses 5–7 times higher than those used with S(−) PPX. Future Phase I plans are to escalate daily R(+) PPX doses further to achieve serum levels ~ neuroprotective [PPX] observed in cell culture and to monitor reduction of oxidative stress in the ALS group. A Phase II early efficacy trial should begin in mid 2005.

Discovery of Novel CDK Inhibitors as Potential Neuroprotective Agents

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Multiple *in vivo* and *in vitro* studies, including our own, show that induction of cyclins and upregulation of CDK activity contributes to neuronal apoptosis, whereas administration of CDK inhibitors provides neuroprotection. Despite substantial achievements made recently in developing CDK inhibitors, the number of truly selective inhibitors remains limited. We have begun to design novel, selective CDK modulators using molecular modeling methods. To identify potential CDK specific inhibitors, we employed state-of-the-art Ligand-based as well as Structure-Based Design methods, including homology modeling, using our "in-house" database of small organic molecules. This database includes over 30 million chemical structures, representing about 11 million unique structures from 160 chemistry suppliers with broad diversity (more than 18,000 unique ring systems) and from other databases such as NCI, Maybridge, LeadQuest, Virtual Chemistry, Drug-like Compounds. Based on our *in-silico* screening and scoring functions we identified a number of molecules and tested these against CDK2 activity using radiolabeled ATP. We also examined the compounds *in vitro* using a model of rat cortical neuronal cultures subjected to etoposide-induced cell death. Five compounds showed good inhibitory activity against CDK2 with IC_{50} in the range of 200 μM; among them two compounds showed significant neuroprotective effect in our cell culture model, as revealed by LDH release assay. Taken together, these data indicate the potential value of molecular modeling methods to identify novel neuroprotective agents.

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The Integrative Effects of Brain Function Squatemetry and Acetyl L-Carnitine in the Management of Cognitive Disorders

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Introduction: This study examines an innovative model of cognition disorder investigation and the integrative management with brain function squatemetry and Acetyl-L-Carnitine.

Brain function squatemetry is a cerebral information procession profile device based on the Brodmann's cerebral area mapping that scopes calculatively, the electrochemical activities of the cortex while Acetyl L-Carnitine is (ALC) is an ester of the trimethylated amino acid, L-carnitine, and is synthesized in the human brain, liver, and kidney by the enzyme ALC-transferase. Acetyl-L-carnitine facilitates the uptake of acetyl CoA into the mitochondria during fatty acid oxidation, enhances acetylcholine production, and stimulates protein and membrane phospholipid synthesis. ALC, similar in structure to acetylcholine, also exerts a cholinomimetic effect.

Methods: Patients were grouped into four namely Control, Acetyl test, Normosquate, and Acetyl squate and were provided with the device, tutored and asked to recall and respond to the instructions immediately and after 5, 15, 30, and 60 minutes, respectively. Oral administration of Placebos were given to the control and Normosquate groups while Acetyl L-Carnitine 1000 mg Capsule were given to the Acetyl Test and Acetyl squate groups twice daily for 3 months, respectively. They all had electroencelography (EEG) diagnosis and neurofeedback training.

Result: The Acetyl squate group showed significant memory facilitation over all other groups except normosquate. The control, Acetyl test and acetyl squate were made up of patients with history of addictions and memory retardations, marched appropriately by ages, health and orientative profiles.

Conclusion: The integrative device of brain function squatemetry and Acetyl L-Carnitine innovative administration diagnoses and facilitates memory.

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A Diagnostic Algorithm of de Novo Parkinson Disease Differentiated from Parkinsonism-Plus Syndromes Using Discrimination analysis of Cerebral Perfusion SPECT

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Introduction: Parkinson disease (PD) is the most popular age-dependent neurodegenerative disorder. A variety of pharmacological agents continue to be developed and searched in order to improve motor function and to prevent pathological progression of PD. Accuracy of diagnosis in PD, especially de novo PD in clinical trial may be of great importance. It may be true that administration of neuroprotective agent to the patients with PD in earlier phase stop disease process of more effectively. β-CIT SPECT can differentiate easily both PD and parkinsonism-plus syndromes including Progressive Supranuclear Palsy (PSP) and Striatonigral degeneration (SND) in early phase from other motor disorders. However it may not be possible that β-CIT SPECT can differentiate PD from parkinsonism-plus syndromes.

Method: I-123 iodoamphetamine single photon emission computed tomography (IMP-SPECT) were performed on PD, n = 23, mean age = 66.0 + 9.8, H&Y = 2.8, PSP, n = 8 langfenp1041, mean age = 71.3 langfenp1041, and SND (MSA-P), n = 6. All the patients were diagnosed by three neurologists according to neurological sign, drug efficacy and clinical course. SPECT images were transformed to the standard brain by means of three dimensional stereotactic surface projection technique (3D-SSP). Relative regional cerebral blood flow was measured according to the predefined 35 cortical and subcortical volume of interests (VOIs) (Bohnen et al., *Neurology*, 1999; 52:541–546). Statistical analysis steps were described below.

Results and Discussion: Principal component analysis was firstly performed on each value of VOIs in all patients. Three principal components could explain 58% of all variance. Using those three principal components, discrimination analyses between PD, PSP, SND were done and Mahalanobis square distances (show below) and linear discrimination functions (equation not shown) were calculated. Error rate of these functions was 8.6% in cross validation. IMP-SPECT of three de novo patients diagnosed as PD were taken and discriminated by these functions. Accuracy of diagnosis and results of discrimination analysis were reevaluated after 6 months.

Conclusions: Linear discrimination functions that were composed by three principal components can discriminate accurately PD from PSP and PD from SND. This diagnostic algorithm may be very useful in clinical trials of new drug in PD.

	PD	PSP	SND
PD	0	13.085	12.195
PSP	13.085	0	15.973
SND	12.195	15.973	0

Reduction of Secondarily Generalized Tonic Clonic (SGTC) Seizures with Pregabalin

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Background: Pregabalin has been approved in the EU as adjunctive therapy for partial seizures with and without SGTC and for peripheral neuropathic pain. It is not known whether pregabalin reduces the number of SGTC seizures in this patient population.

Purpose: To determine if pregabalin reduces SGTC seizures in medically refractory epilepsy.

Methods: This post hoc analysis was performed on pooled data from 3 double-blind, fixed dose pregabalin, placebo-controlled studies of similar design. These studies included patients with partial seizures that have failed two or more antiepileptic medications at maximally tolerated doses and approximately 75% were taking 2 or more concomitant AEDs. This analysis excluded patients that became seizure free or did not have a SGTC seizure during baseline or treatment. Absolute and conditional reduction analyses examined change from baseline in SGTC seizure rates. The absolute reduction analysis used the response ratio (RRatio), a symmetrized percent change. RRatio measures seizure rate reduction during a 12-week treatment period (T) from an 8-week baseline period (B), RRatio = ((T-B)/(T+B)) * 100. Negative RRatio values indicate seizure improvement and an RRatio of −33 is equivalent to a 50% seizure reduction. The conditional analysis examined the proportional risk of having secondarily generalization given a partial seizure has occurred. The Pearson's chi-square test was used for comparisons.

Results: A total of 409 patients (from a total of 1052 intention-to-treat patients) were included in this analysis. Of the 409, 16 were seizure free and were not included in the conditional analysis (total N = 393). A significant reduction in absolute SGTC seizures from baseline was seen in patients treated with 600 mg/day (RRatio = −33 for treatment vs. −3.7 for placebo, p = 0.0005) and 300 + 600 mg/day (RRatio = −31.7 for treatment vs. −3.7 for placebo, p = 0.0047). The conditional SGTC analysis showed a slight reduction in the proportion of SGTC seizures, but did not reach statistical significance.

Conclusion: Pregabalin, as adjunctive therapy, is effective in reducing the absolute frequency of SGTC seizures in patients with refractory partial epilepsy.

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Apathy: A Clinical Condition Worth Treating? Does Anyone Care?

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Apathy is a term engineered by Greek philosophers. They referred to apathy as a condition of being free from emotions

and passions, such as fear, pain, desire, and pleasure. Contemporary neuropsychiatric text books don't go much further, yet the scientific literature has an increasing number of references to apathy. In contemporary references, apathy is defined as the absence or lack of feeling, emotion, interest, concern, or motivation not attributable to a decreased level of consciousness, cognitive impairment, or emotional distress. Reliable scales have been available to quantify apathy for more than ten years, and these scales clearly demonstrate apathy is not the same as depression. Indeed, apathy has been reported to be a significant clinical syndrome in a number of conditions such as stroke, Alzheimer's disease, schizophrenia, and traumatic brain injury. Recent imaging studies have demonstrated the involvement of the frontal cortex in patients with apathy. Is it reasonable to assume that drugs which effect neurotransmission in this area of the brain might influence apathy? Although a number of drugs have been used, and continue to be used, in an attempt to treat apathy, none have proven effective. In fact, in a recent small focus group, 90% of neurologists believed current treatment of apathy to be inadequate. Clearly, effective therapeutic intervention for the patient with apathy would be a benefit, not only to the patient, but also to the caregiver. So what would a clinical trial for apathy look like? Will such a study have one primary endpoint, apathy, or will an additional co-primary endpoint be required which includes a functional scale? One major challenge will be equating a clinical change in apathy with clinical benefit to the patient. Whatever the design of clinical studies, it is clear that apathy poses some significant challenges in the design of a meaningful clinical study. Current status, treatments, and possibilities for quantifying the benefits of therapeutic intervention in apathy will be presented.