SENSITIVITY TO NEGATIVE SYMPTOM CHANGE: SANS, NSA, AND BPRS-R

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Accurate assessment of symptom changes in schizophrenic patients is crucial to determining the efficacy of new antipsychotic medications and other treatments. Because of their chronically debilitating nature, recent emphasis has been placed on identification and treatment of negative symptoms. Previous studies have shown that the Brief Psychiatric Rating Scale's Retardation factor (BPRS-R - motor retardation, blunted affect, and emotional withdrawal) is highly correlated with more specific negative symptom measures-the Scale for the Assessment of Negative Symptoms (SANS) and the Negative Symptom Assessment (NSA). The present study examined the sensitivity to change over the course of hospitalization in negative symptomatology assessed by the SANS, NSA, and BPRS-R in a sample of 59 schizophrenic patients. Symptoms were assessed when the patients were acutely ill and when they were stabilized. Scores for the SANS were calculated three ways-with and without the subjective items, and using only global subscale ratings. Effect size (ES), a measure of instrument sensitivity, was compared across all three rating scales. While the total BPRS score had a large ES (.93), the BPRS-R had a relatively small ES (.22). ES for the total NSA was .39 and ranged from .47-.61 for the SANS. Thus, both negative symptom scales were more sensitive to change than the BPRS-R. ES values for NSA subscales ranged from .13-.50 and from .20-.64 for the SANS, allowing for more specific information about the nature of negative symptom changes to be obtained. The addition of a negative symptom assessment instrument to research protocols increases the ability to detect changes in negative symptoms with substantially fewer subjects than would be required with the BPRS-R as the only assessment measure.

EFFECTS OF FELBAMATE ON VIGABATRIN PHARMACOKINETICS

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The effects of felbamate (F) on vigabatrin (V) pharmacokinetics were examined in 18 healthy volunteers. In this double-blind 2-way crossover study, subjects were administered V 1 gm q12h p.o. with F 1200mg or placebo (P) q12h p.o. for 8 days. Concentrations of the inactive R-(-) and active S-(+)-enantiomers of V were measured by GCMS, and AUC_{0-12} and Cmax values compared following F and P treatment.

Mean Vigabatrin Pharmacokinetic Parameters

	Enantiomer	V + F (%CV)	V + P (%CV)
AUC_{0-12} (μg·hr/ml)	R-(-)	66.3 (18)	67.4 (16)
	S-(+)	52.5 (13)	46.3 (13)
Cmax (μg/ml)	R-(-)	17.9 (24)	19.0 (21)
	S-(+)	10.2 (18)	9.8 (17)

The pharmacokinetics of both enantiomers of V were similar during concurrent treatment with either F or P. Furthermore, coadministration of F and V was well tolerated by the volunteers.

POPULATION PHARMACOKINETICS OF FELBAMATE - EFFECT OF AGE ON APPARENT CLEARANCE

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The effect of age on plasma felbamate (F) clearance was examined through a retrospective analysis of concentration data from pediatric and adult epileptic patients in six clinical studies. Patients received F either as monotherapy (MONO), or in combination with either carbamazepine (F+C), valproate (F+V) or phenytoin (F+P). A total of 3345 evaluable F concentration values were available from 700 patients aged between 2 and 74 years. These were analyzed using a non-linear mixed effect pharmacostatistical modeling technique (NONMEM). Factors in the model included age, body weight, and concomitant AED. A comparison of 2-12 yr and 13-65 yr age groups is given below.

Mean (CV%) Felbamate Clearance (ml/hr/kg)

Age Group	MONO	F+C	F+P	F+V
2-12 yrs	35.7 (20.1)	50.5 (22.5)	50.1	31.1 (16.8)
13-65 yrs	25.8 (20.3)	34.5 (18.5)	35.6	22.4 (18.0)
% difference	38.7	46.5	41.0	39.3

F clearance, as calculated by NONMEM, was higher in young compared with adult patients across all groups, and the magnitude of this difference was similar (≈40%). The magnitude of the enzyme-inducing effect of C and P on F clearance was similar in children and adults.

RESPONSES TO YOHIMBINE IN SOCIAL PHOBIA

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A recent report by Tancer et al.(1993) observed that the growth hormone response to clonidine was blunted in social phobics relative to controls. The current project aimed to further evaluate NE functioning in social phobia (SP) patients by administration of an IV challenge dose of the alpha 2 adrenoreceptor antagonist, yohimbine. METHOD: Six medication-free patients with a principal DSM-III-R diagnosis of SP (4 males, 2 females), without a history of spontaneous panic attacks, participated in the protocol. Two of the six patients met criteria for the specific SP subtype. Patients received 2 challenge tests approximately 1 week apart. On one test day yohimbine 0.4 mg/kg IV was infused, while a saline placebo was administered on the second day. Tests were administered in a double-blind, balanced manner. Within challenge measures included the Social Anxiety Questionnaire (SAQ) (0-10 intensity scale), a clinician-rated instrument designed to be sensitive to changes in social anxiety symptoms and a visual analog anxiety scale (VAS) rated by patients (0-100 mm scale). In addition blood samples were drawn serially for analysis of the NE metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG). RESULTS: The mean peak change from baseline score in SAQ intensity was = 2.8±1.6 during the yohimbine test and = 0±0 (paired t-test t=3.8, df=4, $p<0.05$) during the placebo. The mean peak change±SD from baseline score in VAS anxiety was =10±12 mm for yohimbine vs 3±11 mm for placebo (t=0.89, df=5, p=0.42). Peak behavioral effects were noted 15 minutes post-yohimbine infusion. Peak change scores for plasma MHPG were = 2.1±0.9 ng/ml following yohimbine vs 0.7±0.9 ng/ml following placebo (t=2.7, df=4, $p<0.06$). CONCLUSIONS: These data suggest that yohimbine exacerbates social anxiety intensity and that this behavioral change is paralleled by concomitant increases in plasma levels of the NE metabolite, MHPG. Presynaptic dysfunction in the brain NE system may play a role in the pathophysiology of social phobia. Further studies are indicated to delineate the nature of this abnormality and its implications for treatment.