Title: PREDICTING CHRONIC PAIN RESPONSE TO ANTIDEPRESSANT THERAPY

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Introduction. Chronic pain patients are often depressed and treated empirically with tricyclic antidepressants. Despite apparent lack of "analgesic" properties, antidepressants appear useful for chronic pain symptoms, depressed behavior, and related depression. In a double-blind comparison in 30 chronic pain patients between placebo and the tricyclic antidepressant, doxepin hydrochloride (Sinequan®), we have observed doxepin related improvement in depression, pain incidence, sleep, mood, and muscle tension.[1] In the present study, improvements in chronic pain parameters were related to baseline factors and plasma levels of doxepin and/or its metabolite, nordoxepin (desmethyldoxepin). Purpose was to define predictive criteria for positive response to antidepressant therapy in chronic pain patients.

Methods. With informed consent and Human Subjects Committee approval, 30 patients with chronic (> 6 months) lumbar or cervical pain and clinical depression (Hamilton Depression Scale $\geq$ 18) were studied for 6 consecutive weeks. Diagnoses included disc disease, post traumatic and post-surgical epidural scarring, and myofascial syndrome. Concomitant medication (other than tricyclics) and/or treatment (trigger point injections, biofeedback, acupuncture) were continued at the patients' regular frequency. Variables included Hamilton Depression Scale, Clinical Global Assessment, Profile of Mood States, and a series of subjective ratings of pain related effects by 0-100 visual analogue scales (higher numbers indicating worsening conditions): pain severity, pain incidence, muscle tension, effect of pain on mood, sleep, and activity as well as plasma beta endorphin and enkephalin activity, and plasma doxepin, nordoxepin, and the sum of doxepin and nordoxepin. Patients received either doxepin or placebo (randomized, double blind) starting at 50 mg and increasing to 300 mg unless marked improvement or side effects were noted. Patients were coded as to whether or not they received doxepin (1 = doxepin group, 0 = placebo) and/or concomitant treatment (1 = other treatment occurrence, 0 = no treatment). Data were analyzed with stepwise linear regression,[2] with significance of the bivariate linear regression functions defined at $p \leq 0.05$.

Results. Study patients included 15 males and 15 females, average age 46.6 ± 2.3 years with 1.4 ± 0.6 cervical or lumbar surgical procedures per patient. Predictive equations are shown in Table 1.

Discussion. Tricyclic antidepressant plasma levels are related to improvement in several chronic pain parameters. Important predictive indices appear to be patients' subjective ratings of the effects of their pain on sleep and activity. Although sleep disturbance and reduced activity are cardinal symptoms of depression, these terms have negative signs in the predictive equations. Thus, patients with minimal initial sleep and activity impairments were more responsive at doxepin doses studied (maxima of 2.5 mg/kg daily oral doxepin dose: 70 ng/ml plasma doxepin plus nordoxepin). Tricyclic therapy potentiated other interventions (trigger point injections, biofeedback, acupuncture) as indicated by reduced pain severity and incidence. The results also demonstrate that nordoxepin is an active metabolite.

Conclusion. Chronic pain patients with sleep and activity impairment respond to tricyclic antidepressants. Pain severity can be improved by a combination of active treatment plus tricyclic therapy.

Table 1

Dependent Measures	Bivariate Predictors: Plasma Tricyclic	Condition
Global Improvement	$=0.03\{\text{Plasma Nordoxepin}\} - 0.02\{\text{Initial Sleep Impairment}\} + 1.8$	
	$R = 0.67,\ p = 0.008$	
Sleep Improvement	$= 27\{\text{Doxepin Group}\} - 0.41\{\text{Initial Activity Impairment}\} + 27$	
	$R = .65,\ p = 0.013$	
Depression Improvement {Hamilton Scale}	$= 5.4\{\text{Doxepin Group}\} - 0.16\{\text{Initial Activity Impairment}\} + 16$	
	$R = 0.59,\ p = 0.034$	
Pain Severity Improvement	$=0.35\{\text{Plasma Doxepin}\} + 10$	$\{\text{Other Treatment Occurrence}\} - 13$
	$R = 0.55,\ p = 0.05$	
Mood Improvement	$=0.36\{\text{Plasma Nordoxepin}\} - 0.33\{\text{Initial Activity Impairment}\} + 22$	
	$R = 0.55,\ p = 0.05$	
Pain Incidence Improvement	$=0.18\{\text{Plasma Doxepin + Nordoxepin}\} + 13$	$\{\text{Other Treatment Occurrence}\} - 7.4$
	$R = 0.54,\ p = 0.06$	

1. Hameroff SR, Crago BR, Cork RC, et al: Doxepin effects on chronic pain, depression, and serum opioids. Anesth Analg 61:187, 1982.

2. Nie NH, Hull CH, Jenkins JG, et al: Statistical Package for the Social Sciences (SPSS), New York, McGraw Hill, 1975, pp. 320-237.