

# Effectiveness of Stages of Change and Adinazolam SR in Panic Disorder: A Neural Network Analysis

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**Abstract**—We ascertained the relationship of stages of change (SOC) and adinazolam SR on panic disorder in a randomized double-blind study. Outpatients ( $n = 133$ ) with panic disorder and agoraphobia were assessed for readiness to change and then were randomly assigned to adinazolam SR or to placebo in a 4-week double-blind trial. The active drug was significantly more effective than the placebo. After 4 weeks, patients on the drug treatment had significantly lower anxiety on two of the measures. Two neural networks were trained with gender, history of depression, agoraphobia, readiness to change, and

five anxiety measures at  
baseline data as inputs, and  
the five anxiety measures  
4 weeks later as outputs.

The five anxiety measures  
were the Clinical Anxiety Scale, the Hamilton Anxiety Scale, the number of panic attacks, the Clinical Global Impression Scale, and the Phobia Severity Scale. The networks were validated and sensitivity analyses showed that, in agreement with the stages of change model, patients with low predisposition to change (Precontemplators) changed more slowly than those in Contemplation or Action stages of change.

## I N T R O D U C T I O N

Although short-term programs for smoking cessation or weight control encourage people to change their behavior, a year later, 70%–80% of them have not yet changed (Hunt & Bespalec, 1974; Stunkard, 1977). Prochaska suggested that we have two misconceptions of behavior change: first, we treat behavioral disorders as acute disorders when they are often chronic behaviors, and second, we regard behavior change as a binary variable (old habits, new habits) when, in practice, people move through a series of stages (DiClemente & Prochaska, 1982; Prochaska & DiClemente, 1983; Prochaska, DiClemente, Velicer, Gimpil, Requests for reprints should be sent to John C. Reid, Professor of Psychiatry and Education, Medical Informatics Group, 605 Lewis Hall, University of Missouri, Columbia, MO 65211.

& Norcross,

1985). Prochaska described four stages of change (SOC) that people move through on their way toward stable, healthy behavior: Precontemplation, Contemplation, Action, and Maintenance. People in the Precontemplation stage are not seriously thinking about changing. People in the Contemplation stage are thinking about changing. The Action stage involves a conscious, ongoing effort to change behavior, and the Maintenance stage is the period following the Action stage in which people try to maintain their changed behavior.

Researchers developed the SOC questionnaire (McConaughy, Prochaska, & Velicer, 1983; McConaughy, DiClemente, & Prochaska, 1989). Their 32-item test had eight 5-response items for each of the four stages of change scales: Precontemplation, Contemplation, Action, and Maintenance. A person's stage of change predicts change of behavior in smoking cessation (DiClemente, Prochaska, & Fairhurst, 1991) and in weight-control programs (Prochaska, Norcross, & Fowler, 1992b). For instance, people in the Precontemplation stage change little, whereas people in the Action stage change more. We hypothesized that SOC would also predict patients' change in a randomized controlled medication trial for panic disorder as measured by the Snaith Clinical Anxiety Scale (CAS; Snaith, Bangh, & Claydan, 1982), the Hamilton Anxiety Scale (HAM-A; Hamilton, 1969), patient diary reports of panic attack frequency (PAF), the Clinical Global Impression scale (CGI; Guy, 1976), and the Phobia Severity Scale (PSS; Sheehan, 1986).

We developed two neural networks to model the five outcomes of this research. A neural network is a nonlinear mathematical model that applies weights to input variables to map them to output variables. Nonlinear neural networks can quantify complex mapping characteristics in a compact and elegant manner (Hopfield, 1982; Mistry & Nair, 1993). They have been successfully applied in several areas including medical diagnosis, economic analysis, pattern recognition, speech recognition and synthesis, and control systems (McCord-Nelson & Illingworth, 1991). Interest in neural networks is due in part to powerful new neural models such as the multilayer perceptron, the feedback model of Hopfield, the Adaptive Resonance Technique (ART) networks, Kohonen network, and to learning methods such as back propagation (all cited in Rumelhart & McClelland, 1987).

Neural networks have been used in general psychiatry in a broad range of problems such as modeling brain functioning in schizophrenia (Hoffman & McGlashan, 1993), classifying PET scans (Kippenhan, Barker, Pascal, Nage, & Duara, 1992), and modeling humans on a continuous performance task under CNS stimulants (Servan-Schreiber & Cohen, 1992). An introduction to neural network models in psychiatry was given by Cohen and Servan-Schreiber (1992). The present study is a novel extension of neural network modeling techniques using patient response data for finding the factors that have the greatest influence on the outcome.

Because little has been written about the relationship of SOC with anxiety outcome measures, the purposes of this study were (a) to see whether adinazo-

lam SR was effective relative to placebo on five panic disorder measures after 4 weeks of treatment and (b) to identify the most important variables to predict outcome at Week 4, including the patient's readiness to change by modeling these relationships using neural networks, and to determine how changing the input variables affected five panic disorder outcomes.

## METHOD

In this section we describe the sample and the neural networks and validation methodology and explain the sensitivity analysis procedure.

### *Sample*

A total of 206 patients met the *DSM-III-R* criteria for panic disorder with agoraphobia as determined by the Structured Clinical Interview for DSM-III-R (Upjohn version, SCID-UP-R; Spitzer & Williams, 1987), and who had had at least one panic attack a week for each of 4 weeks prior to baseline. The interview was followed by a 2-week treatment washout and then a one-week single-blind placebo phase, during which a physical examination, EKG, and hematologic and urinary assays were conducted. Of the 206, 133 completed the SOC questionnaire before patients were randomly assigned to either treatment or placebo groups. Sixty-seven of the 133 were in the treatment group and 66 were in the placebo group. At one week and again at 4 weeks after this random assignment, patients were administered five outcome measures: the CAS, the HAM-A, the CGI, the PSS, and reported number of panic attacks (PAF). Further details appear in Davidson et al. (1994). Out of 133 patients, 9 from the treatment group and 11 from the placebo group were not considered due to incomplete data, leaving 58 in the drug treatment and 55 in the placebo group for the SOC analysis.

### *Neural Network Modeling*

In a neural network, a multilayered architecture is interposed between inputs and outputs (Fig. 1). Elements of these interposed layers are called neurons. Each element, or neuron, of the interposed layer has weights and biases. Changing the weights and biases of a neuron alters its output and, ultimately, the output of the entire network. The goal is to choose the weights and biases of the neurons to make a mathematical model to map the inputs to the outputs. The neural network is initialized with random weights and biases, which are adjusted based on an error-minimization criterion in a process called training the network. Learning (or training) is accomplished by adjusting these weights iteratively (typically, to minimize some objective function) when input/output pairs are repeatedly presented to the network. When the network has analyzed all the patterns once, it has trained for one epoch. These weights and biases provide the necessary memory for the learning process. A two-layer neural network with an arbitrarily large number of neurons in the interposed layers can approximate a continuous function over a compact set (Hornik, Stinchcombe, & White,

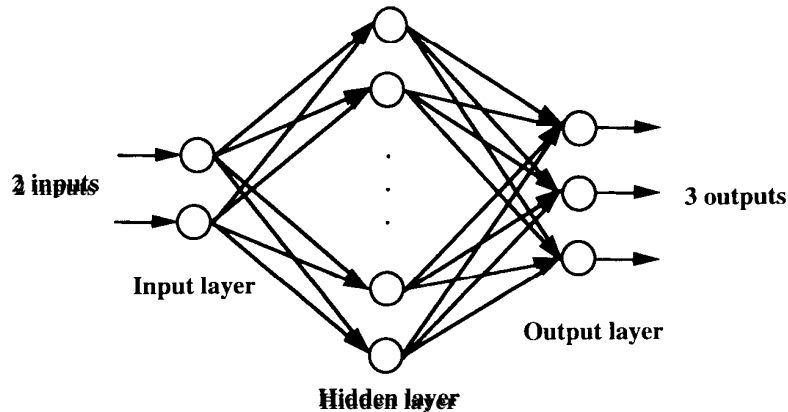


FIGURE 1. A MULTILAYER NEURAL NETWORK WITH 2 INPUTS, A SINGLE HIDDEN LAYER AND 3 OUTPUTS.

1989). This result has motivated much research interest in the area of using neural networks as a nonlinear tool to analyze complex nonlinear systems.

To determine the efficacy of adinazolam SR over placebo and the relationship between drug and the four SOC with the five outcome measures, we trained two separate neural networks, one using drug patients and one using placebo patients. Both neural networks had patient information including gender, history of depression, agoraphobia, patients' responses to the 32 SOC questions and five anxiety measures at baseline as inputs, and the CAS, the HAM-A, the CGI, the PSS scores, and the number of panic attacks at Week 4 as outputs. Our aim was to train each of the two networks to predict scores of the five anxiety measures at Week 4, from which we could determine the change in a patient's anxiety level. By using the five baseline measures as inputs, we could find the change in patient's behavior when the anxiety levels at baseline were different. The networks that modeled the complex relationships among the variables in the study had 40 inputs, 5 outputs, and 30 and 15 neurons in two hidden layers. The patient's responses to the inputs formed 58 and 55 training "patterns" for the drug and placebo neural networks, respectively. We developed all the necessary software using the C language (Mistry & Nair, 1993). The data were normalized before training the neural networks. The errors dropped exponentially during training and were within  $\pm 1\%$  (i.e., in prediction of five outcome measures at Week 4) for each of the patterns after 50,000 epochs of training, which was deemed satisfactory.

#### *Neural Network Validation*

After being trained in the manner described above, a neural network can act as an expert for predictions. If a new case is presented to the network, it should be able to predict the outcome scores for that patient, based on the "training" that it has received, as an expert would do. While an expert would probably

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have problems drawing inferences from such a large number of variables, a neural network handles the complexity easily. In addition, the neural model can describe the relative importance of each input variable, which may be a difficult problem for an individual expert. The networks were presented with the "case history" of each patient to validate the neural network training. After the networks were trained, they were each validated using a random sample of 80% to predict the remaining 20%. These trained and validated neural network weights and biases were then used to conduct sensitivity analysis, described below.

#### *Sensitivity Analysis*

The sensitivity analysis reveals the dominant factors that affect patients' anxiety level. The sensitivity analysis describes the change in the outputs that may be expected for unit change in the inputs. The sensitivity analysis considers one variable at a time, keeping the remainder constant. Each neural network was queried to see how changing each of the four SOC scales would affect anxiety outcome scores at Week 4. This is a powerful way to change one or a group of variables and see the overall impact of that change on the system. We perturbed each of the responses to questions related to the patients' four SOC scales (Precontemplation, Contemplation, Action, and Maintenance) to study the effect of such change on the five panic disorder outcome scores at Week 4. Each of the four SOC scales was perturbed from its minimum value to its maximum value for every patient, and a mean of rate of change of outcome scores was computed for each scale. The result represents the change in outcome measures at Week 4 for a specified change in any of the input variables. For instance, based on this study we can predict the change in CAS score (one of the outputs) when the patient's SOC at baseline (one of the inputs) changes from low Precontemplation to high Precontemplation or from low to high Contemplation (Prochaska, DiClemente, & Norcross, 1992a). Sensitivity analysis thus quantifies the relative importance of each of the SOC scales on scores of five outcome measures. A separate analysis was performed for both drug and placebo groups. For each of the five outcomes an analysis of covariance (ANCOVA) was performed to test the effectiveness of the drug and placebo neural networks using initial scores as the covariate. Linear statistical models also evaluated the effect of individual SOC scales when combined in a model with drug/placebo to predict anxiety changes.

## RESULTS

This  
section  
describes  
the results

of neural network modeling and validation study and reports the results from the sensitivity analysis.

#### *Validation Study*

The network predictions agreed with the obtained five anxiety outcome mea-

sures to  $\pm 5\%$  for about 90% of the training data set and to within  $\pm 15\%$  for the

remaining 10% of the training data set. This showed that the neural networks were able to learn the nonlinear relationship between 40 inputs and 5 outputs very well; this was considered very good since the data set was randomly divided in training and testing data sets. Since Week 4 scores obtained from patients and Week 4 scores obtained from the neural network models were almost identical, we have not distinguished between them in the discussion below.

As a cross-validation we tested the drug net with the placebo data and vice versa. When drug network was tested with placebo data, it predicted only 10% of the placebo data within  $\pm 5\%$ , whereas the remaining 90% of the placebo data had prediction errors as high as 99%. Thus drug network was unable to predict the placebo data for SOC scales for the five outcome measures. Similarly the placebo network was unable to predict drug data, as only 8% of the drug outcome measures were predicted within  $\pm 5\%$ . Thus the drug and placebo groups had distinctly different characteristics. These results are discussed in detail in the following section.

#### *Drug and Placebo Neural Networks*

The networks indicated that the drug group showed more improvement than the placebo group and that patients' SOC scores also helped to explain decreased anxiety as explained below. Table 1 shows the means of change between baseline scores (one of the inputs) and Week 4 scores in panic disorder outcome measures for the drug and placebo groups.

For the adinazolam SR drug neural network, the mean of the network CAS scores at Week 4 decreased by 3.86 from the baseline, while for the placebo network, the mean network CAS scores decreased by 1.54 from the baseline (Table 1). Thus the mean network CAS scores for the drug group decreased by about an additional 150%,  $(3.86-1.54)/1.54$ , as compared to the decrease in network CAS scores for the placebo group. The adjusted network means for Week 4 were 5.16 and 7.11 for the drug and placebo groups, respectively. The difference between these two adjusted Week 4 CAS scores for the drug and placebo groups was significant, as determined from an ANCOVA using initial CAS scores as a covariate ( $F = 9.69$ ,  $df = 1, 110$ ,  $p < .002$ ).

TABLE I  
MEAN OF CHANGE IN PANIC DISORDER NEURAL NETWORK  
OUTCOME SCORES FOR DRUG AND PLACEBO GROUPS

Panic Disorder Outcome Measure	Drug Group	Placebo Group
CAS	3.86	1.54
HAM-A	15.6	4.88
CGI	3.2	0.78
PSS	3.6	2.87
PAF	3.4	2.70

In the case of HAM-A scores, as seen from Table 1, the mean change for the drug group between baseline and Week 4 scores was 15.68, while that for the placebo group was 4.88. This indicated that the decrease in the HAM-A score of a patient taking the drug would be about 220% more than that of the patient being treated with placebo. The adjusted Week 4 means were 10.31 and 12.93 for the drug and placebo groups. Using initial HAM-A scores as a covariate, the difference between the model network HAM-A scores for the drug and placebo groups was significant ( $F = 4.48$ ,  $df = 1, 110$ ,  $p < .04$ ).

A comparison of drug and placebo network results showed that adinazolam SR treatment (as compared to the placebo treatment) lowered the CGI-severity scores at Week 4. The mean decrease in the CGI scores for the drug group was 3.25 as compared to 0.78 for the placebo group (Table 1). The adjusted Week 4 means were 3.20 and 3.53 for the drug and placebo groups. This difference did not reach classical significance,  $F = 3.70$ ,  $df = 1, 110$ ,  $p < .06$ , using CGI initial scores as a covariate.

The mean decrease in PSS and PAF scores for the drug and placebo groups were in the expected direction but were not significant ( $F = 0.31$ ,  $df = 1, 110$ ,  $p = 0.58$ ;  $F = 0.06$ ,  $df = 1, 110$ ,  $p = .81$ ).

The drug group thus had significantly lower CAS and HAM-A Week 4 scores than the placebo group.

We then investigated whether SOC variables were related to reduced panic disorder after four weeks. Individual linear models using treatment (placebo, drug) and one of the SOC variables to explain CAS differences showed treatment effects but showed only one significant SOC effect, for Precontemplation ( $F = 4.79$ ,  $df = 1, 110$ ,  $p = .03$ ). The other three SOC variables did not explain CAS differences.

Individual linear models using treatment and one of the SOC variables to explain HAM-A difference showed no treatment (placebo, drug) effect, but Precontemplation scores had a significant effect ( $F = 5.11$ ,  $df = 1, 110$ ,  $p < 0.03$ ). None of the other three SOC variables explained HAM-A differences.

Individual linear models using treatment and each of the SOC variables in turn to explain CGI differences showed a significant treatment effect ( $F = 5.05$ ,  $df = 1, 110$ ,  $p < .03$ ) when Maintenance was included in the model. The Maintenance scores were also related to CGI differences ( $F = 3.46$ ,  $df = 1, 110$ ,  $p < .05$ ).

Individual linear models using treatment and each of the SOC variables to explain PSS difference showed no treatment effect but Precontemplation ( $F = 6.90$ ,  $df = 1, 110$ ,  $p < .01$ ), Contemplation ( $F = 15.72$ ,  $df = 1, 110$ ,  $p < .0001$ ), and Action ( $F = 4.44$ ,  $df = 1, 110$ ,  $p < .04$ ) scores were all significantly related to changes in PSS scores. There were no significant treatment or SOC effects for PAF differences. Thus, various stages of change scores predicted patient outcome.

#### *Sensitivity Analysis of the Drug Neural Network*

A sensitivity study is expected to show trends in the relationships, especially the relative importance of the input variables. Table 2 lists the normalized

slopes about the mean obtained from the sensitivity analyses of the Precontemplation, Contemplation, Action, and Maintenance variables for the drug and placebo groups. Positive slopes indicate that the rate of change of outcome measure increases as the variable varies from its lowest to highest value (in other words, it indicates faster improvement in outcome scores), while negative slopes indicate decreasing rate of change in outcome measures (i.e., slower improvement in patients' outcome scores). Figure 2 shows the sensitivity results for CAS measure for the drug group. In the figure, "Min" on the x axis represents the lowest score while "Max" represents the highest score for the Precontemplation (P), Contemplation (C), Action (A), and Maintenance (M) scales. The y axis shows the normalized change in CAS scores between baseline and Week 4. The scales on the y axes are different for each outcome difference in Figures, 2-6.

The sensitivity analyses showed that for the drug group, the change in a patient's CAS scores at Week 4 were related to the patient's SOC. The normalized slope of the Precontemplation scores (Fig. 2) was -1.54, indicating that people with high scores on Precontemplation — ignoring their other SOC scores — had little change in CAS scores over the course of the study. This slope of -1.54 indicates that change in the difference of Week 1 and Week 4 CAS scores per unit change in Precontemplation scores would be -1.54/normalization factor. The negative slope (= -1.54) for the Precontemplation variable indicates that the rate of change in CAS scores decreases as the patient's SOC moves from low Precontemplation to high Precontemplation. That is, the more the patients do not admit to having a problem, as determined by their Precontemplation score, the more slowly clinical anxiety score differences decrease. Considering just the Contemplation scores, for instance, the slope of the Contemplation variable was 3.21 indicating that the normalized change in CAS score would be 3.21. The positive slope on the Contemplation variable (= 3.21) indicates that when a patient moves from low Contemplation to high Contemplation, the patient's CAS score at Week 4 should decrease at a faster rate. In other words, as patients appear more deter-

TABLE 2  
NORMALIZED SLOPES OBTAINED FROM SENSITIVITY ANALYSIS OF THE DRUG NETWORK

	Drug				Placebo			
	Outcome Measure	P	C	A	M	P	C	A
CAS	-1.54	3.21	-0.90	2.33	-4.56	-3.41	2.31	-4.00
HAM-A	-7.06	-1.02	-0.80	1.27	-2.62	-4.60	3.92	-6.29
CGI	-1.14	-0.38	-0.06	1.04	-1.05	-1.20	0.71	-1.37
PSS	-1.39	2.30	-2.25	1.28	-4.21	-2.12	-1.70	-0.98
PAF	-5.44	-1.32	-0.13	5.75	0.37	-1.03	1.69	-0.60

Note. P = Precontemplation, C = Contemplation, A = Action, M = Maintenance.

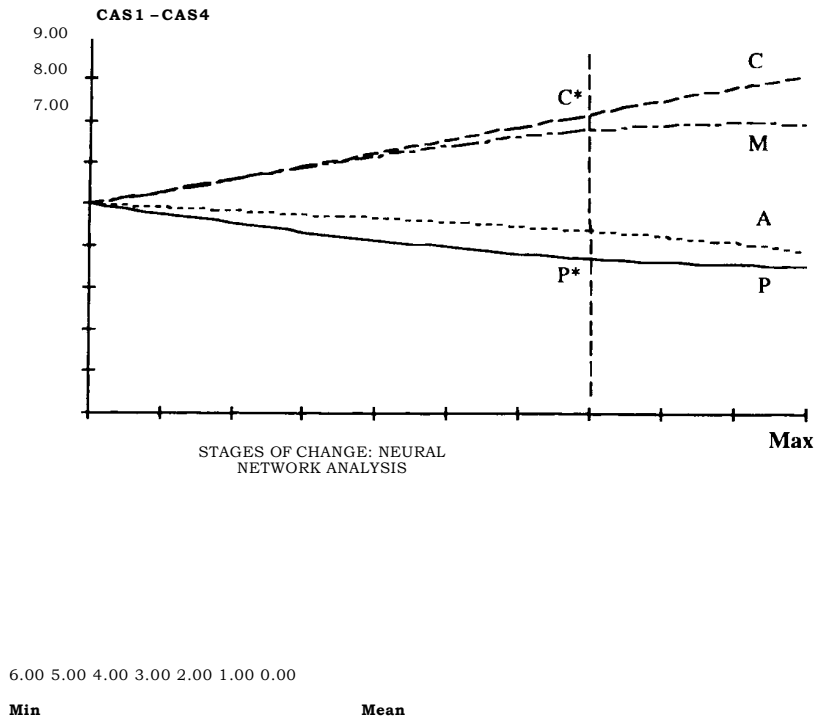


FIG. 2. SENSITIVITY ANALYSIS FOR THE CAS DIFFERENCES VARIABLE USING THE DRUG NETWORK.

mined to change, their rate of improvement on the CAS increased. Of the four SOC scales, only the association of Precontemplation scores with CAS differences was statistically significant. As mentioned earlier, the more negative the slope, the smaller the change in panic outcomes; the larger the slope, the greater the change in panic outcome. For example, in Figure 2 the patient at point P\* with a negative slope has a smaller change in panic outcome, whereas the patient at point C\* with a larger slope has a larger change in panic outcome.

A similar relationship was found from the analysis of the HAM-A variables (Figure 3). High Precontemplation scores (slope = -7.06) were associated with little change on the HAM-A, and high Contemplation scores (slope = -1.02) were associated with greater change in HAM-A.

In the case of the CGI variable, high scores on Contemplation (slope = -0.38) were indicative of high degree of change in CGI scores, while high scores on Precontemplation (slope = -1.14) were indicative of little change in the CGI scores (Figure 4).

High Precontemplation scores (slope = -1.39) were indicative of little change in the PSS scores and high Contemplation scores (slope = 2.30) were predictive of high levels of change in PSS (Figure 5).

From the sensitivity analysis on the PAF variables, high Precontemplation

scores (slope = -5.44) were indicative of little change in PAF. Greater reduction in PAF was found in patients with high Contemplation (slope = -1.32) stage as compared to patients in the high Precontemplation stage (Figure 6).

All these results agree with SOC theory and suggest that anxious patients who are on medication and are less ready to change will have less change in anxiety. The results of sensitivity analysis of the placebo neural network are discussed in the next section.

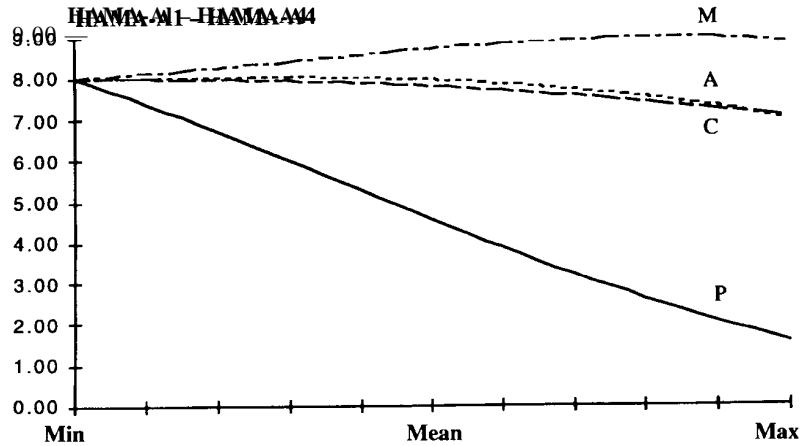


FIG. 3. SENSITIVITY ANALYSIS FOR THE HAM-A DIFFERENCES VARIABLE USING THE DRUG NETWORK.

### DISCUSSION

The neural network models demonstrated the greater effectiveness of adina-zolam SR over placebo after four weeks for certain measures, and they also showed that stages of change predicted change for several anxiety measures, particularly for the drug group.

#### *Drug and Placebo Neural Networks*

As seen from Table 1, the means of change in neural network outcome scores for the drug group were relatively higher for CAS, HAM-A, and CGI scales

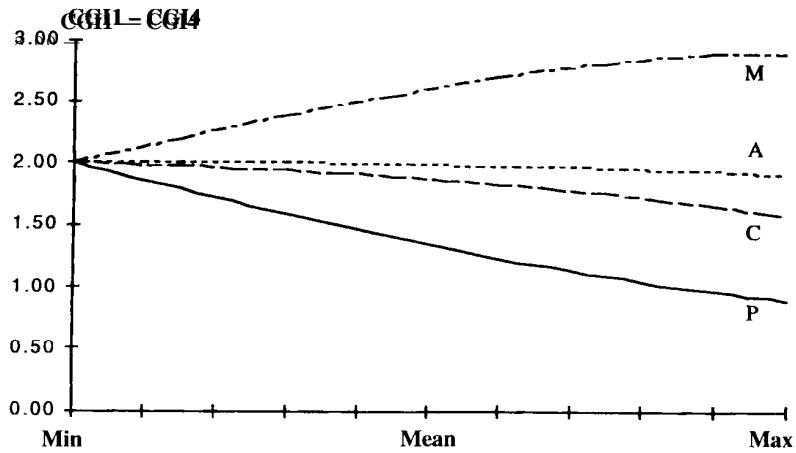
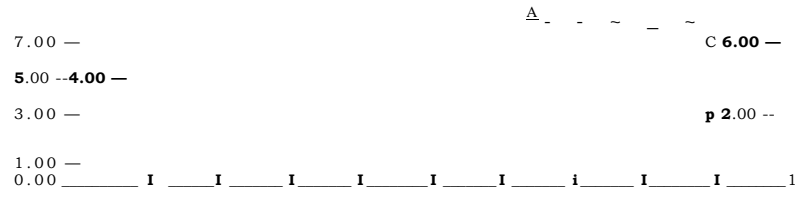


FIG. 4. SENSITIVITY ANALYSIS FOR THE CGI DIFFERENCES VARIABLE USING THE DRUG NETWORK.



**Min** **Mean**  
 FIG. 3. SENSITIVITY ANALYSIS FOR THE HAM-A DIFFERENCES VARIABLE USING THE DRUG NETWORK.

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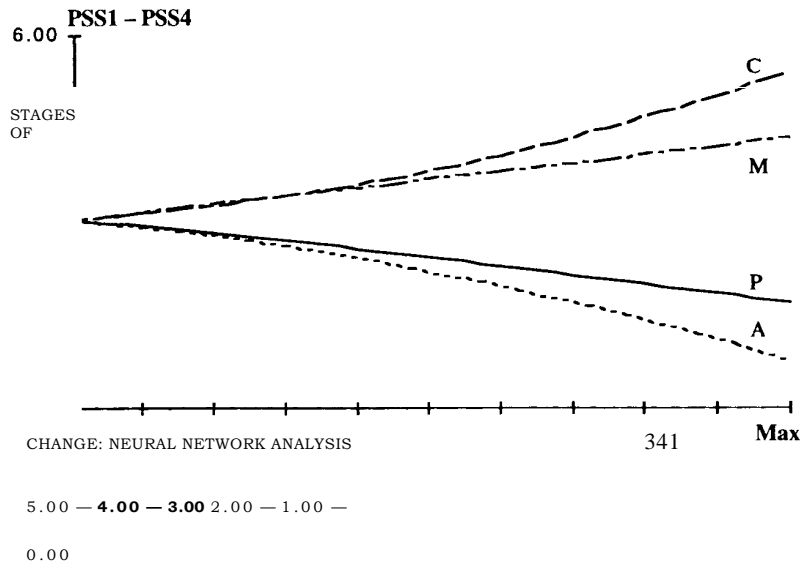
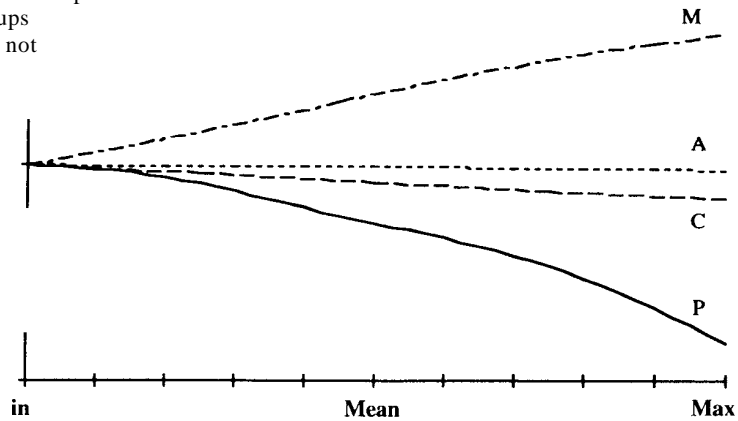


FIG. 5. SENSITIVITY ANALYSIS FOR THE PSS DIFFERENCES VARIABLE USING THE DRUG NETWORK.

compared to the placebo group. The differences for CAS and HAM-A for drug and placebo groups were statistically significant, while the CGI was close to classical significance. This indicated that the CAS, HAM-A, and CGI scores were lower at Week 4 among the patients treated with adinazolam SR compared to the patients treated with placebo. For the PSS and PAF scores a similar trend was observed, but the difference in results between the drug and placebo groups was not



significantly different. The neural network models agreed with the results of Davidson et al. (1994), who demonstrated that the adinazolam SR drug was more effective than placebo on several measures for the treatment of panic disorder.

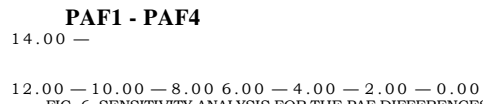


FIG. 6. SENSITIVITY ANALYSIS FOR THE PAF DIFFERENCES VARIABLE USING THE DRUG NETWORK.

### *Sensitivity Analysis*

For the drug group, the neural network model showed that high Contemplation scores were associated with significantly greater change in CAS and HAM-A scores compared to high Precontemplation scores (Figs. 2-6). The sensitivity functions (Figure 2) from the neural network model clearly show the relative amount of change in outcome for each of the four SOC variables. Beitman et al. (in press), who combined drug and placebo groups in a regression model, did not detect the association between Contemplation and change of CAS outcome that neural network model did. For the placebo group a similar trend was observed, but the amount of change in CAS score was less than that in the drug group. The changes for the other three outcome variables were in the expected direction but were not significant. For the placebo group the results were less clear cut.

The sensitivity analysis on the drug neural network indicated that patients who were ready to change had fewer panic attacks than patients who were not ready to change. The sensitivity analysis of the placebo group did not show a similar trend. Why stages of change did not seem to operate for people in the placebo group is unclear.

Beitman et al. (in press) also reported that people in the Precontemplation stage had little change in CAS, HAM-A, and panic attack frequency, and that people in the Contemplation group were more likely to change in CGI scores from baseline to posttest a month later. The agreement of the neural network sensitivity analysis with Beitman's statistical results validate the relatively new approach of sensitivity analysis and also show its effectiveness for this type of nonlinear modeling and analysis problem. In sum, the neural networks showed that stages of change predicted outcome in a medication trial.

### *Neural Network Modeling and Analysis Tool*

Neural networks can be compared and contrasted with statistical approaches. Neural networks are model-free estimators, whereas most statistical techniques are model based. Neural network models are inherently nonlinear, whereas statistical methods are typically, though not necessarily, linear. Hypothesis testing tools for neural network techniques do not exist at this time, but hypothesis testing in statistics is well developed. In addition to their ability to learn, neural networks also possess several important properties. Two relevant properties for our study are generalization and retrieval from partial description. Generalization means that a neural network can interpolate and predict the outputs, even when it is presented with input cases that it has not "seen." This property has been used to obtain the slopes from the sensitivity analyses in our study. Similarly, the network can provide useful results even with partial input information. A consequence of these properties is that a neural network is more robust in noisy environments with incomplete information. Such a scenario could exist when scales are administered to a varied set of respondents who may not answer all

questions very accurately. Current statistical techniques are usually linear. Nonlinear multivariate techniques exist but are tedious and require some a priori knowledge about the model. Neural networks, on the other hand, represent simple and elegant tools that are inherently nonlinear with several attractive properties, as cited. The property that neural networks can "fit" data sets to any desired accuracy is exploited to train and validate the SOC data set in our study. As mentioned earlier, the neural network model also detected association between Contemplation and change in CAS outcome that a regression analysis by Beitman et al. (in press) did not reveal.

The unique contributions of this study include: (a) obtaining nonlinear models using neural networks that relate the inputs to the outcomes of panic measures, (b) graphically depicting some of the functions so the researcher has a visual impact of the relative effectiveness of the SOC variables, and (c) demonstrating a novel methodology called sensitivity analysis to rank the importance of SOC variables, something not reported in the literature.

### CONCLUSIONS

In a randomized control trial, subjects assigned to drug (adinazolam SR) had significantly greater decreases in Clinical Anxiety Scores and in Hamilton Anxiety scores (in one model) than subjects receiving placebo. Stages of change also predicted decreased anxiety. Precontemplation scores predicted Clinical Anxiety decreases and Hamilton Anxiety decreases; Maintenance scores predicted Clinical Global Impression decreases; and Precontemplation, Contemplation, and Action scores all were related to decreases in Phobia Severity scores.

Predisposition to change influenced outcome of short-term treatment of panic disorder with adinazolam SR with demonstrated effectiveness in the treatment of panic disorder with agoraphobia. This finding is consistent with previous studies (Prochaska, Norcross et al., 1992). We recommend that future drug studies consider stages of change as a predictor of outcome.

Clinicians should consider enhancing the effect of medication by assisting patients to move to a readiness-to-change state. However, SOC was not always as effective in the placebo group as in the drug group, suggesting an interaction or symbiotic effect that needs further study. Designs of current medication trials have not taken into account this potentially powerful influence on outcome of patient predisposition to change. We recommend that stages of change should be considered in drug studies, as there is evidence that such stages of change are related to panic disorder outcome.

Panic disordered patients who were not yet predisposed to change were least likely to have a good outcome after 4 weeks of medication treatment. It may be possible to develop psychotherapeutic techniques that will help these "reluctant changers" progress along the stages-of-change continuum. If so, such techniques may become an adjunct to pharmacotherapy for selected patients.

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