Biobehavioral Therapy: Interactions Between Pharmacotherapy & Behavior Therapy in Schizophrenia

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As the first author of this chapter, I looked back over the 30 years of my work in schizophrenia and saw the dawn of behavior therapy for psychotic disorders starting in the 1950's and 1960's in the work of Skinner and his students--Azrin, Ayllon, and Lindsley. I also saw the disaffected eclipse of psychodynamic psychotherapy, which 30 years ago, was completing a decades-long stint as the "only hope" for curing schizophrenia. Antipsychotic medications had arrived and were "flexing their muscles," as psychiatry was finally entering its scientific period through the door of controlled, clinical trials of drugs like chlorpromazine, thioridazine, and trifluoperazine. Soon to follow were the empirical validations of the token economy and other applications of behavioral learning principles to schizophrenia (Liberman et al., 1973, Paul & Lentz, 1977; Liberman & Mueser, 1989).

But behavior therapy never fulfilled its promise in the treatment of schizophrenia (Moss, 1994; Boudewyns, 1986; Bellack & Mueser, 1993) and most practitioners--whether they be psychologists, social workers, nurses, or psychiatrists--now believe that the only answers to the cause and treatment of schizophrenia lies in the biological realm through optimal pharmacotherapy. This belief system has been recently buoyed by the arrival of a new generation of antipsychotic drugs that appear more effective with fewer side effects than the conventional

antipsychotics (Marder & Meibach, 1994).

However, over this 30 year period, I have not given up the effort to help persons with schizophrenia using behavioral techniques. Perhaps this eternal optimism, coming from a middle--aged, grizzled warrior of institutional wars, derives from my never having encountered a person with schizophrenia whose quality of life I have not been able to help improve, at least to some extent, using biobehavioral techniques. Having participated in the development of the community mental health movement (Liberman et all, 1976) and the field of psychiatric rehabilitation (Liberman, 1992), I am fully aware of the inadequacies and limitations of our current "state-of-the-art" in treating schizophrenia--both biologically and behaviorally. For this reason, we must be encouraged to witness a new generation of psychological methods for schizophrenia, described in this text, that holds promise for improving the impairments, disabilities, and handicaps of persons with schizophrenia. At the same time, to avoid later disappointments and derogation of the effects of cognitive behavior therapy with schizophrenia, it is essential that psychological treatments be applied to individuals who have well-diagnosed schizophrenia, a criticism already leveled at the first crop of studies in this genre (Bouchard et al., 1996). The first blush of successful case studies must also be extended to the arena of randomized, controlled research, where double blind assessments and standardization of antipsychotic medications are rigorously employed.

Before describing two "state-of-the-art" studies of biobehavioral therapy for schizophrenia from our Clinical Research Center for Schizophrenia & Psychiatric Rehabilitation, an important

points needs to be made; namely, there is no such thing as "psychological therapy for schizophrenia! Psychological and social therapies are always accompanied by pharmacological treatment and to ignore the latter is to obscure the contributions of the former. In other words, "psychological therapy" is a misnomer, a fantasy, born of those blinded to the essential role of antipsychotic medication in what is almost always a joint biobehavioral or **biopsychosocial intervention**.

Paying "lip service" to the importance of drug therapy in schizophrenia by stating that all subjects were "stabilized on medication prior to beginning their psychological treatment" belies the following realities:

1. Different medications, different doses, and different combinations of medications yield different degrees and duration of stabilization; furthermore, different side effect profiles can importantly influence learning (such as benztropine, or Cogentin; an anticholinergic agent often used to treat side effects, which has potent effects on impairing memory).

2. Prescribing psychiatrists who are not intrinsically on the research team studying a new psychological therapy, may often change the type and dose of medication ad lib without considering the phase of the protocol that the subject is in nor the control vs. experimental group assignments.

3. A new generation of more effective antipsychotic agents are being introduced, some of which will powerfully affect the cognitive functions being described in the psychological therapies found in the other chapters of this book. For example, risperidone appears to improve and even normalize verbal working memory in schizophrenic individuals who had been refractory to other, more conventional medications (McGurk & Green, 1996).

In this chapter, we shall describe two studies that were designed to tease out the joint pharmacological and behavioral effects of treatment of schizophrenia. Both studies were carried out within our Clinical Research Center for Schizophrenia & Psychiatric Rehabilitation. One study took place at the Camarillo-UCLA Clinical Research Unit at the Camarillo State Hospital where the inpatient population was primarily treatment refractory, with many years of continuous illness, disability, and hospitalization; the other study took place at the Psychopharmacology Unit of the West Los Angeles VA Medical Center where outpatients were studied who had a history of responding to conventional antipsychotic drugs but where noncompliance leads to a rapidly "revolving door" of admission-discharge-readmission.

A careful reading of this chapter will illustrate the importance of identifying the differences between schizophrenic populations, treatment settings, clinicians, pharmacological regimens, and types of behavior therapy used. These variables often make interpreting the results of published accounts of psychological therapies difficult: They should be clearly articulated in all studies that seek publication where both pharmacological and psychological or behavioral treatments are being used.

Optimal Drug & Behavior Therapy for Treatment Refractory Schizophrenic Patients

Despite the advent of clozapine, many thousands of patients with schizophrenia remain refractory to pharmacotherapy and customary forms of psychosocial treatment. Estimates of

treatment refractoriness approximate 25% of persons with schizophrenia, a problem of public mental health magnitude given the residence of these individuals in state hospitals, community facilities, prisons, and on the streets. Since many of these patients receive high doses of neuroleptics for extended time periods with adverse effects (Brenner et al., 1990; Liberman et al., 1994) and because virtually nothing is known about the utility of high-dose neuroleptics in the refractory schizophrenic patient, we conducted a systematic trial of decremental dose-reduction of haloperidol in 13 institutionalized schizophrenic patients. Once the optimal dose was identified, each patient participated in an intensive and individualized behavior therapy program.

The hypotheses of this pilot, exploratory study were:

1. The benefit-risk ratio of therapeutic to side effects of haloperidol (HPL) would improve with lowering of the HPL dose as it reached the same therapeutic window in the plasma that has previously been documented for acute, treatment responsive schizophrenic patients (Van Putten et al., 1990).

2. Subsequent to reaching the optimal dose, patients would show further improvements in negative symptoms, social communication, instrumental role functioning, self-care skills and intolerable, deviant behaviors when exposed to personalized behavior therapy.

Methods

Subjects & Setting

Ten male and 3 female patients ranging in age between 20-42 (mean=32), who met DSM-IIIR criteria for schizophrenia and were receiving at least 50 mg per day of haloperidol or its equivalent, were entered into the study at different times over an 18 month period. Treatment refractoriness (Brenner et al., 1990) was defined as psychotic symptoms rated as "moderately

severe" or worse on the BPRS persisting for at least two years despite prolonged trials of treatment with various neuroleptics; at least 14 months of continuous treatment at Camarillo State Hospital (mean=57 months) without prospect of release; two or more trials of neuroleptics at dose levels of 1000 mg/day chlorpromazine equivalents; and functional behavioral deficits and deviances that were incompatible with community adaptation. Ten of 13 patients had a history of assaultiveness.

The study was conducted on the 11 bed, Camarillo-UCLA Clinical Research Unit where nursing staff were trained in systematic behavioral observations and interventions. The ward environment was standardized by operationalized, planned and scheduled biobehavioral treatments that included training in activities in daily living, training in social and independent living skills, recreation therapy, time-out from reinforcement for aggression of property destruction, and a token economy (Glynn et al., 1994).

Procedures

All patients were maintained at their referral levels of high daily, oral doses of neuroleptic drugs for at least two months, during which time those not on HPL were converted to an equipotent dose of HPL. All other medications were stopped except anti-Parkinson drugs; lorazepam or sodium amytal were used on an as-needed basis for behavioral dyscontrol.

HPL dose was reduced every five weeks according to a fixed schedule: 65, 50, 35, 20, 15, 5, and zero mg/day. Dosage was reduced as long as the patient was rated as "unchanged" or "improved" by a staff consensual rating on the Clinical Global Impression Scale (CGI) (Guy,

1976). If the patient was rated "slightly worse", the dosage was held steady for another five weeks; if there was no subsequent deterioration, the dosage was further reduced. If a patient was rated "much worse" or "very much worse" on the CGI, dosage reduction was stopped, and the patient was returned to the previous higher effective dosage and kept at that dosage. Each dosage level was tested for a minimum of five weeks; one week to attain a new steady state plus four weeks for evaluation of clinical outcome at this level.

With blood drawn in the morning, 10-12 hours after the last dose, plasma HPL assays were done by a very sensitive high performance liquid chromatographic (HPLC) method (Midha et al., 1988) that has limits of quantitation of less than 50 pg/ml HPL or reduced HPL.

At entry into the study, each patient had three target problem behaviors specified, and quantified on the Idiosyncratic Target Symptom Scale (May, 1968), that were viewed as the principal obstacles to discharge readiness. Problems included polydipsia, screaming and agitation, assaultiveness, incontinence, incoherence, and mumbling, inaudible speech. After at least five weeks at the optimal dose (with maintenance of this dose throughout the rest of the study), patients received individualized behavior analysis and therapy for their target problems. Therapeutic interventions included required relaxation, overcorrection, shaping and fading of prompts and reinforcement, discrete trials conversation skills training, and self-control procedures. The phase of individualized behavior therapy ensued for up to one year and typically more than one intervention before optimal improvement of the target problems was noted.

Assessment Measures

Psychopathology, functional behavior, and side effect ratings were conducted at entry into the study and on the fifth week of each dosage level, as well as during the final week of the

behavior therapy phase, using the following instruments: the Brief Psychiatric Rating Scale (BPRS), Activities of Daily Living Checklist, Mobility-Affect-Cooperation-Communication Scale (Ellsworth, 1957), Idiosyncratic Target Symptom Scale, CGI, Social Interaction Scale, violations of unit rules as reflected by token fines, Columbia Unified Parkinson's Disease Rating Scale (Fahn & Elton, 1987), Barnes Akathisia Scale (Barnes, 1989) and the Assessment of Involuntary Movement Scale (AIMS).

For the purposes of data analysis, study periods were delimited as follows: the **dosage** baseline was the last rating period prior to the start of dosage reduction; and **optimal dose** was the average of all rating periods that occurred after the lowest effective dose was determined, but before the start of intensive behavior therapy. For the analyses of changes associated with intensive behavior therapy, the pre-treatment ratings were taken from the last rating period during the optimal dose phase prior to the start of the behavior therapy, and posttreatment scores were based on the five week rating period during which the behavior therapy had its maximal impact on behaviors targeted for change. Two subjects left against medical advice prior to participating in the behavior therapy phase.

Results

The 13 patients tolerated a mean reduction of 63 percent (median=70%) from a mean of HPL of 63.1 mg/day (SD + 12.5, range 50-80 mg/day) to 23.1 mg/day (SD +16.3, range 0-65 mg/day). The dosage reduction was parallel by a comparable drop in HPL plasma levels. At the higher dose of HPL, patients had proportionately higher levels of reduced HPL, which is thought to be associated with poor response to this drug. At the clinically optimal dose of HPL, plasma levels of HPL in acutely psychotic and drug-responsive schizophrenic patients for all but one of the

patients (Van Putten et al., 1992).

On the average, the 13 patients improved on the BPRS total score (mean change -5.6, SD +8.71 t=2.31, df=12, p=0.04) and the BPRS anxious-depression cluster (mean change-1.3, SD +2.0, t=2.43, df=12 p=0.03), with a trend toward improvement on the BPRS thought disturbance cluster (mean change -1.9, SD +3.5, t=2.0, df=12, p=0.07). On the CGI index, 3 patients were rated as worse, four were the same, and six were improved. At the optimal dose, the benefit/risk ratio of symptoms/side effects improved substantially since all patients experienced fewer side effects in akathisia (total Barnes score 2.1 vs. 1.2, t= -1.99, df=10, p=0.04), one-tailed) and less EPS (total Columbia score 13.2 vs. 5.8, t=2.64, df=10, p=0.01, one-tailed). All statistical tests were two-tailed except for those evaluating for those evaluating side effects, in line with prior predictions of change.

No statistically significant changes were noted on the AIMS (tardive dyskinesia) which was expected since the substantial reduction in HPL dose would be associated with uncovering of the dopamine receptors in the basal ganglia which produce tardive dyskinesia. There were no significant improvements noted in the functional behavioral measures concurrent with dosage reduction to the optimal dose, including assault and property destruction. When reaching their lowest dose (mean 7.5 mg/day), 10 of 13 of the patients showed global worsening on the CGI, which triggered their titration upward to the next higher dose that was found to be optimal. During the period at lowest dose, seven of the patients required 1-2 doses of adjunctive, prn lorazepam for behavioral control. One patient was remarkably improved at a dose of 0 mg, but this individual eventually relapsed into a florid psychosis after 20 weeks on placebo. Except for this patient, the other 9 who either improved or remained clinically the same sustained the clinical

status on their optimal dose for a minimum of one year of follow-up.

At the end of the behavior therapy phase, three patients showed further marked improvement on the CGI beyond their clinical status at the optimal dose phase, with two reaching successful discharge from hospital. As hypothesized, the negative symptom, withdrawal-retardation cluster improved, but nonsignificantly, during the behavior therapy phase. Twenty-six functional and behavioral measures were examined that were hypothesized to improve with behavior therapy. Only one improved significantly by univariate t-test for correlated means, that being a reduction in patient's refusals to perform activities of daily living--such as showering and making their beds ($t=2.43$, $df=10$, $p=.036$). This single result could clearly have been due to chance.

However, we did observe consistent results across these correlated measures, with 23 of the 26 measures showing a mean improvement during the behavior therapy phase. The first principal component in these measures accounted for 46% of the variance, and appeared to represent overall improvement. Eighteen of the measures had loadings on this component of 0.50 or greater and the signs of the loadings were all consistent in direction, with measures of positive qualities loading positively, and those representing negative characteristics loading negatively. An overall improvement index, or measure of the first principal component, was computed by standardizing each measure, and then summing change scores (appropriately reflected as indicated by the loading on the first component) across the standardized items. Improvement on this overall index of daily, functional behaviors was significant ($t=2.84$, $df=10$, $p=.017$).

Discussion

This study shows that it was possible to gradually reduce the dose of neuroleptic in 11 of

13 very chronic, treatment refractory schizophrenic patients who were thought by their treatment staff to all require high-dose neuroleptic therapy. As a result of the dosage reduction to the optimal level, the patients on average were globally somewhat improved, were less dysphoric, and definitely experienced fewer side effects; thus, their benefit/risk ratios markedly improved without jeopardy of increased aggression or behavioral dyscontrol.

The use of an individualized dosage decrement protocol such as was done in this study, titrating the dose against measurable psychopathology, side effects and disturbing behaviors, may provide an antidote to the "ratched" effect of non-rational "creeping dosage" escalation of neuroleptic drugs in response to short-term behavioral events in patients who are limited responders to neuroleptics at best. Thus, we recommend that clinicians utilize empirically guided treatment with the BPRS or target symptom scales assisting in the adjustment or titration of medication dose.

Interestingly, the two patients who could not tolerate substantial dosage reduction were also the only two subjects characterized by substantially aberrant performance on the degraded stimulus. Continuous Performance Test and the Span of Apprehension Test (Green et al., 1993). This suggests a relationship between markedly impaired central nervous system information processing and a higher threshold for therapeutic effects from neuroleptics. If these two patients were removed from the analysis, the mean dosage reduction tolerated by the other 11 was 88 percent.

Treatment-specific effects were noted, with HPL-dose reduction producing improvements in positive symptoms, depression, anxiety, and side effects while the addition of intensive behavior therapy yielded improvements in functional behavior and negative symptoms. The

findings partially replicate studies that reported improvements in psychopathology with reduction of neuroleptic medication in schizophrenic outpatients (Leblanc et al., 1989) and inpatients (Faraone et al., 1989) and with cognitive-behavior therapy in neuroleptic-resistant schizophrenic patients (Paul & Lentz, 1977; Tarrier et al., 1993); Glynn & Mueser, 1992). While the causal relationship of dosage reduction to clinical improvement requires testing in a random assignment of patients to dose reduction vs. Continuation of former dose, it appears that many institutionalized, treatment refractory schizophrenic patients can benefit from a systematic and monitored dosage reduction in league with intensive and personalized behavior therapy.

We will now shift from neuroleptic resistant, institutionalized schizophrenic patients to outpatients with frequent relapses and rehospitalizations. With outpatients, the intensive techniques of individualized behavior therapy are not feasible and the behavioral therapy of choice has been social skills training.

Behavioral Skills Training vs. Supportive Group Psychotherapy for Outpatients with Schizophrenia: Two Year Outcome

Among the most promising psychosocial approaches for schizophrenia has been the use of social skills training (SST) (Wallace & Liberman, 1985). The interest in this treatment results from the observation that impairments in social functioning are largely responsible for the poor quality of life and social isolation of individuals with schizophrenia (Bellack & Mueser, 1993; Bellack et al., 1984; Liberman et al., 1985.) Methods for SST have largely been based upon learning principles. As a result, SST uses structured educational methods with social

reinforcement, modeling, and role playing.

There are several good arguments for combining a skills training psychosocial treatment with a low-dosage, antipsychotic medication strategy. On the one hand, the combination of skills learned and support provided by the psychosocial intervention may buffer or reduce stress and enhance coping skills, reducing relapse risk and the need for higher doses of medication. Another argument is that the extrapyramidal side effects of antipsychotic medications, particularly akinesia and akathisia, interfere with patient participation in psychosocial treatments (Van Putten & Marder, 1987.) Thus, reduced doses of antipsychotic medication could facilitate rehabilitation through reductions in secondary negative symptoms and side effects, such as drowsiness, lack of motivation, anhedonia, lack of responsiveness to social or other reinforcement, and poor concentration.

This study was carried out in the context of a larger investigation that also focused on strategies for treating patients with reduced doses of maintenance antipsychotic medication. We have previously described the advantages and limitations of a strategy that included combining a low dose of fluphenazine decanoate (5 to 10 mg every 14 days) with supplemental oral fluphenazine hydrochloride when patients demonstrated early evidence of impending relapse (Marder et al., 1994.) In that study patients who received oral supplementation were more likely to remain stable during the second year following randomization. We have also previously described the efficacy of skills training in this study for the acquisition and durability of medication and self management skills (Eckman et al., 1992.) This report describes the effects of SST and supportive group therapy (SGT) on the risk of psychotic relapse and social adjustment for patients who participated in this trial.

Methods

The subjects were 80 male outpatients undergoing treatment at the West Los Angeles VA Medical Center. All fulfilled DSM III-R criteria for schizophrenia based upon a review of medical records and symptom profiles which were documented using the Present State Examination. Each subject had at least two documented episodes of acute schizophrenic illness or at least two years of continuing psychotic symptoms. The average patient was close to 40 years old, and had been ill for more than 10 years. Most were unmarried and non-white.

Stabilization

Prior to study entry each patient was stabilized on a low dose of fluphenazine decanoate (5 to 10 mg every 14 days). The dose was set at 5 mg unless there was a history that a higher dose was needed to prevent psychotic exacerbations. Patients who could not be stabilized for two or more months on 10 mg or less of fluphenazine decanoate (FD) every two weeks for a two month period were dropped from the study during the stabilization period.

Psychosocial Conditions

After completing the prestudy stabilization, patients were randomly assigned to receive either behavioral skills training (SST) or supportive group therapy (SGT). Each treatment was administered twice weekly for 90 minutes each visit the first six months, then weekly for 90 minutes for up to a total of two years if subjects remained engaged in the protocol. The entry of new study subjects was timed so that patients could begin the study in cohorts of approximately 10 patients with five assigned to each condition.

Behavioral Skills Training (SST)

Subjects participated in a series of skills training modules (Liberman et al., 1989) that

were administered in a group setting. Subjects participated in modules on Medication Self-Management and Symptom Self-Management during the first six months of the trial. As the names denote, these modules comprise skill areas with educational objectives for recognizing symptoms and side effects, self-administration and monitoring of medication, negotiating medication issues with doctors and other providers, avoiding street drugs and alcohol, and identifying warning signs of relapse. A social Problem Solving Module was completed during the second six months. This module was designed to enhance the ability to recognize social barriers to attaining life goals in the community and to generate, select, and implement appropriate solutions to these barriers. Finally, a Successful Living Skills Module was completed by subjects who continued into the final year of the study. This module enabled subjects to identify and pursue individualized and personal goals using the basic model of social skills training (Hierholzer and Liberman, 1989).

The SST procedures were designed to compensate for the symptom and cognitive deficits that are associated with schizophrenia. Cognitive restructuring principles, repeated behavioral rehearsal, video modeling, and abundant positive social reinforcement were used by the group leader to overcome the intrusions of symptoms, distractibility, and lack of motivation that some patients demonstrated.

Each of the modules had a similar structure. They began with an "Introduction to Self-Management" (highlighting the rationale for the training, and the goals and benefits of the training, enhancing motivation to participate); moved to a "Training Segment" (in which the substantive knowledge and skills were trained); next moved to phases that taught problem-solving skills in the areas of "Resource Management" and "Overcoming Outcome Problems"; and finally

terminated in "In Vivo Exercises" and "Homework Assignments" where patients practiced the acquired skills in their natural environments. The training was continued for each patient until criteria for mastery of the knowledge and skills were reached.

The SST modules were administered by one or two therapists per session. The therapists included a Ph.D. psychologist, an occupational therapist, a masters level psychologist, a registered nurse, and a social science technician.

Supportive Group Psychotherapy (SGT)

To provide a rigorous test of the value of the specific skill-building elements in the behavioral skills training, a comparison psychosocial therapy was delivered to a control cohort that provided a comparable intensity of treatment and was considered the standard psychotherapeutic approach for chronic schizophrenics. The comparison treatment was supportive group psychotherapy (SGT) which was guided by goals for reality adaptation. This approach has been shown to be effective for outpatients with schizophrenia in controlled studies (Malm, 1982; May, 1984) and has received consensual support in reviews of psychosocial treatments (May, 1976; Rutan & Cohen 1989; Liberman, 1994).

The SGT therapist was a Ph.D. level psychologist with experience in working with persons having schizophrenia. Group size (4-8 members per cohort) and frequency (90 minutes twice weekly) were comparable to the SST condition. In SGT the therapist encouraged patients to set personal goals and harnessed group dynamics, such as cohesion, to assist patients in exploring problems and obstacles that were associated with meeting these goals. In addition, the therapist encouraged the group members to work together to learn new methods of coping with everyday life stressors, problems and situations, using open-ended questions, reflection, empathy,

warmth, and gentle encouragement.

Information about mental illness and its treatment was provided by the therapist in a supportive atmosphere and discussion of the information by the group was encouraged. However, the therapist, who was trained in expressive and supportive therapy principles, assiduously avoided using structured behavioral or skills training techniques, such as modeling, homework assignments, and in vivo practice. As an independent indicator of the "attractiveness" of SGT and the satisfaction of patients with its value, there were no differences between the attendance and attrition in the two psychosocial conditions.

Drug Treatment Conditions

The drug treatment conditions were described in detail in a prior publication (Marder et al., 1994). Patients were evaluated weekly with the Idiosyncratic Prodromal Scale (IPS), an instrument which continued the symptoms that were reported to occur most reliably before relapses for each individual patient. For each item a scale (with 100 points) was developed with anchor points which described the range in severity for that symptom, and the threshold for meeting prodromal criteria. At each clinic visit, the severity of these symptoms was rated and the total compared with their baseline severity during the pre-study period of stabilization. When increases in severity met individualized criteria, patients were considered to be in a prodrome.

About half (n=36) of the patients did experience a prodrome at some point during the study. When subjects experienced a prodrome, they were randomly assigned either to receive oral fluphenazine (5 mg) or a placebo, administered twice daily under double-blind conditions. Patients receiving either oral fluphenazine or placebo were then followed until they either became stable, or worsened to the point of fulfilling criteria for a "psychotic exacerbation" or

relapse. During exacerbations, open label, oral medication was provided, usually consisting of fluphenazine, 5 mg twice daily. When patients stabilized they were returned to their original fixed dose of fluphenazine decanoate. If they again fulfilled criteria for a prodrome at a later time, they were treated under the same double-blind condition as they were for the first prodrome.

All of the recruited patients participated in the clinical trial of SST versus SGT, but only half of them met criteria for a prodrome during the study and participated in the drug supplementation trial. Analyses of the combined benefits of supplemental medication and skills training were only done with that subsample.

Outcome Measures

Severity of psychotic and other symptoms was assessed "blindly" at monthly clinic visits by a trained clinical assessor using the Brief Psychiatric Rating Scale. Since the patients were well stabilized at study entry, average symptom severity over the two year study period showed little change from baseline. For this reason, the principal measure of symptom outcome was psychotic exacerbation. The exacerbation criterion was a worsening of 4 points or more on the sum of the BPRS cluster scores for Thought Disturbance and Hostile-Suspiciousness, or an increase of 3 or more on either cluster.

Psychosocial outcome was measured at baseline and every six months for the two year duration of the study using the patient version of the Social Adjustment Scale II (Schooler, 1979). The rater was a clinician who was not blind to the psychosocial treatment condition. This scale assesses social functioning using a semistructured interview. The validity of this instrument in outpatients with schizophrenia has been previously demonstrated (Glazer et al., 1980). Subjects were rated on subscales which evaluated work role (including student role), household

role, parental role, extended family role, conjugal and nonconjugal sexual role, romantic involvement, social and leisure activities, and personal well-being.

Data Analyses

The basic data analytic model for the SAS II cluster scores and total was the general mixed model ANOVA with repeated measures. The design included two between subject treatment factors, psychosocial treatment and drug, crossed to form a 2 (SST, SGT) x 3 (Drug, Placebo, Never Assigned) factorial design. About half of the subjects were never assigned to a supplemental drug condition because they never had an identified prodrome. The other half were randomized either to drug or placebo after the first prodrome. Repeated measures were obtained at four follow-up points (every six months over two years), and linear effects of time were also included in the statistical model as a within-subject factor. Each SAS II cluster was analyzed separately. Follow-up tests included simple effects analyses of psychosocial treatment differences within each drug condition, within the same framework. These planned contrasts used pooled error terms and pooled error df. Baseline level was included as a covariate in each analysis.

In addition to using drug condition as a fixed design factor, crossed with psychosocial treatment, it was also included as a time-varying covariate. The reason was that, at the time of the first testing, a substantial number of subjects who subsequently entered the drug supplementation study had not yet been assigned. Treating such subjects as equivalent to those who were never assigned to drug was incorrect, because subjects who ultimately entered the drug supplementation study were much less stable clinically. The inclusion of time-varying covariates in the models permitted evaluation of the "intent to treat" category, but also allowed for variation

association with whether or not subjects were actually receiving supplementation at the time of testing. Estimated values were thus adjusted for changes in actual drug treatment status and for linear trends within treatment groups over time (estimated at the mean time to follow-up, which was just over one year or roughly 59 weeks). Analysis of exacerbation risk was done with proportional hazards regression models, using the fixed treatment factors and time-varying drug treatment covariates as described (SAS Proc PHREG).

Results

Effects of Psychosocial Condition on Social Adjustment

In our analysis of the effects of the psychosocial and drug treatment condition on cluster totals for the SAS II, we found significant main effects favoring SST over SGT on two of the six cluster totals examined. These were Personal Well-Being (treatment main effect, F=6.95, df=1.95, p=.010), and the total SAS II (treatment main effect F=6.05, df=1.94, p=.016). In both cases, outcomes were better with SST. Neither main effects of time nor interactions of time with psychosocial effects were significant in any SAS area (p-levels ranged from .19-.90, median=.57).

The interaction of psychosocial treatment and drug treatment condition was also significant in three areas. The clusters involved were Social-Interpersonal (treatment x drug interaction F=3.96, df=1.95, p=.022), External Family (treatment x drug interaction F=3.S8, df=2.94, p=.032). We therefore compared the psychosocial treatments separately within each drug treatment stratum. A fairly consistent trend was seen for the advantage of SST over SGT to be greatest in the context of combined treatment with active drug supplementation. The SST-SGT difference was greatest in the active drug supplementation condition for all SAS II clusters except work. In fact, among patients assigned to active drug supplementation, significant

differences favoring SST were found in the Social-Interpersonal (t=2.16, df=95, p=.034, effect size=.89), Personal Well-Being (t=2.92, df=93, p=.004, effect size=1.30) and total SAS II areas (t=3.2, df=94, p=.002, effect size=1.22). In contrast, no added benefit was observed with SST in any SAS II scale area among patients assigned to placebo supplementation.

Prediction of Psychosocial Treatment Effects

We also used general linear mixed model analyses to study interaction between clinical and demographic variables and the psychosocial treatments. We first focused on the possibility that symptom severity at baseline was related to social outcome, but did not find any interactions with treatment condition for baseline BPRS cluster scores for thought disturbance, paranoid hostility, retardation, or depression with the total SAS score (MANOVA, F<1, df 5.74, p=.71).

The relationships of demographic variables with social adjustment were then examined. Interactions of psychosocial treatment modality and age, ethnicity (dichotomized as white versus minority), education level, illness duration, or marital status (dichotomized as ever married versus never) were all nonsignificant. However, the interaction of the psychosocial treatment condition and age of onset (dichotomized at the medican of 24 years) was highly significant (F=10.59, df=1.89, p=.0016; Bonferroni-adjusted p=.01). Significant benefits of SST were only seen among those subjects with a younger age of onset (n=27, F=13.83, df=1.24, p=.001, see Table 4). Patients with a younger age of onset who received SST had the best overall social outcomes, as measured by the SAS II Total, differing significantly from all three of the other groups (all ps<.01 by pairwise contrast).

Effects of Psychosocial Condition on Rates of Exacerbation

The factorial proportional hazards regression model revealed no appreciable difference

between the full cohorts of patients treated with SST or SGT in the risk of psychotic exacerbation. For example, of patients who received SST, 46% survived without exacerbations at the end of the first year while in the SGT condition, 42.6% survived after the first year.

On an exploratory basis, we used stepwise proportional hazard regression (SAS Proc PHREG) with time-varying covariates to examine the specific differential risk associated with each combination of psychosocial and drug treatment, both before entering the drug supplement study as well as afterward. Among the subjects who were randomized to placebo supplementation, exacerbation risk was significantly higher among patients in the SGT-control psychosocial condition. Prior to drug randomization, there were no significant differences between SST and SGT (X^2=.52, df=1, p=.47) in terms of exacerbations, and after supplementation began, there was still no difference between psychosocial conditions for those assigned to active drug (X^2=.22, df=1, p=.64). However, among patients assigned to placebo supplementation risk of exacerbation was significantly higher for those in the SGT control psychosocial condition (X^2=5.14, df=1, p=.02). The difference between the groups was most dramatic in the period immediately after randomization to drug condition. Eight weeks after randomization, for example, survival rates were 90% in the SST group, and 40% in the SGT group; by twelve weeks, the difference was 90% versus 27%. After twelve weeks, survival rates began to converge, and over the whole two-year follow-up period, all but four patients in the placebo supplementation group eventually exacerbated.

Discussion

We found that a program of behaviorally-oriented social skills training can result in improvements in important areas of social adjustment. This result was affected by the concurrent

drug treatments, being most pronounced among those patients who had been assigned to active drug supplementation. There were no differences between psychosocial modalities in terms of social adjustment outcomes for patients who were assigned to the placebo group.

We also found that an early age of onset had important effects on social adjustment outcomes. The difference between SST and SGT was much larger among patients with a relatively early onset of schizophrenia. Among those with later age of onset (i.e., after the median 24 years), social outcomes with SST and SGT appeared equal. One might speculate that patients with later age of onset had more time prior to the first schizophrenic break to develop mature social and interpersonal skills, while those with early onsets were more deficient in those areas and thus more responsive to focused behavioral skill training. Consistent with this, the patients with earlier onsets in this sample had poorer SAS scores in every cluster area at baseline.

SST, in comparison to SGT, was associated with a reduced risk of psychotic exacerbation for patients who were randomly assigned to placebo supplementation. Among patients who were assigned to active drug supplementation, and among those never assigned to supplementation at all, the two psychosocial treatments did not differ with regard to exacerbation rates. Both of those groups were less vulnerable to exacerbation than the placebo patients, the former because of the protection afforded by active supplementation, and the latter because they were more stable and less prone to exacerbation in general. The "control-control" group was expected to be a highest risk, and in fact exacerbation rates were signficantly higher in that combined treatment condition than in any other. These findings suggested that SST confers a protective effect against relapse that may be similar to and substitutive with antipsychotic medication.

Our results regarding the benefits of SST for social outcomes are consistent with most of

the prior literature. With regard to reducing exacerbation risk, several investigators have found that social skills training, alone or combined with family pscyhoeducation, was associated with reduced relapse rates when compared with controls over a one-two year time period (Tarrier et al., 1993; Falloon et al., 1985; Hogarty et al., 1986; Hogarty et al., 1991). Two recent meta-analyses of SST in schizophrenia have found that, while the benefits of SST are stronger for improvements in social skills functioning, significant effects were also identified for symptom improvement, acceleration of discharge from hospital, and reduced relapse rates (Benton & Schroeder, 1990; Corrigan, 1991). Our own finding of the value of SST on relapse prevention applied only to the subgroup of patients who were unstable enough to enter the drug supplementation study, and then received only placebo. Thus, SST may reduce exacerbation risk most in high-risk individuals whose medication management is sub-optimal. In customary clinical settings where patients compliance with medication is often less than optimal, SST may be of considerable value in delaying or preventing relapse.

In the current study, the effects of SST were most substantial on subscales measuring social and leisure functioning and personal well-being, areas that are commonly perceived as being the most refractory to treatment. These findings -- together with the previous studies of skills training -- provide additional support for the effectiveness of skills training methods for improving the social adjustment of patients with schizophrenia (Bellack et al., 1984; Liberman et al., 1986; Mueser, Wallace & Liberman, 1995). In contrast, patients who received a relatively intensive program of supportive group psychotherapy demonstrated very little change in their social adjustment.

Our study -- together with the work of others -- suggests that in schizophrenia,

pharmacological and psychosocial treatments can be targeted at specific manifestations of the disorder. Optimizing a patient's pharmacotherapy can play an important role in minimizing the risk of psychotic relapse. Social skills training may confer some protection against relapse also, at least among relatively unstable patients whose medication regime is not optimal. Furthermore, in the context of adequate drug maintenance, SST appears to play an important role in treating the deficits in social skills that are an important component of the disorder. The art of treating chronic schizophrenia rests in the design of long-term treatment strategies that combine biological and psychosocial treatments that are tailored to the deficits of the individual patients.

Finally, it was observed that the combined strategy of providing active drug supplementation at the time incipient worsening of psychotic symptoms is first observed, and consistent skills training throughout the follow-up period, resulted in the best social outcomes.

Clinicians might raise the question of whether it is possible to teach skills effectively across the range of residual positive and negative symptoms. In this regard, this report supplements a previous publication in which we studied whether patients who participated in SST were able to acquire the skills that were taught in the modules. Using standardized role play tests, we found that patients who received SST demonstrated statistically significant improvements in skills that were included in the Medication and Symptom Management Modules (Eckman et al., 1992). Moreover, patients maintained their skills in an assessment that took place one year later. It was also notable that patients with high levels of both positive and negative symptoms were able to acquire skills. This suggested that behavioral skills training may be effective for a large proportion of severely disabled patients with schizophrenia.

Summary

These two studies have shown the value and limitations of behavior therapy in the treatment of schizophrenia. Treatment of symptoms and psychopathology, as well as prevention or delay of relapse, are still predominantly a matter for pharmacotherapy. Especially with the new generation of atypical antipsychotic drugs, we can expect a broader array of patients with previously refractory symptoms to respond to antipsychotic drug therapy. The protective effects of maintenance antipsychotic drugs against relapse also are much greater than can be documented with a psychological treatment, such as social skills training.

On the other hand, when the targets of treatment are psychosocial functioning, the treatment of choice is behavior therapy. Both intensive and focused behavioral treatment of self-care skills and deviant behaviors for long-term, hospitalized, inpatients and social skills training for the social and community functioning of outpatients appear to be prepotent over medication. For a truly comprehensive treatment effect, **biobehavioral therapy** that combines behavioral and biological components must be utilized.

The future promise of new psychological treatments for schizophrenia will be realized only if: (1) subject populations are clearly and reliably evaluated using structured and replicable methods of symptom solicitation, ratings and diagnosis; (2) concomitant pharmacotherapy is well specified and controlled; and (3) hypotheses are drawn from a conceptual framework that connects treatments with their specified and expected outcome dimensions.

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