

At Issue Predicting Drug.-Free Treatment Response in Acute Psychosis From the Soteria Project

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Abstract

Although an estimated 25 to 40 percent of acute psychoses remit without antipsychotic drug treatment, only limited efforts have been made to identify individuals in early episodes who might be able to recover without medications. This retrospective exploratory study uses baseline information from the Soteria project (young, unmarried, first and second episode DSM-IV schizophrenia, $n = 179$) to develop a preliminary model for this purpose. Forty-three percent of experimentally treated subjects received no antipsychotic medications during the 2-year followup period and were designated "drug-free responders." At followup, this group had better outcomes (+ 0.82 of a standard deviation [SDI] on a composite outcome scale (representing rehospitalization, psychopathology, independent living, social and occupational functioning). A predictive model using three variables (age, the Goldstein Adolescent Social Competence Scale score, and number of diagnostic symptoms) correctly identified this subgroup 79 percent of the time (bootstrapped 95% confidence interval [CI], 65-90%). Predicted drug-free responders exhibited moderately better outcomes (effect size: 0.38 to 0.61 of an SD) when treated at Soteria. These data advance the hypothesis that an identifiable subgroup of individuals with early episode psychosis might fare better when receiving specialized psychosocial intervention and minimal or no use of antipsychotic medications.

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Conventional antipsychotic medications have been used in the treatment of schizophrenia and other forms of acute psychoses for nearly 50 years. They are generally regarded as having contributed to the deinstitutionalization of former mental hospital patients (Mechanic 1989) and as having greatly improved treatment for psychotic disorders (Dixon et al. 1995). Antipsychotic medications are widely used as the first line treatment for virtually all forms of acute psychoses (Davis et al. 1980) in spite of many serious short- and long-term toxicities and occasionally lethal side effects (Gelenberg 1996). Along with the development of newer medications with more tolerable side effect profiles (Voruganti et al. 2000), low-dose, intermittent use, and targeted intervention strategies have been investigated in an effort to improve the risk-benefit profile of maintenance antipsychotic medication treatment through reducing medication use and thereby reducing the incidence of medication-induced toxicities (Buchanan and Carpenter 1996; Schooler 1996). In this article we investigate a related approach to improving the risk-benefit profile of medication treatment by asking whether it is possible to identify a subgroup of acute first and second episode individuals likely to fare well in the absence of antipsychotic drug treatment.

From the earliest days of research comparing antipsychotics to placebo treatment, the existence of a subgroup of individuals who do well in the absence of antipsychotic drug treatment has been recognized (Lieberman et al. 1984). For example, the early National Institute of Mental Health (NIMH) Psychopharmacology Service Center (PSC) Collaborative Group multisite first episode schizo-

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phrenia study found 37 percent of placebo-treated subjects exhibiting "much" or "very much" improvement in psychopathology at the 6-week evaluation (Cole et al. 1964; Goldberg et al. 1965; Young and Meltzer 1980). However, these investigators were unable to find significant correlates of placebo response (Cole et al. 1966).

Estimates of the size of a drug-free responder subgroup have varied considerably, from 0 to, 65 percent. On the low end, Davis et al. (1989) note:

The finding that 10 percent of persons with schizophrenia recover without drugs raises the question of whether some patients might do just as well or better without drugs ... currently there is no means of reliably identifying such patients before a therapeutic trial is undertaken, nor is there any evidence that such a subgroup exists. (p. 1597)

A recent review of previously published reviews of the literature estimates drug-free response in schizophrenia at about 25 percent (Dixon et al. 1995). May's early (1968) first episode schizophrenia study reported hospital release rates (within 6-12 months) for milieu treatment and psychotherapy at 58 and 65 percent, in spite of excluding approximately one-third of subjects as "good prognosis" patients that were "already showing signs of rapid recovery during the initial evaluation period ~ (average sixteen days)" (p. 59). At the 3- to 5-year followup, these drug-treated "successes ... functioned at least as well, if not better, than the successes from the other treatment(s)" (May et al. 1968, p. 783).

No meta-analysis of antipsychotic drug versus placebo studies has been completed, leaving open the question of whether there is selective publication or other bias in existing literature reviews (Beaman 1991; Dickersin and Min 1993). However, a systematic meta-analysis of chlorpromazine versus placebo studies in schizophrenia is currently under way in the Cochrane Schizophrenia Group (Thornley et al. 2000) and preliminarily indicates a placebo responder subgroup of approximately 40 percent.

The proportion of individuals who recover without drug treatment also varies by duration of study. Long-term followup studies conducted prior to the widespread use of antipsychotic drugs report functional recovery rates above 50 percent. Manfred Bleuler's (1978) 20-year followup study of schizophrenia found a 25 percent full recovery rate, with more than 50 percent of subjects exhibiting functional recovery. Ciompi's (1980a) long-term (average 37 years) followup study of schizophrenia found a 26 percent full recovery rate with 59 percent either recovering or "showing definite improvement" (p. 615). Huber et al. (1980) reported 22 percent complete remissions and 56 percent social remissions in their long-term (average 22.4

years) followup study of schizophrenia. In the era after antipsychotic agents became available, Harding et al. (1987), reporting on a 20- to 25-year followup of "backward patients" retrospectively diagnosed with *DSM-III* schizophrenia, found that "one-half to two-thirds ... were ... considerably improved or recovered" (p. 722).

While available research syntheses and long-term followup studies do not challenge the overall effectiveness of antipsychotic medications, these studies do not address the latter part of NIMH's (1991) directive to study "what works, under what circumstances, and for which kinds of individuals" (p. iii). In other words, to avoid a one-size-fits-all approach, individualization of treatment requires knowledge of how client characteristics interact with treatment options (Carpenter and Heinrichs 1981). In particular, prior identification of individuals who may not benefit from antipsychotic medications could spare these individuals exposure to the toxicities associated with both conventional and atypical antipsychotics. This point has been made by a substantial group of clinicians and researchers (Carpenter et al. 1977; Rappaport et al. 1978-1; Marder et al. 1979; Mosher and Meltzer 1980; Young and Meltzer 1980; Carpenter and Heinrichs 1981; Buckley 1982; Liberman et al. 1984; Warner 1985; Carpenter 1997). Identifying subgroups of patients who respond well to psychosocial treatments without accompanying antipsychotic medications would both reduce the risk of iatrogenesis and address consumer calls for alternatives to antipsychotic drug treatment (National Association of Psychiatric Survivors 1991; National Association of Rights Protection and Advocacy 1991) when appropriate.

Some early attempts were made toward the identification of individuals likely to recover from psychosis without medications. Langfeldt (1939, 1969) postulated that "schizophreniform psychosis" is distinguishable from schizophrenia by prognostic criteria (symptoms of psychotic depression, family history of depression, absence of schizoid personality, acute onset, confusion, and precipitating cause) and has a tendency toward spontaneous remission. Eitinger et al. (1958) used Langfeldt's (1939) criteria to divide a group of first episode hospital patients into schizophrenia versus schizophreniform disorders. At followup 5 to 15 years later, 32 percent of the schizophreniform group was "quite free of symptoms and fully capable of working" (p. 47) and an overall 78 percent were considered as completely or nearly free of symptoms (Eitinger et al. 1958).

Vaillant (1962) reviewed the early literature on predicting recovery using prognostic criteria and demonstrated a clustering of Langfeldt's prognostic criteria in individuals who had recovered from schizophrenia. Adding a seventh prognostic criterion (concern with dying during the acute phase), Vaillant (1964) used a score of

five or more of the seven criteria to correctly predict long-term clinical course in 82 percent of patients ($n = 72$). Schooler et al. (1967), using the NIMH nine-site schizophrenia collaborative study data, found that having acute onset and being older were related to having more favorable outcomes and that individuals treated with placebo had fewer rehospitalizations. Goldstein (1970) found that individuals who were diagnosed with acute schizophrenia with good prognostic features and who were nonparanoid fared better on placebo. Working with Goldstein, Evans et al. (1972) observed among these same patients that good prognostic status and placebo treatment were associated with early discharge (28 days or less). Judd et al. (1973) found that the **good-prognosis nonparanoid individuals** showed "minimal medication response" and did "fairly well on placebo" (p. 271). Rappaport et al. (1978), studying largely first and second episode patients, found that those who had good premorbid features and short-lived paranoid characteristics and who were treated with placebo tended to have greater long-term improvement, to have lower levels of pathology, to be less frequently rehospitalized, and to be functioning at higher levels at the 3-year followup than any of the other groups. Marder et al. (1979) retrospectively identified a subgroup of "drug-free improvers" (p. 1082) using the criteria of (1) short duration of prior hospitalization, (2) acute onset with symptoms for less than 6 months, (3) absence of premorbid schizoid adjustment, and (4) recent sexual adjustment. Thus, indicators for a drug-free responder subgroup of individuals in psychosis cluster around good prognosis and nonparanoid features and a diagnosis of schizophreniform psychosis.

The present investigation uses data from the Soteria project (Mosher and Merin 1978; Mosher et al. 1995), a study of psychosocial milieu treatment in the community compared with a control condition of antipsychotic medication treatment in the hospital for patients with first and second episode *DSM-II* schizophrenia (American Psychiatric Association [APA] 1968). These data are used because they are from one of a very few early episode schizophrenia studies that included an active psychosocial treatment rather than simply a placebo control group. Soteria was also a prospective quasi-experimental study that conducted followup evaluations until 2 years postadmission. The use of existing data is preferred in beginning to address the question of which individuals recover from early episode psychosis without drugs because of suggestions that early intervention with medications improves the long-term course of first episode clients (Wyatt 1991) and, therefore, that withholding medications may be unethical (Kirch et al. 1992).

The major questions addressed in the present study are (1) what proportion of experimentally treated individu-

als used no antipsychotic medications during the 2-year followup period, (2) how well were the non-drug-treated subjects functioning at the 2-year followup point, (3) did experimental treatment reduce average antipsychotic medication use for all subjects or for only a subgroup of subjects, (4) how well can the non-drug-treated subgroup be predicted from diagnostic and prognostic information available at entry to the study, and (5) do predicted drug-free responders have better outcomes when treated at Soteria?

Research Design and Methods

Study Design. The Soteria project was developed as an innovative approach to the treatment of persons newly identified as having schizophrenia (*DSM-II*, APA 1968) that targeted individuals at risk for long-term disability (young and unmarried) (Mosher and Menn 1978; Matthews et al. 1979). Subjects ($n = 179$) were recruited into the study in two cohorts from early 1971 through mid-1979 and followed for 2 years postadmission. Assignment to standard medical treatment or alternate psychosocial treatment was made on a consecutive space-available basis in the first cohort and by simple randomization in the second, resulting in a prospective quasi-experimental design (experimental $n = 82$, control $n = 97$; Bola 1998). In both cohorts, data were collected at four points in time, at admission (day 1 and day 3), and at 6 weeks, 1 year, and 2 years postadmission. In the experimental facilities, antipsychotic medications were ordinarily not used during the first 6 weeks of treatment. However, there were explicit criteria for their short-term use during this period. After 6 weeks, if the client was still in residence, medication prescription decisions were made, based on improvement or lack thereof, at a treatment conference that included the client, facility staff, and the consulting psychiatrist. Only conventional antipsychotic medications were available at the time of the study (1970-1980s); they were used at the discretion of the treating psychiatrist. The Soteria study employed an initial assignment design, in that participants were assigned to treatment without being first medicated with antipsychotics (Warner 1985). This avoided the potential bias, introduced through dopamine supersensitivity (Chouinard et al. 1978), in a drug withdrawal design.

Study Sites and Interventions. Subjects were recruited from two County Hospital psychiatric emergency screening facilities in the San Francisco Bay Area. Standard psychiatric treatment was conducted at the 30-bed psychiatric wards of these general hospitals. Alternate psychosocial treatment was conducted at either the original Soteria resi-

dential treatment program or at a replication program (Emanon).

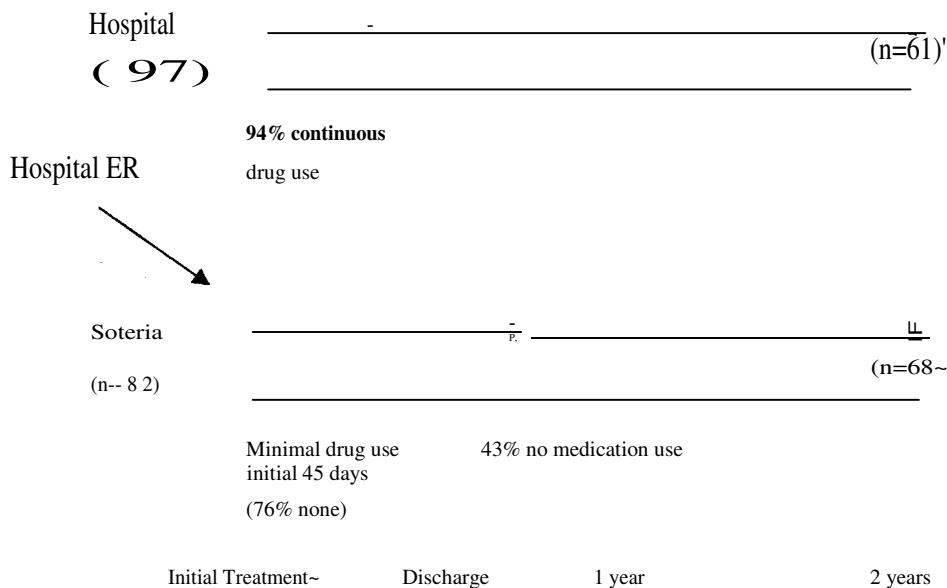
Soteria was predominantly an extramedical treatment, employing a "developmental-crisis approach" (Mosher 1972, p. 232) to assist clients in recovering from psychosis. Treatment involved providing a small, homelike, intensive, supportive "therapeutic milieu" with a **nonprofessional** staff who related with clients in ways that did not "result in the invalidation of the experience of madness" (Mosher and Menn 1978, p. 716). As mentioned above, the use of (the then-available conventional) antipsychotic medications was minimized during the first 6 weeks of Soteria treatment (75.6% received none).

Control facilities were well-staffed inpatient psychiatric services organized around a medical model and geared toward "rapid evaluation and placement in other parts of the county's treatment network" (Mosher and Menn 1978, p. 717). Virtually all control subjects (94.4%) were treated continuously with dose in-hospital courses of conventional antipsychotic medication (averaging 700 mg of chlorpromazine equivalents per day), and nearly all were prescribed postdischarge medications. In the present study, this is regarded as "usual treatment."

In both groups, postdischarge treatment was based on the clinical judgment of the treating psychiatrist in consultation with the client and may have included readmission and use of antipsychotic medications. A study design and medication use timeline (figure 1) summarizes these components of the study.

Selection Criteria. Because this study was originally designed in an effort to reduce long-term disability among at-risk individuals, participants needed (1) to have an initial diagnosis of schizophrenia by three independent clinicians (*DSM-II*; APA 1968), (2) to be judged in need of hospitalization, (3) to have had no more than one previous hospitalization for 4 weeks or less with a diagnosis of schizophrenia (*DSM-II*, APA 1968), (4) to be between 15 and 32 years old, and (5) to be unmarried. This produced a sample with mixed prognostic features, including individuals with both acute onset psychoses (schizophreniform disorder, APA 1994) and the poor prognostic features of being younger and unmarried (Strauss and Carpenter 1978). Requirements for participation were explained, and informed consent was sought from patients and their families, if available.

Figure 1. Study design and medication use timeline



1 Study attrition in the hospital treatment group was 36 of 97 (37.1 %).

2 Study attrition in the Soteria treatment group was 14 of 82 (17.1 %). The differential attrition by treatment group was statistically significant ($t = 3.037, p = 0.003$), making correction for possible attrition bias in subsequent statistical estimates necessary (cf. Heckman 1979).

3 Initial treatment in Soteria was designed to be substantially longer than treatment in the hospital (mean use: 163.7 vs. 33.7 days).

Emergency room staff psychiatrists made initial diagnoses. All subsequent assessments were made by an independent research team trained and regularly reassessed to maintain an interrater reliability coefficient (kappa) of 0.80 or better on all measures. This team conducted diagnostic assessments prior to entry and again at 72 hours. If both reassessments confirmed a *DSM-II* diagnosis of schizophrenia, and at least four of the seven cardinal symptoms of schizophrenia (thinking or speech disturbances, catatonic motor behavior, paranoid ideation, hallucinations, delusional thinking other than paranoid, blunted or inappropriate emotion, disturbance of social behavior and interpersonal relations [only two were required in the original Cole et al. 1964 NIMH-PCS study]) were observed, patients were included (n = 179). The 3-day reassessment was conducted in order to exclude rapidly recovering subjects (e.g., with drug-induced psychoses) from the study.

Subjects were re-diagnosed into schizophrenia and schizophreniform disorder (*DSM-IV*, APA 1994) using mode of onset information available in the data. All *DSM-II* schizophrenia subjects with symptoms evident for

6 months or longer (insidious onset) were re-diagnosed with schizophrenia (42%; 71 of 169), because the addition of the 6-month length of symptom criterion was the primary change from *DSM-II* to *DSM-III* (APA 1980), and it has been carried forward into *DSM-IV*. Subjects having an onset with symptoms evident for less than 6 months were re-diagnosed with schizophreniform disorder (58%; 98 of 169). Of the subjects observed throughout the 2-year followup period (n = 129), 68 percent of those initially diagnosed with schizophreniform disorder (52 of 77) were rehospitalized during the period. Thus, at the time of their rehospitalization, a large proportion of the subjects initially diagnosed with schizophreniform disorder would likely have met *DSM-IV* criteria for schizophrenia.

Sample characteristics. Individuals (n = 171) admitted to the study were 80 percent European-American, 9 percent African-American, and 11 percent other ethnic groups. The sample (n = 179) was 64 percent male and 36 percent female. There were a few differences between treatment groups on baseline diagnostic and prognostic variables (table 1), underscoring the quasi-experimental nature of the study (Bola 1998). These differences point

Table 1. Comparison of baseline characteristics for Soteria (n = 82) versus hospital (n = 97) subjects (n = 179)

Variable	Soteria ¹	Hospital ¹	t value	p value ²
Age	21.5	22.0	-0.86	ns
Goldstein Adolescent Social Competence Scale ³	20.7	21.7	-0.91	ns
Venables and O'Connor Paranoia Scale ⁴	12.7	12.9	-0.22	ns
Hollingshead Socioeconomic Scale ⁵	45.3	39.2	2.43	0.02
Confusion ⁶	0.80	0.76	0.43	ns
Stressful precipitants	0.63	0.54	1.33	0.19
Previous hospitalization	0.39	0.32	0.98	ns
Schizoid personality ⁷	0.56	0.64	-0.82	ns
Prior work experience	0.81	0.85	-0.62	ns
Some college	0.56	0.50	0.80	ns
Insidious onset (schizophrenia vs. schizophreniform disorder)	0.49	0.36	1.69	0.09
Number of cardinal symptoms of schizophrenia ⁷	5.3	5.4	-1.17	ns
Certainty of schizophrenia diagnosis ⁸	6.0	6.1	-0.20	ns
Global Psychopathology Scale ⁹	5.1	5.3	-1.51	0.13

Note.--ns = nonsignificant.

¹Group mean scores.

²Only p values < 0.20 are reported; others are indicated as ns.

³Goldstein Adolescent Social Competence Scale (Rodnick and Goldstein 1974; range: 7-35, higher is greater competence).

⁴Venables and O'Connor (1959) Paranoia Scale (range: 5-25, higher is more paranoid).

⁵Hollingshead (1957) Socioeconomic Scale (range: 1-77, higher is lower status, n = 159).

⁶Second cohort only (n = 100: 45 at Soteria, 55 at hospital).

⁷Includes thinking or speech disturbances, catatonic motor behavior, paranoid ideation, hallucinations, delusional thinking other than paranoid, blunted or inappropriate emotion, disturbance of social behavior and interpersonal relations (Cole et al. 1964).

⁸Certainty of Schizophrenia Scale (Mosher et al. 1971; range: 1-7, higher is more certain).

⁹Global Psychopathology Scale (Mosher et al. 1971; range: 1-7, 1 = not ill, 4 = moderately ill, 7 = extremely ill).

toward the Soteria-treated group as having a somewhat poorer prognosis.

Measures. Seventeen independent variables were used in the present investigation. Ten prognostic variables were available for differing numbers of individuals: age (mean [SD]: 21.8 [3.4], range: 15-32, $n = 179$), the Goldstein Adolescent Social Competence Scale (Rodnick and Goldstein 1974; mean [SDI]: 21.2 [5.8], range: 7-35, higher is greater competence, $n = 101$), the Venables and O'Connor Paranoia Scale (Venables and O'Connor 1959; mean [SDI]: 12.8 [4.31], range: 5-25, $n = 170$, higher is more paranoid), socioeconomic status (SES, defined as the ordinal scale forming the basis of Hollingshead's [1957] five social classes; mean [SDI]: 42.3 [16.1], range: 11-77, higher is lower status, $n = 159$), and binary indicator variables for the presence (coded 1 = presence, 0 = absence) of confusion (78%, $n = 100$), stressful antecedent events (64.2%, $n = 162$), prior hospitalization (39.1%, $n = 161$), schizoid premorbid personality development (60%, $n = 100$, described by Vaillant 1964 as a "chronic inability to relate to nonfamily figures and a tendency toward autistic preoccupation" [p. 5101; operationalized in this study as "few, if any, intimate friends, and little or no heterosexual contact"), having some college education (52.9%, $n = 172$), and having some prior work experience (83.1%, $n = 166$). Four diagnostic variables were used, representing an indicator for schizophrenia versus schizophreniform disorder (described above; 42%, $n = 169$), the number of cardinal symptoms of schizophrenia (Cole et al. 1964; range: 4-7, $n = 169$), an ordinal scale representing the certainty of a diagnosis of schizophrenia (Mosher et al. 1971; range: 4-7, higher is

more certain), and an ordinal scale rating global psychopathology at intake (Mosher et al. 1971; range: 2-7, $n = 154$, 1 = not ill, 4 = moderately ill, 7 = extremely ill). Independent variables representing experimental treatment (0 = experimental, 0 = usual treatment; 45.8%) and a derived function of the probability that a given observation was available at followup were also used. The latter corrects for differential attrition bias in multivariate effect estimates (see analysis section below, Heckman 1979). An additional variable representing the number of days between discharge from initial treatment and the 2-year followup point was used to address the concern of a differential risk of readmission due to longer initial treatment (Wyatt 1991), and thus a shorter postdischarge followup period, of Soteria clients (range: 0-730, $n = 170$).

Twelve dependent variables were used. They include eight outcome measures evaluated at the 2-year followup point (representing the five domains of rehospitalization, psychopathology, independent living, working, and social functioning), one composite outcome measure (described below), one indicator of drug-free treatment status, a summary indicator of the frequency of antipsychotic medication use during the followup period, and one indicator of nonattrition. The individual outcome measures for individuals completing the 2-year followup ($n = 129$; table 2) are readmission to 24-hour care (1 readmitted, 0 not; = 67.4%, $n = 129$), number of readmissions (mean [SDI]: 1.8 [1.8], range: 0-7, $n = 129$), days readmitted (mean [SDI]: 62.8 [109.3], range: 0-618, $n = 129$), the Global Psychopathology Scale (Mosher et al. 1971; mean [SDI]: 2.8 [1.3], range: 1-7, $n = 108$; described above), global improvement in psychopathology (Mosher et al. 1971; mean [SDI]: 2.3 [1.31], $n = 114$, coded 1-7, 1 = much

Table 2. Two-year outcomes: Completing subjects (n = 129)

Outcome Variable	Mean	SD	Range	n
Composite outcome scale ¹	0.00	1.10	-2.6 to 2.3	129
Global Psychopathology Scale ²	2.80	1.30	1-7	108
Improvement in psychopathology ³	2.30	1.30	1-7	106
Readmission to 24-hr care ⁴	0.67	0.47	0-1	129
Number of readmissions	1.80	1.80	0-7	129
Days in readmission	62.80	109.30	0-618	129
Living independently or with peers ⁵	0.40	0.49	0-1	121
Working (approx. hrs/wk)	13.90	16.80	0-40	118
Social functioning ⁶	1.90	0.70	0-3	111

Note.--SD = standard deviation.

¹Composite, in standard deviation units, of the eight individual outcome measures listed below in the table.

²Global psychopathology scale (Mosher et al. 1971; higher is more symptomatic).

³Global improvement in psychopathology (Mosher et al. 1971; coded 1-7, 1 = much improvement, 4 = no change, 7 = much worse).

⁴Readmission to 24-hour care (1 readmitted, 0 = not; 67.4%).

⁵Living alone or with peers (1 = yes, 0 = no; 38%).

⁶Social functioning subscale of the Brief Follow-up Rating Scale (BFR; Sokis 1970; higher is better social functioning).

improvement, 4 no change, 7 = much worse), living independently or with peers (1 = yes, 0 no; 40%, $n = 121$), an ordinal approximation (0 = not working, 50%; 13.3 = working part-time, 23%; 40 = working full time, 27%, $n = 118$), and a variable representing the social functioning subscale of the Brief Follow-up Rating Scale (Sells 1970; mean [SD]: 1.9 [0.7], range 0-3, $n = 118$, higher is better social functioning). In the second cohort, information is available on only two of the three items measured by the social functioning subscale (number of friends and frequency of contact with friends or family). The item indicating number of organizational memberships was not available. Second cohort scores on this scale were therefore approximated using the observation that 10 percent of the first cohort received a score of 3 on this scale, then assigning a score of 1.1 for each of the two items completed to individuals in the second cohort. This method results in slight but not statistically significant differences between cohorts.

The eight individual outcome measures were then combined into a composite outcome indicator in the following manner. Each was converted to standardized scores with means of 0 and SDs of 1. When a case had a missing value for one or more of these outcome variables, this value was set to the mean (0) in order to minimize the loss of cases in the composite score. As can be seen in table 2, this procedure was applied in from 8 to 23 cases in five of the eight outcome variables and represents mean substitution in constructing the composite outcome measure for about 8 percent of missing information among subjects completing the 2-year followup ($n = 129$). For the variables in which a higher score represented a poorer outcome (rehospitalization, all three items; psychopathology, both items), the scores were multiplied by -1 in order to reorient the items, so higher scores represent better outcomes for all variables. These eight standardized variables were summed to form a composite index. Cronbach's alpha for this index is 0.74. (When considering only cases with no missing information, Cronbach's alpha for the composite outcome scale is 0.71.) The composite index was then itself standardized so that subsequent analyses could be interpreted in SID (effect size) units (Neter et al. 1996) of this composite outcome scale (mean [SD] 0.0 [1.1], range: -2.6 to 2.3, $n = 129$). Table 2 presents descriptive statistics for the composite outcome measure and its eight components.

Two additional dependent variables were included. A binary (1/0) indicator of drug-free treatment response was defined as experimentally treated subjects who were observed throughout the followup period ($n = 68$) and who used no antipsychotic medications during this time (45 days to 2 years; 42.6%). This means that the clinical threshold for medication use employed by followup psy-

chiatrists was not crossed during the followup period. Because nearly all of the hospital-treated individuals were medicated during initial treatment, these individuals were not given the opportunity to respond without medications and therefore could not be considered drug-free responders.

An approximation to the number of days of antipsychotic medication use during the followup period was created from ordered categorical medication use variables (0 = no use, 0.33 = occasional use, 0.67 = frequent use, 1.0 = continuous use) measured at the 1- and 2-year followup points; each was multiplied by the length of the respective followup period (day 45 to 1 year = 320 days, 1 to 2 years = 365 days) and summed across the two periods (mean [SD] = 327.5 [275], range: 0-685) for those with no missing followup observations ($n = 129$). An additional binary variable was created to indicate nonattrition from the study (1 nonattrition, 0 attrition; 72.1%, $n = 179$) and was used to correct for attrition bias in multivariate effect size estimates (Heckman 1979).

Analysis. The analysis was conducted in four stages. First, we ascertained the proportion of experimentally treated subjects using no antipsychotic medications during the followup period, calculated descriptive statistics for their outcome measures at 2 years, and contrasted them with outcomes from the whole sample. Second, we assessed whether the experimental treatment operates to reduce medication use for all subjects or only some. Third, we developed a retrospective "best fit" model to predict drug-free response in experimental treatment that adjusts for potential bias due to the differential attrition across the treatment groups, and we assessed its predictive accuracy both within the observed sample and through use of a bootstrap resampling procedure (Efron 1982). Fourth, we assessed the potential clinical value of treating predicted drug-free responders in Soteria facilities using an analysis of covariance (ANCOVA) approach on the 2-year composite outcome scale score. The primary variable of interest in this analysis is the interaction term representing the treatment of predicted drug-free responders at Soteria.

Analysis was conducted using the statistical software packages SPSS (Statistical Package for the Social Sciences) and LEVMEP (acronym for LIMited DEpendent variables [Greene 1995]). Throughout multivariate analyses, a method described by Maddala (1977) for dealing with missing observations was used. This involved setting missing values to 0 and creating a missing value indicator variable equal to 1 when the original information was missing and 0 otherwise. The two variables were used together. This approach enables more complete use of available information while not biasing the coefficient estimates (Greene 1997).

Stages one and two. An assessment of the proportion of experimentally treated individuals who did not use antipsychotic medications during the followup period (and were not lost to followup) was made. Excluding individuals not using medications during the followup period, the frequency of antipsychotic medication use was compared between the experimentally treated individuals and individuals initially receiving usual treatment.

Stage three. The development of a retrospective exploratory model identifying drug-free response status among experimentally treated individuals contains several elements. First, we note the differential attrition by treatment. Of the 179 individuals beginning the study, 72.1 percent ($n = 129$) were observed throughout the followup period, representing 68 of 82 experimental subjects (82.9%) and 61 of 97 control subjects (62.9%). The overall 28 percent attrition rate gives rise to some concern for the representativeness of the individuals observed at followup, and, because rates of attrition are different across treatment groups, for the possibility of an attrition bias. The 20 percent difference in attrition rate by treatment group is statistically significant ($t = 3.037$, $p = 0.003$). The concern that differential attrition may bias estimates is therefore addressed with the Heckman (1979) procedure for correcting this type of bias. This procedure involves developing a probit model predicting nonattrition (1 = nonattrition, 0 = attrition, 72.1%, $n = 179$) and saving the inverse Mills ratio from this model for use as an independent variable in estimating the model predicting drug-free response. The inverse Mills ratio is a function of the probability that a given individual is observed at followup, and its inclusion in subsequent estimations statistically adjusts for the higher likelihood of experimental subjects to be observed at followup.

The selection of predictor variables for nonattrition was conducted in two sequential procedures. First, each diagnostic and prognostic variable and its missing value indicator (if necessary) were separately regressed on nonattrition using a probit estimator. Variables indicating modest levels of bivariate relationship ($p < 0.20$) with nonattrition were saved for the second step of selection. A comparison of baseline prognostic and diagnostic variables for subjects retained versus lost to followup is presented in table 3. Second, variables indicating modest association in step 1 were included in a backward stepwise probit analysis (inclusion criterion: $p < 0.10$).

The prognostic variables used in this procedure were age, the Goldstein Adolescent Social Competence Scale, the Venables and O'Connor Paranoia Scale, the Hollingshead Socioeconomic Scale, and binary indicator variables representing the presence or absence of confusion, stressful precipitating events, previous hospitalization, schizoid personality, previous work experience, and previous col-

lege experience. Also included were the diagnostic variables representing schizophrenia versus schizophreniform disorder, number of cardinal symptoms of schizophrenia, the Certainty of Schizophrenia Scale score, and the Global Psychopathology Scale score at admission.

Correction for attrition bias was then addressed in two steps: (1) variables predictive of nonattrition were selected (as above) and a probit model on nonattrition was estimated, and (2) the inverse Mills ratio (a function of the probability that a given observation is selected into the sample) from this model was saved (Heckman 1979) and included as a control variable in the two subsequent procedures of predicting drug-free response status and then evaluating its clinical utility.

In developing a model predicting drug-free response, a similar two-step variable selection procedure was used. However, no variable selection at this stage, experimental treatment was not included as a possible predictor because it was only in the experimental treatment that drug-free response was possible. In addition, the inverse Mills ratio from the model on nonattrition was included at each step so that both variable selection and model estimation accounted for attrition.

A final estimation of the probit model on drug-free response status, corrected for attrition, optimizes the predictive contribution of the independent variables and in this way is likely to be somewhat overfitted to the data (an issue we address below). The resulting model was then tested for a possible cohort effect (none was found). Effect size estimates were converted into probabilities and are reported as the marginal effects of a one-unit change in an independent variable on the probability of being a drug-free responder (table 4).

We also conducted a post hoc Bayesian analysis to estimate the proportion of the entire experimental group likely to be drug-free responders. This involves adjusting the observed (not lost to followup) proportion of drug-free responders for their higher than average likelihood of not being lost to followup in order to create an estimate of the proportion of likely drug-free responders that was applicable both to the entire experimental group and to a new sample.

The accuracy of the model predicting drug-free response was assessed in two ways: first, in its observed accuracy when applied to the data, and second, through 250 bootstrap reestimates of the model using a sampling with replacement technique. The bootstrap estimates provide a more plausible estimate of the accuracy of the predictive model when applied to a new sample (table 5).

Stage four. Assessment of whether assignment to predicted treatment resulted in superior outcomes was conducted using an analysis of covariance on the composite outcome scale score at the 2-year followup. The pri-

Table 3. Comparison of baseline characteristics for retained (*n* = 129) versus lost to followup (*n* = 50) subjects

Variable	Retained ¹	Lost ¹	t value	p value ²
Age	21.8	21.7	0.20	ns
Goldstein Adolescent Social Competence Scale ³	21.9	19.5	1.92	0.06
Venables and O'Connor Paranoia Scale ⁴	13.3	11.5	2.38	0.02
Hollingshead Socioeconomic Scale ⁵	41.3	45.6	-1.39	0.17
Confusion ⁶	0.80	0.67	1.15	0.13
Stressful precipitants	0.66	0.58	0.92	ns
Previous hospitalization	0.86	0.34	0.21	ns
Schizoid personaliv	0.65	0.33	2.33	0.02
Prior work experience	0.84	0.81	0.43	ns
Some college ⁶	0.52	0.54	-0.23	ns
Insidious onset (schizophrenia v. schizophreniform disorder)	0.39	0.51	-1.41	0.16
Number of cardinal symptoms of schizophrenia ⁷	5.4	5.2	1.56	0.12
Certainty of schizophrenia diagnosis. ⁸	6.1	5.9	1.10	ns
Global Psychopathology Scale ⁹	5.2	5.2	-0.07	ns

Note.-ns = nonsignificant.

¹Group mean scores.

²Only p values < 0.20 are reported; others are indicated as ns.

³Goldstein Adolescent Social Competence Scale (Rodnick and Goldstein 1974; range: 7-35, higher is greater competence).

⁴Venables and O'Connor (1959) Paranoia Scale (range: 5-25, higher is more paranoid).

⁵Hollingshead (1957) Socioeconomic Scale (range: 11-77, higher is lower status, *n* = 159).

⁶Second cohort only (*n* = 100: 85 retained, 16 lost to followup).

⁷Includes thinking or speech disturbances, catatonic motor behavior, paranoid ideation, hallucinations, delusional thinking other than paranoid, blunted or inappropriate emotion, disturbance of social behavior and interpersonal relations (Cole et al. 1964).

⁸Certainty of Schizophrenia Scale (Mosher et al. 1971; range: 1-7, higher is more certain).

⁹Global Psychopathology Scale (Mosher et al. 1971; range: 1-7, 1 = not ill, 4 = moderately ill, 7 = extremely ill).

Table 4. Predictors of "drug-free response" among experimental subjects (*n* = 68)¹

Variable	Marginal effect ²	p value
Age	0.05	0.03
Goldstein Adolescent Social Competence Scale ³	0.03	0.06
Number of diagnostic symptoms ⁴	-0.14	0.06

¹The overall probit model is evaluated with a chi-square statistic ($\chi^2 = 17.6$, *df* = 5, *p* = 0.003). Additional control variables include a missing indicator for the Goldstein scale and a variable representing the probability of nonattrition.

²Marginal effects are reported as the estimated effect of a one-unit change in the independent variable on the probability of being a drug-free responder.

³Rodnick and Goldstein 1974.

⁴Number of diagnostic symptoms (thinking or speech disturbances, catatonic motor behavior, paranoid ideation, hallucinations, delusional thinking other than paranoid, blunted or inappropriate emotion, disturbance of social behavior and interpersonal relations; Cole et al. 1964, National Institute of Mental Health-Psychopharmacology Service Center study).

Table 5. Assessing the accuracy of predicting "drug-free response" among experimental subjects (n = 68)

	Observed model accuracy ^a	Bootstrapped accuracy (mean)	Bootstrapped accuracy (median)	Bootstrapped 95% confidence interval
Proportion correct	0.79	0.77	0.78	0.65,0.90
Sensitivity	0.72	0.69	0.71	0.43,0.88
Specificity	0.85	0.82	0.83	0.58,0.98
Positive predictive power	0.78	0.75	0.75	0.58,0.92
Negative predictive power	0.80	0.79	0.78	0.64,0.90

^aModel accuracy figures were calculated from the classification table of the probit model on drug-free response among experimental subjects (n = 68, correct positives = 21, false positives = 6, correct negatives = 33, false negatives = 8).

mary variable of interest in this analysis was the interaction term representing the treatment of predicted drug-free responders at Soteria. Control variables were experimental versus control treatment, predicted drug-free response (yes or no), diagnosis of schizophrenia (yes or no, incorporated because of the higher proportion of individuals with this diagnosis in experimental treatment among subjects not lost to followup, 0.47 vs. 0.29, $t = 2.055$, $df = 124$, 2-tailed $p = 0.042$), days at risk for rehospitalization, and a variable representing the probability of nonattrition (Heckman 1979). Although it has sometimes been suggested that socioeconomic status is related to outcome in schizophrenia, it is not related here ($r = -0.04$, p non-significant [ns]), and therefore was not included as a statistical control. This evaluative ANCOVA procedure was conducted in three ways to represent the possible range of sampling variability in this assessment of the possible benefit of treating predicted drug-free responders in experimental facilities (1) by applying the predictive model to the full available sample, (2) by applying the 250 bootstrapped predictive models to the full available sample, and (3) by applying the 250 bootstrapped predictive models to 250 bootstrapped resamplings of the available sample (table 6). These procedures increase sampling variability in steps as a way to describe a range of benefit estimates for treating predicted drug-free responders in the experimental facilities. For the first of these procedures

Results

The subgroup of experimentally treated individuals who did not use antipsychotic medications during the followup period was observed to be 42.6 percent of those not lost to followup (29 of 68). These designated drug-free responders were functioning quite well at the 2-year followup point. Less than a third had been readmitted to 24-hour

care (9 of 29), with those readmitted averaging stays of less than 20 days during the followup period. On the whole these individuals exhibited low levels of psychopathology and good psychopathology improvement scores. Eighty percent were living independently or with peers; they were working, on average, between part- and full-time (60% worked at least part-time) and had good social functioning scale scores. On the composite outcome scale, this group was functioning at eight-tenths of an SD above the mean for all study participants (table 7).

The Bayesian estimate of the unconditional probability of drug-free response in the experimental group is 31.8 percent. This estimate is the product of three factors: the observed proportion of drug-free responders among experimental subjects not lost to followup (29 of 68 = 0.4265), the unconditional probability of attrition (50 of 179 = 0.7207), and the inverse of the estimated probability of nonattrition for those not lost to followup (from the probit model on nonattrition: $1/0.9655$).

Because a large proportion of experimentally treated individuals used no antipsychotic medications during the followup period, these individuals were excluded in a comparison of days of antipsychotic medication use during the followup period in experimental and control groups. The experimentally treated individuals who used some antipsychotic medications during the followup period did not use medications significantly less frequently than control subjects (experimental mean = 428.1 days, control mean = 449.4 days, mean difference = -21.3, $t = -0.42$, standard error = 50.8, $df = 96$, $p = 0.68$, 95% CI for mean difference: -122.2, 79.6). This points to a reduction in the frequency of medication use in the experimental group for only those who responded to milieu treatment during the initial 45-day period (when medication use was experimentally controlled) rather than for all experimentally treated individuals.

In preparation for developing a model to predict drug-free responders, a probit model predicting nonattrition (n = 129 of 179) from the study was estimated as a first step in

Table 6. Estimated advantage of assigning predicted "drug-free responders" to Soteria treatment (n = 129)¹

	Composite outcome~ (mean)	Composite Outcome2 (median)	p value	95% confidence Interval
ANCOVA	0.64	NA	0.093	-0.10, 1.37
First bootstrap ⁴	0.51	0.51	< 0.055	0.13, 0.85
Second bootstrap ⁶	0.38	0.43	ns ⁷	-0.60, 1.30

Note.-ANCOVA = analysis of covariance; NA = not applicable; ns = nonsignificant.

¹All models control for experimental treatment, predicted drug-free response status, insidious onset schizophrenia, days at risk for relapse, missing schizophrenia information, days at risk for rehospitalization, and differential attrition by treatment.

²Composite outcome scale is in standard deviation units.

³Power to detect significant differences (11 - 0) = 0.40.

⁴The first bootstrap evaluation uses 250 resampled estimates of the model predicting drug-free response and evaluates each of them for the effect of treating predicted drug-free responders at Soteria in the full sample available at the 2-year followup (n = 129).

Probability is estimated from the observation that the 95 percent confidence interval does not include 0.

⁶The second bootstrap evaluation uses 250 resampled estimates of the model predicting drug-free response and evaluates each of them for the effect of treating predicted drug-free responders at Soteria in 250 resamplings from the subjects available at the 2-year followup (n = 129).

⁷Probability is estimated from the observation that the 95 percent confidence interval contains 0.

Table 7. Two-year mean outcome scores: Comparing experimental drug-free responders (n = 29), non-drug-free responders (n = 39), and control subjects (n = 61)

Outcome variable	Experimental Treatment		
	Drug-free	Drug	Control
Composite outcome scale (SD units)	0.82	-0.52	-0.06
Global Psychopathology Scale ¹	2.05	3.03	2.77
Improvement in psychopathology ²	1.83	2.19	2.28
Readmission to 24-hr care	0.31	0.92	0.69
Number of readmissions	0.48	2.46	1.90
Days in readmission	6.17	108.80	60.16
Living independently or with peers	0.80	0.22	0.33
Working (approximate hrs/wk)	17.60	10.50	14.20
Social functioning ³	2.04	1.88	1.89

Note.-SD = standard deviation.

¹Global Psychopathology Scale (range 1-7, higher is more symptomatic).

²Global improvement in psychopathology (coded 1-7, 1 = much improvement, 4 = no change, 7 = much worse).

³Social functioning subscale of the Brief Follow-up Rating Scale (range 0-3, higher is better social functioning).

the process of correcting subsequent estimates for attrition bias. This model indicates that experimental subjects are more likely (16.9%, p = 0.007) to remain in the study, as are individuals with schizoid personality development (20.1%, p = 0.010), and individuals with higher socioeconomic status are marginally more likely to remain (0.4% per SES point, p = 0.091; see Bola 1998 for details).

In developing a model predicting drug-free response among experimental subjects, the stepwise approach (described above) identified three variables as predictive (age; score on the Goldstein Adolescent Social Competence Scale; and number of cardinal symptoms of schizo-

phrenia [Cole et al. 1964]). This model indicates that older individuals (at onset) are 5 percent per year of age (p = 0.03) more likely to be drug-free responders, individuals with higher Goldstein scale scores are 3 percent per point (p = 0.06) more likely to be drug-free responders, and individuals with more diagnostic symptoms are 14 percent per symptom less likely to be drug-free responders (p = 0.06; table 4).

When evaluated in this sample, the model predicting drug-free response status achieves a 79 percent accuracy rate, with sensitivity of 72 percent, specificity of 85 percent, positive predictive power of 78 percent, and negative predic-

tive power of 80 percent. When evaluated with a bootstrap resampling procedure that introduces additional sampling variability to more closely approximate the model's predictive accuracy in another sample, the assessment scores for the predictive model drop a few percentage points (table 5). In these 250 resamplings, the median proportion of drug-free responders was 0.43 (95% CI- 0.32,0.54).

Assessment of the likely influence of treating predicted drug-free responders in Soteria facilities produced a positive, medium-sized effect (0.64, in SD units) that was not statistically significant ($p = 0.09$), although statistical power was limited ($1-P = 0.40$). The first of two bootstrap evaluations assessed this same question by applying each of 250 predictive models estimated in the experimental subjects to the sample available at the 2-year followup point, yielding a somewhat smaller but still medium-sized effect (0.51) that was statistically significant ($p < 0.05$; footnote 4 in table 6). In the procedure adding additional sampling variability by applying each of the 250 predictive models to 250 resamplings of the subjects available at followup, a slightly smaller effect size (0.38) resulted, and it was not statistically significant. These results are presented in table 6.

Study Limitations

This secondary analysis of an older study of first and second episode psychosis has several unavoidable limitations, including the consecutive admission space-available assignment protocol in the first cohort (making this a quasi-experimental study), the use of *DSM-H* criteria for diagnosing schizophrenia (leading to the possible inclusion of some affective psychoses), and the use of older instruments that are rarely used today. In addition, because it was often possible to identify which treatment group a subject was in, there is a possibility of rater bias in measurements requiring a subjective judgment. Because followup treatment was not controlled, there was a certain amount of treatment crossover, with a few former Soteria clients being readmitted to the hospital. Thus the project had elements of both a quasi-experimental treatment comparison and a naturalistic followup study. The model developed here to assess predictors of attrition is only 79 percent accurate in identifying the followup status of subjects and hence may not fully remove the bias related to attrition in predicting drug-free response to Soteria treatment. In addition, the inclusion of tardive dyskinesia, client satisfaction, social network, and additional family measures would also have strengthened the study, as would more frequent followup measurement and a longer followup period.

Despite these limitations, we believe that the Soteria data can still make important contributions to knowledge

in the field. In particular, we note that this is one of only a few available data sets in which a quasi-experimental comparison of intensive psychosocial treatment was followed up for 2 years, making it all the more valuable. The measures used were state of the art at the time, and many were adopted from the NTfMH psychopharmacology treatment group and in consultation with NEVIH staff. Selection criteria were rigorous, requiring an independent diagnosis of schizophrenia from three diagnosticians, a score of 5 or more on a 7-point certainty of schizophrenia measure, and at least four of the seven cardinal symptoms of schizophrenia (only two were required by the original Cole et al. 1964 study). A 3-day waiting period at the beginning of the study was also imposed to screen out drug-induced psychoses. In spite of these limitations and the qualifications that thereby must be applied to the conclusions drawn here, we think that the results of this study clearly relate to the contemporary question of optimal individualized treatment, to concerns of minimizing antipsychotic medication-induced side effects through minimal use strategies, and to the ongoing question of how to reduce heterogeneity in schizophrenia.

Discussion

Results from the present investigation find the size of the subgroup of drug-free responders, at 43 percent of subjects completing the 2-year followup, to have been somewhat larger than would be expected from the literature. There are three immediate reasons why a larger than expected subgroup might have been observed. First, this study included only first and second episode clients. Even though married and older individuals were excluded, first and second episode clients can be expected to have, on the whole; somewhat better outcomes than those of a more chronic population. Second, the 43 percent observed to be drug-free were not lost to followup. We estimate that the proportion of drug-free responders would likely be closer to 32 percent if the lost-to-followup subjects in the experimental group were able to be included. Third, this study compared antipsychotic drug treatment in the hospital with a supportive therapeutic milieu in the community, not with placebo treatment in the hospital. If therapeutic milieu treatment in the community is more effective than placebo treatment in the hospital, the drug-free responder subgroup in this study would have been expected to be larger than in studies comparing drug to placebo treatment in the hospital (e.g., 38% placebo response at 6 weeks in the NIMH-PSC study [Cole et al. 1964]). On the other hand, because we were observing individuals being maintained in the community without antipsychotic medication during a 2-year period, we might have expected a smaller subgroup than studies having a shorter followup period.

However, a recent report from a Finnish first episode intensive psychosocial approach reports an almost identical proportion (42.9%) of individuals maintained in the community without antipsychotic medications over a 2-year period (Lehtinen et al. 2000). This suggests that a rather large proportion of drug-free responders can be expected in first episode schizophrenia spectrum psychosis when intensive psychosocial interventions are provided.

Excluding individuals who received no medication during the followup period, the mean number of days of medication use was nearly the same in the experimental and control groups (428 vs. 449 days). This indicates that, rather than creating an across-the-board reduction in antipsychotic medication usage for all clients, initial treatment at experimental facilities appears to facilitate a natural selection of individuals who do not need antipsychotic medications for the resolution of their psychoses. For individuals not receiving antipsychotic medications, a reduced risk for tardive dyskinesia and other medication-induced side effects would likely continue beyond the 2-year study period.

In our study, observed drug-free responders were functioning at the 2-year followup point at a level that was considerably above clinical expectations for schizophrenia clients, and perhaps for schizophreniform clients as well. The outcomes were desirable: 60 percent working, 80 percent living alone or with peers, and less than a third readmitted to 24-hour care for a short stay (6 days on average). However, the question arises as to whether these desirable results were due to good-prognosis clients doing well irrespective of treatment or to an interaction of experimental treatment and good prognostic status. Indications from our evaluation of treating predicted drug-free responders in Soteria suggest the second answer (discussed below): that this subgroup of individuals may fare better with psychosocial treatment in the absence of medications.

The effort here to predict drug-free responders using baseline information employed one diagnostic and two prognostic variables, each exerting influences in the direction expected from the literature. Having fewer symptoms diagnostic of schizophrenia (Cole et al. 1964), being older, and having a higher score on the Goldstein Adolescent Social Competence Scale (Rodnick and Goldstein 1974) all increased the likelihood of an individual being a drug-free responder. It was striking that the variable indicating insidious onset schizophrenia was not a significant predictor of drug-free response among these first and second episode clients. While this may be partly a function of the limited power available in a small sample, it may also point to a better-than-expected response of individuals with schizophrenia to the intensive psychosocial intervention provided in Soteria. We consider differential response to Soteria treatment for schizophreniform disorder and

schizophrenia subjects in a subsequent paper (Bola and Mosher, in press).

The median bootstrapped accuracy of the model predicting drug-free response (78%) offers a 21 percent improvement over simply predicting all individuals to not be drug-free responders (57%). In addition, the positive predictive power (ability to correctly identify the drug-free responders) of 75 percent offers a large increase (from 0%) in identifying individuals who might respond to psychosocial treatment without medications, when compared to the common clinical practice of medicating all schizophreniform and schizophrenia clients. While use of this predictive model will require cross-validation, these results suggest that it may be possible to develop a model predicting drug-free response through the use of modern multivariate statistical methods. This cross-validation should initially proceed with existing data, to test the model developed here and to evolve a more robust set of predictors, prior to prospective assessment.

In this study, individuals predicted to be drug-free responders exhibited moderately better outcomes when treated in experimental facilities. While this beneficial effect was only statistically significant in one of three assessments, the magnitude of the benefit (range, m SD: 0.38, 0.64) is of a medium effect size and therefore appears to be clinically important. This interpretation is consistent with, for example, the earlier findings of Goldstein (1970), Carpenter et al. (1977), and Rappaport et al. (1978), each suggesting the existence of a subgroup that does better without medications.

In this line of research, developing a model to predict drug-free responders, additional consideration will need to be given to the consequences of both kinds of predictive errors. (We are indebted to Lisa Dixon for this suggestion.) For example, falsely predicting a drug-free responder would mean withholding medications during a psychosocial treatment trial period of 4-6 weeks and then, when the individual fails to respond, instituting drug treatment. There are important and reasonable concerns for the safety of human subjects in this kind of research. However, recent indications are that short-term withholding of medications can be done without negatively altering the course of psychotic illness (Johnstone et al. 1999). In addition, rigorous guidelines for minimizing risks to human subjects, as well as a discussion of the importance of drug-free research for knowledge development, have been presented in some detail by Carpenter (1997, 1998).

Because current knowledge is inadequate to identify drug-free responders, nearly all individuals with psychosis are medicated. Therefore, clinical practice makes all possible false negative errors (the error of medicating those who do not need medications, 43% in this sample) and never makes false positive errors (the error of not medicating

those who need medications, 0% in this sample). This, of course, is only one way to manage the risk-benefit continuum. In our view, there is another way that may yield greater benefits with some additional, different, and perhaps manageable risks. In part, this assessment derives from a sense that the side effect profiles of both conventional and atypical antipsychotic medications deserve greater weighting in medication decision making. Certainly, a more selective use of antipsychotic medications targeted to client characteristics involves an increase in the risks associated with falsely predicting that an individual does not need medication and a decrease in the risks associated with medicating individuals that may not need medication.

In a comparison of the predictive accuracy of the model developed here with standard clinical practice, some areas of contrast emerge. The predictive model produces both types of errors, the false negative and the false positive. Using the medians from our bootstrapped estimates of predictive accuracy, the model's false negative error rate is 12 percent. Therefore, use of this predictive model would result in unnecessarily medicating an estimated 12 percent of clients.

On the other hand, false positives occur when the model predicts an individual to be a drug-free responder and he or she is not. This type of error is estimated to occur in 10 percent of cases. In other words, by using this predictive model we would fail to medicate about 10 percent of clients who would later be discovered to not respond without medications. The combination of these two types of error results in an overall error rate of 22 percent, reducing nearly in half the 43 percent error rate that (in this sample) would occur with the practice of medicating all subjects. This reduction in the overall error rate comes about, in part, through a willingness to accept some false positives.

The mental health field will, of course, need to carefully consider the risks and benefits inherent in this line of investigation. Because American society has become so litigious, clinicians are understandably concerned with the potential for lawsuits resulting from an unmedicated client who harms himself or another. Yet this concern should be balanced with a concern for the many early episode clients who may be receiving medication unnecessarily and who appear to have poorer outcomes as result.

We submit that it appears possible to develop guidelines to identify early episode clients not in need of antipsychotic medication when appropriate psychosocial interventions are provided. This line of investigation should, of course, be pursued with careful attention to minimizing risks to human subjects. Potential benefits include more favorable outcomes for drug-free responders when treated with intensive psychosocial interventions

with minimal or no antipsychotic medications and a reduction in the rates of medication-induced side effects. These goals are, of course, similar to those pursued in low-dose, targeted, and intermittent drug treatment strategies in the medication maintenance of chronic clients: improving the risk-benefit profile of medication treatment by reducing unnecessary medication use. On balance, we believe that the possible advances in scientific knowledge, and the subsequent improvements in individualizing treatment, warrant the risks inherent in this line of research. We also reiterate that the model developed here is a promising but preliminary step in an effort to prospectively identify an important subgroup of early episode clients. It should receive further testing and development before being considered a tool for clinical decision making.

Since the concept of schizophrenia was introduced by Bleuler (1908), the need to parse the heterogeneity of the "group of disorders" into naturally occurring subgroups has been recognized (e.g., Strauss and Bellack 1979). In this era of enthusiasm about the more favorable risk-benefit profiles of the newer atypical antipsychotic agents, we note that not all evidence points toward greater effectiveness (Geddes et al. 2000) of the novel antipsychotics and that their long-term risks are not yet fully understood (Perkins and Lieberman 1998). Because there is such a high degree of variability in the long-term course of schizophrenia disorders (Ciompi 1980b; Huber 1980; Harding et al. 1987), it seems only prudent to continue work toward identifying treatment-relevant subgroups (Carpenter and Heinrichs 1981). In this context, we think it especially important to pursue identification of individuals in early episodes of psychosis who may have more favorable outcomes when receiving intensive psychosocial intervention in an environment that minimizes the use of antipsychotic medications.

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Misguided Therapeutics

by William T. Carpenter, Jr., and Robert W. Buchanan

In *77te Divided Self* (1965), R.D. Laing made an important contribution to phenomenology and inspired a generation of wrongheaded thinking about the treatment of schizophrenia. The Soteria House project, initiated by Loren Mosher on his return from a visit to Laing's Kingsley Hall, was based on a concept of schizophrenia as an existential crisis to be resolved at a personal and interpersonal level. Disease models and antipsychotic medications were considered impediments to the creative resolution of a psychotic episode, although it was acknowledged that they were sometimes necessary for management. It was an interesting and daring approach to schizophrenia, most constructively construed as a psychosocial restitutive alternative to traditional hospital/medical treatment. However, in sentiment and presentation, the Soteria House model eschewed the medical model and expressed ideology-based negativity toward the use of antipsychotic medications. Previous reports have shown that the Soteria House model can serve as an alternative to hospitalization in selected patients (Mosher et al. 1975; Mosher and Merin 1978; Mosher et al. 1995), but the risks and benefits compared with traditional care are very difficult to evaluate. Bola and Mosher (this issue) present a new analysis of old data. They interpret this analysis to substantiate the view that a minority of persons who are early in their course of schizophrenia can recover without medication. Putting aside the definition of recovery for a moment, substantial improvement and favorable course of illness off medication was noted by Bleuler (1978) in his long-term followup study and was also observed on a research unit with off-medication protocols (Carpenter et al. 1977), in the Chestnut Lodge long-term followup studies (McGlashan 1987), and more recently in the Finnish "need specific" treatment model (Lehtinen et al. 2000). More remarkable is the Bola and Mosher conclusion that the quality of the recovery is superior to on-medication recovery. These data are relevant to current issues in schizophrenia treatment, but the interpretation and conclusions are flawed. We present an alternative interpretation,

Bola and Mosher observed that 43 percent of the patients who completed the 2-year study (approximately

32% of the intent-to-treat sample) recovered without medication and that those destined to recover without drugs actually did better than similar patients treated with antipsychotic drugs. If their interpretation is valid, then the implications are quite profound. Adverse effects of drugs could be avoided, recovery could be enhanced in a very significant proportion of first and second episode patients, and the patients most likely to benefit could be predicted with this picture?

1. Schizophrenia is a disease syndrome, and afflicted patients should be treated by clinicians who are informed about all relevant treatment interventions and are capable of integrating evidence-based therapeutic approaches. It is improper to withhold an effective treatment based on ideology. The biopsychosocial medical model (Engel 1977) provides a valid scientific approach for the integration of therapies drawn from different traditions and initiated at different levels of human function (Carpenter 1986). The Soteria House model is, in part, based on an anti-medication model and anti-disease model ideology. These are not valid models (Strauss and Carpenter 1981; Carpenter and Keith 1986), and invalid models should not be the basis for the diagnosis and treatment of this most severe of human illnesses. However, we would also note that biomedical reductionism has led to very substantial shortfalls in the integration of evidence-based psychosocial and pharmacological treatments. We believe that, partly because of inadequate resources, many front line mental health professionals are relatively uninformed and uninfluenced by scientific testing of psychosocial treatments. Conversely, many front line psychiatrists, often constrained by the systems that employ them, are in a drug-prescribing mode and fail to integrate psychosocial treatments that have been proven efficacious in symptom reduction and relapse prevention (Lehman and Steinwachs 1998).

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2. The Soteria House model has procedures for providing safe haven while natural improvement occurs and involves psychosocial treatment elements that may be efficacious. However, two things are not clear. First, could the model have been created without an anti-medical model ideology and without charismatic leadership? If either of these elements is important to the model, then it will not be able to be initiated or effective in most settings. This is, of course, already the fate of the Soteria House experiment. Second, to what extent is Soteria's effectiveness related to the withholding of antipsychotic medications? Would prudent drug therapy enhance or diminish outcomes? No data are presented to address this question, but the Bola and Mosher conclusion depends entirely on the answer to this question. Rather, two overall clinical care strategies are compared. The situation may be similar to our first targeted drug study where two strategies for maintenance treatment were compared. In the first study (Carpenter et al. 1987), targeted antipsychotic drug treatment combined with a psychosocial program was comparable to continuous medication combined with standard clinical care over a 2-year period. But the conclusion that targeted drug treatment was as effective as continuous medication at relapse prevention could not be inferred because the psychosocial treatment component differed between groups. The fallacy of such an inference is illustrated by the second study (Carpenter et al. 1990), in which targeted and continuous maintenance drug treatment groups both received the enriched psychosocial treatment. When the drug treatment effect was thus isolated, continuous maintenance treatment beat targeted drug treatment for relapse prevention.

3. The authors assert that outcome was more favorable in the drug-free responders because recovery took place off medication. We think the concept of recovery is misleading in this instance, because no evidence for recovery is presented. The study criteria for recovery was staying off drugs. This definition is in contrast to the usual medical definition of recovery. (i.e., absence of psychopathology and unimpaired functioning). This latter definition is a higher standard and more pertinent to the real-life concerns of patients than staying off antipsychotic drugs in a setting devoted to avoiding antipsychotic drug therapy. In the drug-free recovered group, social functioning averaged 2 on a 0-3 scale, work averaged about 18 hours per week, and global pathology averaged 2 on a 1-7 scale. This being noted, the off-medication cohort appeared to do quite well. Given that the worse-course patients fell off the wagon (and onto medication), it is an inevitable methodological artifact that the drug-free responders would be assessed as having the best outcome. While this appears to

The other problem with the Bola and Mosher interpretation is their method for determining which patients were likely to recover in the control group. Predictors of off-medication recovery were derived from the Soteria House cohort. Application of these predictors in any new sample of off-medication patients is likely to have weaker predictive power. The bootstrapping routines do not mitigate the problem of predictors being most effective in the cohort from which they are derived. Another consideration is that variables predicting good outcome off medication may not be the same as variables predicting good outcome in the standard treatment control group. If the predictors of best outcome were derived from the standard treatment group and then applied to the off-medication cohort, the bias would be reversed and recovery would probably appear to be better on medication. Finally, if a subgroup of patients did have a better quality improvement with Soteria House treatment, the cause would be unknown and might be any one element or several elements in the program. Identifying medication avoidance as the cause of good-quality improvement is speculation based on ideology.

The key question is whether the patients who did very well off medication would have done better or worse with the prudent use of medication. The study design does not address this question, and it is the answer to this question that is needed for clinical application.

In contrast to the discussion of the data presented by Bola and Mosher, we would offer the following interpretation of the study results:

1. First and second episode schizophrenia and schizophreniform psychoses are skewed toward good prognosis, and many cases achieve substantial improvement and course stability. A favorable course can be observed in the 2- to 5-year time frames of this and other studies (Johnstone et al. 1992; Scottish Schizophrenia Research Group 1992; Schmidt et al. 1995; Gupta et al. 1997; Vazquez-Barquero et al. 1999; Gitlin et al. 2001; Linszen et al. 2001), including a subgroup not requiring continuous medication. This is an important observation in the context of both the inaccurate view that schizophrenia routinely runs a downhill course and that unmedicated psychosis causes a deteriorating course (see Carpenter 1997 and Wyatt 1997 for a discussion of the hypothesis that psychosis is neurotoxic). However, recovery in schizophrenia is a concept requiring careful definition. The implications of a schizophrenia diagnosis are quite negative and prolonged even in early episode populations (Ram et al. 1992; Mojtabai et al. 2000).

2. Provision of safe haven, a traditional hospital function, can be provided in alternative settings (Stroul 1987). We do not believe hospital care is ill-advised, but it is only one component in the range of necessary services. Today, hospital care is limited and patients are routinely dis-

charged while still psychotic with no provision for safe haven. Homeless and jailed patients bear witness to this social injustice. Soteria House offered safe haven. We believe its proponents' tenacious adherence to an invalid ideology has prevented generalization of this potentially beneficial treatment approach with the perverse effect of impeding its integration into the formulary of evidence-based therapeutics. Born in the pharmacotherapy versus psychotherapy era, it requires very substantial modification in today's clinical care arena (Fenton et al. 1998). Other forms of psychosocial intervention have proven efficacious and effective in clinical trials. Nonetheless, a gap exists between therapeutic methods and residential/life support methods. Soteria House integrated these two elements, perhaps providing a unique treatment environment. pharmacotherapy, psychosocial therapy, and living support clinical care methods. The field has the challenge of developing and testing tripartite models. At this point in time, our failure in meeting this challenge is documented in the paucity of schizophrenia patients who receive the best evidence-based treatment even in the bipartite pharmacotherapy/psychosocial treatment model (Lehman and Steinwachs 1998).

3. The observation that a substantial subgroup of schizophrenia patients can do well off medication is of critical importance (1) in devising treatment strategies for medication-nonadherent patients; (2) in the risk-benefit evaluation of medication withdrawal in single episode patients; and (3) in the risk-benefit evaluation of targeted and very low dose maintenance treatment in patients who wish to avoid risks or dysphoric effects of medication. The observation is also relevant to considering the risks and safety measures important in evaluating medication-free research protocols and placebo-controlled clinical trials (Carpenter et al. 1997).

4. We do not view the current report as supporting the proposition that medication-free treatment is superior to the prudent use of medication in a subgroup of schizophrenia patients. Rather, we suspect that timely and conservative medication use may have been of benefit to the Soteria House drug-free responders. If elements of the Soteria House experience are specifically therapeutic, then it seems doubtful that greater length and intensity of positive psychotic symptoms creates the optimal circumstances for therapeutic response to these elements. In principle, we believe that the integration of pharmacotherapy and psychosocial therapies is a better clinical option (Carpenter 1986; Alanen 1997; Hogarty et al. 1997). We reject the drugs versus psychosocial therapy polemic.

A potential criticism of the Bola and Mosher report is that the issue in question has become irrelevant with the

introduction of second generation antipsychotic drugs. Neuroleptic 'neurotoxicity' issues gave saliency to the Soteria House anti-antipsychotic medication ideology. We believe that the issue of adverse drug effects remains of considerable concern today. Even with the reduction in extrapyramidal symptoms, tardive dyskinesia, and dysphoric affect associated with second generation antipsychotic drugs, there are still substantial problems with adherence. Furthermore, adverse effects on cardiovascular risk indexes, diabetes, and weight are a new basis for concern about the negative implications of long-term treatment beginning early in the course of illness. Issues concerning the optimal and prudent use of antipsychotic medications continue to be a challenge in schizophrenia therapeutics. But a greater challenge is delivering schizophrenia patients with clinical care, including a safe haven, restitutive care, quality of life support, and the best opportunity for a good functional outcome. Soteria House provided an early demonstration of an alternative to hospital-based care but chose ideology over influence and opposition over integration. Valuable lessons were lost and are not recaptured by the eloquent analysis or unsubstantiated conclusions now reported by Bola and Mosher (this issue).

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Clashing Ideologies or Scientific Discourse.

by John R. Bola and Loren R. Mosher

We appreciate the commentary provided on our article by Drs. Carpenter and Buchanan. We want to especially thank them for acknowledging the potentially profound implications of the hypothesis that there -may be a subgroup of early episode schizophrenia spectrum clients who fare as well or better receiving intensive psychosocial interventions while not being treated with antipsychotic medications. In our response to their commentary, we first address what we regard as distracting critique, then substantive issues, followed by a reiteration of the rationale and ongoing plan for our investigation. We conclude with a broader discussion of treatment-response subtyping as a method of developing knowledge to inform the individualization of treatment in schizophrenia.

Ideology and Polemics

In their critique of our article (Bola and Mosher, this issue), Carpenter and Buchanan refer to the Soteria project as engaging in "misguided therapeutics" based on an "invalid ideology." We do not know what "invalid ideology" means, but we realize that one unfortunate consequence of any treatment ideology is that it can become impervious to evidence. In this context, it seems that both an outright dismissal of antipsychotic medication use as well as an uncritical and universal prescription of these medications for all psychoses might be equally regarded as ideological positions. We advocate neither position but are interested in a meaningful scientific investigation of the critical issue of how best to individualize and optimize medication use and psychosocial treatments in early episode schizophrenia spectrum psychosis.

Carpenter and Buchanan also characterize our article as engaging in a "drugs versus psychosocial polemic." This is not our intent, and it does not reflect, in our opinion, the content of our discussion. Soteria used antipsychotic medications, albeit sparingly, during initial treatment (Mosher and Menn 1978a and b; Mosher et al. 1995), as does the ongoing Swiss adaptation of Soteria,

Soteria-Bem (Ciompi et al. 1992, 1993). We are interested in identifying "treatment-response subgroups" in early episode schizophrenia spectrum disorders as a way of individualizing treatment that leads, hopefully, to improved client outcomes and reduced adverse medication effects. In addition, there are likely to be other early episode subgroups requiring modified treatment regimens (Carpenter and Heinrichs 1981), including, perhaps, subgroups requiring medication.

The characterization of Mosher's Soteria study through comparison to R.D Laing's Kingsley Hall is also not accurate, in our opinion. This appears to be more of a "straw man" argument (associate Mosher with Laing, then attack Laing) than a real critique, particularly in view of the selective antipsychotic medication use in Soteria. Unfortunately, it also distracts readers, drawing attention away from the many issues raised in both our articles that are important to today's treatment of early episode schizophrenia spectrum disorders.

Main Issues

As we see it, Carpenter and Buchanan raise two central issues in response to our article:

1. The first issue arises from the misunderstanding that we "assert that outcome was more favorable in the drug-free responders *because* [italics added] recovery took place off medication" (Carpenter and Buchanan, this issue). Our conclusion is that there *may be* an identifiable subgroup of drug-free responders who *appear* to do better with Soteria-type treatment and minimal use of antipsychotic medications. Observed "drug-free responders" in Soteria did have quite good outcomes and were also spared possible adverse drug effects. They appear, as Carpenter and Buchanan note,

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to have been naturally selected as not "falling off the wagon." Our question is whether, as the literature suggests, the contours of this natural selection can be identified and used prospectively to inform treatment. In our view, this is one approach to "carving nature at the joints." Preliminarily, this appears possible because the one diagnostic and two prognostic criteria used in our model each exert influence in the **direction** suggested by the literature, and the model's accuracy is better than expected. Applying the "drug-free responder" model to both groups and comparing their outcomes provides a preliminary estimate of whether Soteria-type treatment of these individuals might be advantageous. The bootstrapping method introduces additional sampling variability to counteract the acknowledged circularity in this process, providing benefit estimates closer to what might be expected in a new sample. This analysis suggests a medium effect size benefit for Soteria treatment of predicted drug-free responders. We do not know if these patients had better outcomes in Soteria because they were not treated with medications. Perhaps they benefited most from the intensive psychosocial treatment. In our article, we raise the *hypothesis* that a subgroup of early episode clients may fare better with intensive psychosocial treatment and minimal use of medications, and we offer a *preliminary* assessment of its plausible viability. We agree with Carpenter and Buchanan that it is not possible to test this hypothesis with these data

(for reasons we detail below).

2. Carpenter and Buchanan then ask the next logical question of whether "prudent drug therapy (would) enhance or diminish outcomes" for this subgroup. This is a vitally important question. However, the answer to it is also unknown, and likely unknowable from the Soteria study for two reasons: (1) as Carpenter and Buchanan point out, there was no psychosocial plus medication group in the Soteria study (as there is, for example, in the Lehtinen et al. 2000 study, where the psychosocial-only group had superior outcomes), and (2) it is not scientifically valid to test a hypothesis in the same data that gave rise to it (because the reasoning would be circular). We do think that this question is ultimately testable, but, in the interest of minimizing risks to human subjects, a prospective evaluation should probably wait for the development of a more robust set of subgroup selection criteria.

Are There Drug-Free Responders? The question of whether there exists a "drug-free responder" subgroup in early episode psychosis has a long history in the literature. We did not generate this question but are attempting, in what seems an uphill battle, to investigate it.

Unfortunately, over the past 50 years the question has received little empirical attention and therefore remains unanswered. We do think that this question, along with many other subgroup and individualization of treatment questions, deserves additional attention in the context of developing knowledge to inform the individualization of treatment.

Why investigate this question? From our perspective, there are five reasons that together form a rationale for investigating the possible existence of a "drug-free responder" subgroup in early episode schizophrenia spectrum psychosis:

1. *Not all clients benefit from antipsychotic medications.*

Treatment resistance to conventional antipsychotic agents is estimated in the range of 20 to 40 percent (Hellewell 1999). Although we know of no estimates of medication treatment resistance specific to early episodes, in the early National Institute of Mental Health multisite study (Cole et al. 1964), after 6 weeks approximately 25 percent of medicated subjects were *minimally* improved or worse (p. 252, figure 2), and 40 percent were moderately ill or worse (p. 253, figure 3). Noncompliance with conventional antipsychotics is estimated at 41 to 55 percent (Fenton et al. 1997). Improved compliance with atypical antipsychotics is generally assumed (e.g., Lieberman 1996) but has not yet been established (Wahlbeck et al. 2001).

2. *Antipsychotic medications have significant adverse effects.* Conventional antipsychotic medications have well-known short- and long-term adverse effect profiles (Popp and Trezza 1998). While atypical antipsychotic agents have a relatively more benign short-term side effect profile (Worrel et al. 2000), not enough time has passed to rule out the emergence of additional long-term toxicities. Recall that the existence of tardive dyskinesia was still being debated in the early 1980s (Crow et al. 1983), more than 30 years after the introduction of conventional antipsychotics. In addition, there is accumulating evidence of structural brain changes induced by antipsychotic medications (e.g., Madsen et al. 1998), excessive weight gain in up to 50 percent of long-term recipients of atypical antipsychotics (Baptista 1999), and a recently reported association between atypical antipsychotics and diabetes mellitus (Sernyak et al. 2002).
3. *Some early episode clients appear to do as well or better without medications* (see a summary of this literature in Bola and Moshier, this issue). For example, Carpenter and colleagues (1977) conducted a quasi-experimental treatment comparison on the treatment of acute schizophrenia without drugs in which 55 percent of National Institutes of Health

(NIH) subjects (27 of 55) received no antipsychotic medications. They report: "The 22 NIH patients receiving medication and the 27 drug-free patients had similar outcomes at one year" (p. 14), and the NIH group as a whole "demonstrated a small but significantly superior outcome" (p. 14) at one year. The authors conclude: "We have demonstrated that failing to use neuroleptics during an acute psychotic episode does not necessarily result in a disadvantageous course and outcome, and it may have some advantages" (p. 10). Rappaport and colleagues (1978) reported that "many unmedicated patients showed greater long-term improvement, less psychopathology at follow-up, fewer rehospitalizations and better overall function in the community than patients who were given chlorpromazine while in the hospital" (p. 100). May and colleagues (1981) reported: "The initial successes from milieu therapy functioned over the follow-up at least as well, if not better, than the successes from the other treatment" (p. 783).

4. *The potential benefits from this investigation are significant.* If a "drug-free responder" subgroup of early episode schizophrenia spectrum clients with comparable long-term outcomes to drug-treated subjects exists and can be prospectively identified, these individuals can be spared the adverse effects of medication without loss of benefit. If a subgroup exists that has had better long-term outcomes when not drug treated, then these individuals might have both benefits: better outcomes and the absence of adverse drug effects. One of these possibilities seems likely [to.us](#), because a preponderance of the few available early episode quasi-experimental or random drug versus psychosocial/nondrug studies report comparable or better long-term outcomes in the non-drug-treated groups (Schooler et al. 1967; Carpenter et al. 1977; Rappaport et al. 1978; Matthews et al. 1979; Ciompi et al. 1993; Lehtinen et al. 2000). In addition to possible benefits for future clients from developing knowledge that may assist in heterogeneity in schizophrenia.
5. *The risks inherent in this investigation appear manageable.* Carpenter and colleagues (Carpenter 1997; Carpenter et al. 1997) have suggested protocols for conducting medication-free research that minimize risks to human subjects, including appropriate patient selection, careful informed consent procedures, use of the shortest possible drug-free period, and prior specification of criteria for instituting drug treatment if inadequate response or clinical deterioration ensues. Carpenter (1997) also clarified the rationale to "justify

the participation of patients" (p. 14), concluding that "off-medication and placebo control studies can be conducted without adversely affecting the longer-term course of illness" (p. 14).

From a cost-benefit perspective, both for clients and for the field, this rationale appears to justify, and perhaps to compel, rigorous and careful investigation into the existence of a "drug-free" subgroup of early episode clients for whom the risks of drug treatment may outweigh its benefits.

How to Proceed? We have proposed cross-validating and evolving the preliminary set of predictors (Bola and Mosher, this issue) of a possible "drug-free responder" subgroup using additional existing early episode studies. In this endeavor, we have received agreement from Dr. Ciompi (Ciompi et al. 1993) and from the Finnish study group (Lehtinen et al. 2000) to use their 2-year outcome data. When a reasonably robust set of predictors is developed, a prospective three-group (medications with usual care, medications plus psychosocial treatment, psychosocial treatment only) comparison study, incorporating rigorous protocols to protect client safety (following suggestions outlined in Carpenter 1997 and Carpenter et al. 1997), might well answer the question of whether prudent drug treatment combined with psychosocial intervention enhances outcomes for this subgroup. At that point we might truly be able to decide between the conclusions of May and colleagues (1981) that this subgroup consists of "good prognosis patients who might do well in any case" (p. 783), or that of Rappaport and colleagues (1978) that there are "schizophrenics for whom drugs may be unnecessary or contraindicated" (p. 100).

Heterogeneity in Schizophrenia

Heterogeneity has long created difficulties for advancing scientific knowledge in schizophrenia research, yet its reduction is critical, because the establishment of diagnostic validity requires homogeneity of research groups (Robins and Guze 1970). Developing knowledge that reduces heterogeneity in schizophrenia also has the potential to assist in individualizing treatment, and thereby to help improve client outcomes. Numerous approaches to reduce heterogeneity in schizophrenia have been suggested and investigated over the last century, including grouping by description, course, prognosis, mathematical algorithms, biological characteristics, genetic markers, and treatment response. In medicine, treatment response has assisted in discriminating different clinical entities and thus contributed to their validation (Guze 1977; Kendell 1989).

Treatment-Response Subtyping. An empirical approach to subtyping on the basis of patterns of clinical response to treatment has been described by Carpenter and Heinrichs (1981). That article provided clinical descriptions of various treatment-response subtypes that might better receive some variation in treatment rather than the "standard treatment approach to all schizophrenic patients (present-day emphasis on long term antipsychotic drugs)" (p. 113). Among the possible groups not needing long-term antipsychotic treatment are patients with brief psychotic reactions, good-prognosis nonparanoid patients, noncompliant patients, patients in low-expressed-emotion environments, patients with neurological risk, and poor medication responders. In addition, paranoid and poor-prognosis patients along with those with an established episodic pattern of illness probably should receive long-term medication (Carpenter and Heinrichs 1981). Carpenter and colleagues (1997) recently delineated several types of research questions appropriate for medication-free research, including several of the treatment-response type. To these questions related to identifying candidates for medication withdrawal, we add the preexisting and still unanswered question, Who may not need medications in the first place?

One-Size-Fits-All Versus Individualized Treatment Planning

In our view, some of the recent emphasis on developing and disseminating best practice models runs the risk of prescribing one-size-fits-all interventions based on "best evidence." This can occur when "best practice guidelines" recommend that all similar clients receive the intervention that has been demonstrated to be, *on average*, superior to others (e.g., Lehman and Steinwachs 1998). While "evidence based" research integration methods offer a great improvement over unsystematic literature reviews, as of yet they primarily provide evidence for the best *average* treatment, not the best *individualized* treatment. In order for individualization of treatment knowledge to develop, the field will need to address questions such as these: Is it possible to develop knowledge of expected individual outcomes for a range of treatment options, and in which situations are expected individual outcomes significantly better than expected group outcomes?

Developing Knowledge for Individualizing Treatment

Two inductive and one deductive approaches suggest themselves in the pursuit of knowledge to inform the individualization of treatment. The literature in psychology

and education on aptitude by treatment interaction (ATI; e.g., Cronbach and Snow 1977; Stenberg 1996; Fisher et al. 1999) suggests a reformulation of the various treatment-response subgroup questions (above) as a search for "prototypes" (Snow 1991). According to Snow, prototypes are "bundles of person and treatment variables that reflect .

successful person-treatment interaction" (1991, p. 215).

Multivariate inductive methods can also serve this line of inquiry. The use of large existing, well-designed studies should assist in suggesting individual interactions and "complex aptitude complexes" (Snow 1991, p. 214) for

further investigation. This type of analysis can yield preliminary "best fit" multivariate estimates of outcome for an individual client for *each* treatment. Refinement of individual treatment outcome estimates can lead to prospective comparison of random assignment versus "estimated best treatment" assignment and result in greater understanding of how best to individualize treatment (Leshner and Burke 1991) than can be achieved through the use of random assignment methods alone.¹

As a complement to these two inductive empirical approaches, pursuit of a deductive approach is also desirable. Using theory to suggest plausible causal mechanisms for interactions of aptitude (client characteristic) and treatment informs the development of appropriate measures and research designs for testing the emerging hypotheses. Effectiveness of an individualized treatment may well be a "function of the degree of congruence between the causal relations relevant to the client's behavioral problem and the causal relations targeted by the treatment" (Haynes et al. 1999, p. 456). Systematically addressing measurement reliability and validity issues (e.g., Fisher et al. 1999) reduces measurement error and its pernicious consequences. Prior identification of hypotheses and statistical evaluation procedures enables a priori power calculations for a range of possible effect sizes.

In concert, these approaches to addressing heterogeneity in schizophrenia may lead us beyond polemics, on a path to developing knowledge for the individualization of treatment that will help clients achieve better outcomes. Collaboration between the type of clinical research we propose and basic research (e.g., biological markers, functional neuroimaging) may help avoid a "silent spring" where burgeoning high-tech knowledge remains unlinked to descriptive psychopathology and clients as individuals (Andreasen 1998). Along the way we might parse some heterogeneity from the concept of schizophrenia, develop theory that variously applies biopsychosocial concepts to different manifestations of the illness, and further our understanding of etiology and pathophysiology.

¹ A more detailed report on this problem is being prepared in collaboration with Leonard S. Miller, University of California at Berkeley.

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