

Factors Involved in Outcome and Recovery in Schizophrenia Patients Not on Antipsychotic Medications: A 15-Year Multifollow-Up Study

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Abstract: This prospective longitudinal 15-year multifollow-up research studied whether unmedicated patients with schizophrenia can function as well as schizophrenia patients on antipsychotic medications. If so, can differences in premorbid characteristics and personality factors account for this? One hundred and forty-five patients, including 64 with schizophrenia, were evaluated on premorbid variables, assessed prospectively at index hospitalization, and then followed up 5 times over 15 years. At each follow-up, patients were compared on symptoms and global outcome. A larger percent of schizophrenia patients not on antipsychotics showed periods of recovery and better global functioning ($p < .001$). The longitudinal data identify a subgroup of schizophrenia patients who do not immediately relapse while off antipsychotics and experience intervals of recovery. Their more favorable outcome is associated with internal characteristics of the patients, including better premorbid developmental achievements, favorable personality and attitudinal approaches, less vulnerability, greater resilience, and favorable prognostic factors. The current longitudinal data suggest not all schizophrenia patients need to use antipsychotic medications continuously throughout their lives.

Key Words: Antipsychotic medications, schizophrenia, outcome, recovery and psychosis, longitudinal 15-year follow-ups, unmedicated patients, prognostic factors.

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The current longitudinal research studies (a) potential differences in functioning, assessed over a multiyear period between patients with schizophrenia who are not on antipsychotic medications versus those on antipsychotics, and (b) if schizophrenia patients not on medications are functioning adequately, which types function adequately without antipsychotics, and what factors influence their adequate functioning? Many investigators have emphasized the importance of

determining which types of schizophrenia patients can function adequately when off antipsychotics for a prolonged multiyear period (Bola and Mosher, 2002; Bola et al., 2006; Fenton and McGlashan, 1987; Gilbert et al., 1995; Harrow et al., 2005b). The importance of determining characteristics which might allow some to go off antipsychotics with partly successful outcomes has been increased by research suggesting the potential side effects of long-term treatment with antipsychotics and data suggesting some similarity of the treatment response to both first and second generation antipsychotics (Hunter et al., 2003; Lewis et al., 2006; Lieberman et al., 2005; McEvoy et al., 2006; Stroup et al., 2006; Wahlbeck et al., 1999).

Multiple carefully controlled efficacy studies and other effectiveness studies of both first- and second-generation antipsychotic medications have assessed the value of antipsychotics (Davis et al., 2003; Gilbert et al., 1995; Hogarty et al., 1974; Janicak et al., 2001; Kane et al., 1982; Lieberman et al., 2005; Moncrieff, 2003; Schooler et al., 1980). On balance, the majority of these studies are positive for antipsychotics, although potential side effects for first-generation antipsychotics (tardive dyskinesia, apathy/sluggishness, depression, etc.) and second-generation antipsychotics (weight gain, diabetes) can present problems (American Diabetes Association, 2004; Carpenter, 1997; Haddad, 2004; Harrow et al., 1994; Lieberman et al., 2005; Marder et al., 1991; Seeman and Tallerico, 1999). To counter these problems, some major investigators have explored alternate approaches to facilitate treatment effectiveness, including withdrawing, tapering, or targeting the use of antipsychotics (Baldessarini and Viguera, 1995; Bola, 2006; Bola and Mosher, 2002; Carpenter, 1986; Herz et al., 2000; Marder et al., 1991). Associated with studies in this area, the issue of the relative safety of periods off medication have been addressed by Carpenter et al., (1997) and in an important article by Bola (2006) followed by commentaries. A problem which arises is that many positive studies on antipsychotics are based on an important population of patients, those involved in clinic treatment and clinic settings. However, after acute hospital treatment, when these patients leave the hospital, not all patients originally treated with antipsychotic medications continue on these medications (Lieberman et al., 2005). Studies of Fenton and McGlashan (1987) and previous studies of ours and others (Bola and Mosher, 2002; Carone et al., 1991; Harrow et al., 2005a; Harrow et al., 1997) suggest that

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when investigated on a longitudinal basis, over many years, within a naturalistic design, a number of schizophrenia patients not on medications may show adequate functioning or even recovery for a period of time. The following questions were addressed:

1. In a naturalistic research design, which includes patients in treatment and those not in treatment, can schizophrenia patients not on antipsychotics function better and show periods of recovery?
2. Which particular types of schizophrenia patients go off medications for a prolonged period, and do factors associated with this influence subsequent outcome and recovery?
3. Do schizophrenia patients who do not remain on medications differ in (a) premorbid developmental achievements and (b) prognostic potential or in personality and attitudinal factors?

METHOD

Patient Sample

The present investigation is derived from the Chicago follow-up study, a prospective multifollow-up research program studying course, outcome, psychosis, and potential recovery in schizophrenia and bipolar disorders longitudinally (Carone et al., 1991; Goldberg and Harrow, 2001; Goldberg et al., 1995; Harrow et al., 1997, 2000, 2005a; Jobe and Harrow, 2005). The sample of 145 DSM-III diagnosed patients included 64 schizophrenia patients and a control sample of 81 nonschizophrenia patients who were psychotic at index hospitalization. All of these DSM III schizophrenia patients met the 6 months duration of illness criteria (none were schizophreniform patients) and none were schizoaffective patients. The 81 nonschizophrenia patients who were psychotic at index included 31 bipolar manic patients, 28 psychotic unipolar depressives, 6 psychotic bipolar depressives, 5 paranoid disorders, and 11 patients with other psychotic disorders.

An initially young sample of patients from 2 Chicago area hospitals (a private hospital and a state hospital) was prospectively assessed at index hospitalization and then reassessed in 5 successive follow-up interviews over a 15-year period at a mean of 2-years, 4.5-years, 7.5-years, 10-years, and 15-years posthospital discharge. All 145 patients were studied at index hospitalization and at the 15-year follow-ups. One hundred ten of the 145 patients (75.9%) were studied at all 5 follow-ups over the 15 years, and another 23 patients (15.9%) were studied at 4 of the 5 follow-ups.

Diagnoses were based on at least one of 2 structured research interviews conducted at index hospitalization that have been used successfully in previous research: (1) the schedule for affective disorders and schizophrenia (SADS) and (2) the schizophrenic state inventory, with each interview tape recorded (Grinker and Harrow, 1987). Inter-rater reliability for diagnosis was obtained (Kappa for schizophrenia was $\hat{e} = 0.88$).

Informed written consent was obtained at index hospitalization and at each follow-up. The inpatients were given a

series of structured interviews and questionnaires at index hospitalization. Trained interviewers who were not informed of diagnosis or results of previous follow-ups conducted later follow-ups.

At index hospitalization, the patients were consecutive admissions within the limitation of giving preference to younger (between 17- and 32-year-old at index) patients with fewer previous hospitalizations. The mean age of the sample at index hospitalization was 22.9 years. The mean education level at index was 13.01 years. Fifty-six percent of the sample was male and 44% were female. There were no significant differences between diagnostic groups in age. There were significant sex differences between the diagnostic groups. A larger percent of the schizophrenia patients was male (67%), and a larger percent of patients with other types of psychotic disorders was female (53%). The sex ratio difference is typical of those found in early young psychotic patients who have been hospitalized and is consonant with recent evidence suggesting a larger percent of patients with schizophrenia is male (McGrath, 2005). Over the 15 years, outcome data on posthospital status were obtained on slightly over 77% of the original sample. Forty-six percent of the sample was first admission patients at index, and another 21% had only one previous hospitalization.

Follow-Up Assessments

To assess global functioning and adjustment during the follow-up assessments, we used the Levenstein-Klein-Pollack (LKP) scale (Grinker and Harrow, 1987) and structured interviews (the SADS and a functioning interview) (Carone et al., 1991) approved by an IRB, to evaluate psychosis (delusions and/or hallucinations) during the follow-up year (Harrow et al., 2004; Harrow et al., 1995); other major symptoms (negative symptoms, anxiety, and affective symptoms), instrumental work performance and self-support, social functioning, family functioning, rehospitalization, and treatment.

The LKP, our major index of global functioning at each follow-up year, has been used successfully by our research team and others (Carone et al., 1991; Grinker and Harrow, 1987; Harrow et al., 2000). The 8-point LKP scale takes into account work and social functioning, life adjustment, level of self-support, major symptoms, relapses, and rehospitalization. In a recent assessment of inter-rater reliability, we obtained an intraclass correlation of 0.92. Ratings for global assessment in the year before follow-up on the 8-point LKP scale range from "1" (adequate functioning and recovery during the follow-up year) to "8" (very poor psychosocial functioning, considerable symptoms, and lengthy rehospitalization). We obtained a correlation of $r = 0.85$ ($p < .0001$) between the 8-point LKP scale and scores on the global assessment scale (Endicott et al., 1976), which is almost identical to the global assessment functioning scale (American Psychiatric Association, 2000).

Operational Definition of Recovery

Recovery was defined by outcome status during the entire follow-up year. Meeting the operational criteria for a period of recovery requires both (1) the absence of major symptoms throughout the follow-up year (absence of psycho-

sis and negative symptoms) and (2) adequate psychosocial functioning (e.g., instrumental work half-time or more and acceptable social functioning during the follow-up year) (Harrow et al., 2005a). The criteria are met by a score of “1” or “2” on the 8-point LKP scale. Recovery at any given follow-up does not automatically prejudge whether recovery will continue during future years, which may be a function of (a) the natural course of schizophrenia, (b) individual characteristics of the patient assessed, and (c) treatment.

Locus of Control and Self-Esteem

To assess attitudinal and personality characteristics that may relate to medication status, a scale to assess locus of control (LOC) (a concept and measure originally advanced by Rotter) (1966), and another to assess self-esteem were administered at the 4.5-year follow-ups. LOC refers to the extent to which an individual perceives events in his or her life as being a consequence of his or her actions. One may believe that events in peoples’ lives result from their own efforts, skills, and internal dispositions (internal control) or that they stem from external forces such as luck, chance, fate, or powerful others (external control). The scale to assess self-esteem was a 7-item inventory derived from a widely used scale (Rosenberg, 1965). It included items such as “I feel I do not have much to be proud of” and “I take a positive attitude towards myself.”

Early Prognostic Potential and Developmental Achievements

To assess earlier prognostic and developmental achievements, we analyzed data from 2 widely used measures collected prospectively, years earlier, at index hospitalization. One, the Zigler-Phillips scale, an index of earlier developmental achievements, is based on patients’ work history, education, marital status, age at first break, and IQ (Zigler and Glick, 2001). The Zigler-Phillips scale has been linked to developmental formulations and theories concerning premorbid competence. It has been used in studies applying developmental theory to adult psychopathology and outcome, to self image, and to mental retardation (Glick and Zigler, 1985; Katz and Zigler, 1967; Westermeyer and Harrow, 1986; Zigler and Glick, 2001; Zigler and Levine, 1983; Zigler and Phillips, 1961). Scoring is reliable (Glick et al., 1985) and the many studies using the scale provide support for its construct validity (Zigler and Glick, 2001). The other is a composite index of prognostic potential derived from factors outlined in

the research of Vaillant (1978), of Stephens (1978), Stephens et al., (1997), and others (Westermeyer and Harrow, 1984). The poor prognostic factors assessed prospectively at index hospitalization included no acute onset, no precipitating stress at index, poor work and social adjustment before index, no preoccupation with death, the absence of depressive symptoms, no confusion, no guilt, being unmarried, and blunted affect.

Medications

Table 1 reports the data on the percent of patients with schizophrenia on medications at each of the 5 follow-ups over 15 years. As frequently found in the natural course of a large series of schizophrenia patients, there was no single, uniform treatment plan which applied to all patients. Rather, at the 15-year follow-ups, 69% of the patients with schizophrenia were on psychiatric medications; this included 61% on antipsychotic medications with or without other medications. Eighty percent of the schizophrenia patients on antipsychotics at the 15-year follow-ups had been on an antipsychotic at the 2-year follow-up, and another 7% had been on other medications, but not antipsychotics. Of the schizophrenia patients not on any medications at the 15-year follow-up, 29% were on antipsychotics at the 2-year follow-ups and another 7% were on other medications, but not antipsychotics. Because the 15-year follow-ups were conducted during the early years of FDA approval of second-generation antipsychotics, 33 of the 39 schizophrenia patients on antipsychotics at the 15-year follow-ups (85%) were still on first generation antipsychotics. At the 15-year follow-ups, 33% of the patients with other types of psychotic disorders also were on antipsychotics with or without other medications, and an additional 20% were on other psychiatric medications, but not on antipsychotics.

RESULTS

Table 2 reports the results on global adjustment and functioning and compares (a) patients with schizophrenia who were on antipsychotic medications with those not on any medications and (b) patients with other types of psychotic disorders on any medications with those not on medications at each of the 5 assessments over 15 years.

Figure 1 presents data on the percent of schizophrenia patients with psychotic activity, comparing patients on antipsychotic medications with those not on any medications at both the 10- and 15-year follow-ups.

TABLE 1. Percent of Schizophrenia Patients on Antipsychotic Medications and Percent Not in Treatment

	Antipsychotics (%)	Other Psychiatric Medications (No Antipsychotics) (%)	In Treatment (No Medications) (%)	No Mental Health Treatment (%)
2 Year FU	64	6	11	19
4.5 Year FU	63	12	5	19
7.5 Year FU	59	16	2	24
10 Year FU	59	16	3	22
15 Year FU	61	8	6	25

TABLE 2. Global Adjustment Over 15 Years for Medicated and Nonmedicated Schizophrenia and Other Psychotic Patients

	Global Adjustment*			
	Schizophrenia Patients		Other Psychotic Patients	
	On Antipsychotic Medications, <i>M (SD)</i>	Not On Any Psychiatric Medications, <i>M (SD)</i>	On Psychiatric Medications, <i>M (SD)</i>	Not on any Psychiatric Medications, <i>M (SD)</i>
2 Year FU	6.17 (2.05)	5.36 (2.56)	5.70 (1.90)	4.00 (2.28)*
4.5 Year FU	6.39 (1.78)	3.43 (2.53)**	5.12 (2.07)	2.64 (1.44)**
7.5 Year FU	5.94 (2.04)	3.47 (1.96)**	5.04 (2.16)	2.84 (1.98)**
10 Year FU	6.62 (1.52)	3.00 (2.45)**	5.31 (1.98)	2.84 (1.91)**
15 Year FU	5.67 (1.94)	3.55 (2.24)**	4.88 (1.99)	2.08 (1.34)**

*Global functioning and adjustment scale (1–8). Low scores represent good functioning.
 p* < .01, *p* < .001.

Although the focus of this report is on the 15-year follow-ups, there were large, significant differences in global functioning between patients on medications and patients not on medications at 4 of the 5 follow-ups (*p* < .001) (Table 2). Patients with schizophrenia who had removed themselves or been removed from antipsychotic medications showed significantly better global functioning and outcome than those still being treated with antipsychotics.

Detailed analyses of those patients with schizophrenia on antipsychotic medications versus those not on medications at the 15-year follow-ups also were conducted. These analyses indicated that in addition to the significant differences in global functioning between these groups, 19 of the 23 schizophrenia patients (83%) with uniformly poor outcome at the 15-year follow-ups were on antipsychotic medications.

The data on psychosis in Figure 1 show that at the 10-year follow-ups, 79% of the patients with schizophrenia on antipsychotics had psychotic activity, whereas 23% of those not on any medications had psychotic activity ($\chi^2 = 12.04, 1 df, p = .001$). Sixty-four percent of the schizophrenia patients treated with antipsychotic medications at the 15-year follow-ups had psychotic activity, whereas 28% of those not on any medications had signs of psychotic activity ($\chi^2 = 6.27, 1 df, p < .01$).

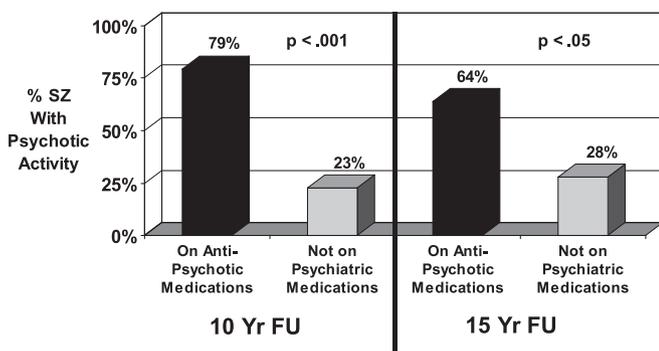


FIGURE 1. Psychosis at 10-year and 15-year follow-ups in medicated and unmedicated schizophrenia patients.

Medication Status of Schizophrenia Patients in a Period of Recovery

Only a minority of patients with schizophrenia were in a period of recovery at the 15-year follow-ups. However, the data show the majority of these schizophrenia patients in recovery were not on antipsychotic medications. Thus, at the 15-year follow-up, 12 of the 64 schizophrenia patients (19%) were in a period of recovery. This includes 8 of the 20 schizophrenia patients (40%) not on any psychiatric medications. It includes significantly fewer (2 of the 39) patients with schizophrenia (5%) on antipsychotic medications ($\chi^2 = 11.42, 1 df, p < .001$). Two of the other 5 schizophrenia patients on other medications but not on antipsychotics also were in recovery at the 15-year period.

Medication Status and Outcome of Patients With Other Types of Psychotic Disorders

The results for the nonschizophrenia patients who had psychotic disorders at index hospitalization also showed very large significant differences; patients with other types of psychotic disorders not on any medications at the 15-year follow-ups showed better outcome than those on medications (*t* = 6.00, 77 *df*, *p* < .0001). Some of the differences could be because of the patients with major symptoms being more likely to be placed on antipsychotic medications, and as a result, in naturalistic samples, patients on these medications are more likely to be more symptomatic and functioning poorly.

Long-Term Characteristics of Unmedicated Patients

We analyzed data providing clues on whether the better functioning of the subgroup of unmedicated patients with schizophrenia versus those on antipsychotics at the 15-year follow-up was a function of their current medication status. An alternative is that other long-term characteristics marked them off as different types of patients. For this analysis, we compared the 2 groups on earlier prognostic and premorbid factors, earlier attitudinal and personality features, and previous periods of recovery.

Figure 2 reports the data on earlier periods of recovery for these 2 groups of schizophrenia patients at each of the previous 4 follow-ups. Those who were unmedicated at the 15-year follow-ups had previously experienced (5, 7.5, and 10.5 years earlier) significantly more periods of recovery ($p < .001$) than those on antipsychotic medications at the 15-year follow-ups.

In addition, we analyzed the earlier personality data on LOC and self-esteem at the 4.5-year follow-ups to determine whether patients with schizophrenia who were not on any medications at the 15-year follow-ups were different in terms of showing earlier signs of having more internal LOC and having more positive self-esteem. Figure 3 presents the data on LOC. The data indicate that the schizophrenia patients on antipsychotics at the 15-year follow-ups had been significantly more external (using the LOC scores from the 4.5-year follow-ups) over 10 years earlier than those on not on medications at the 15-year follow-ups ($t = 2.27, 30 df, p < .05$). There also was a trend for schizophrenia patients who were on antipsychotics at the 15-year follow-ups, when compared with those not on medications at the 15-year

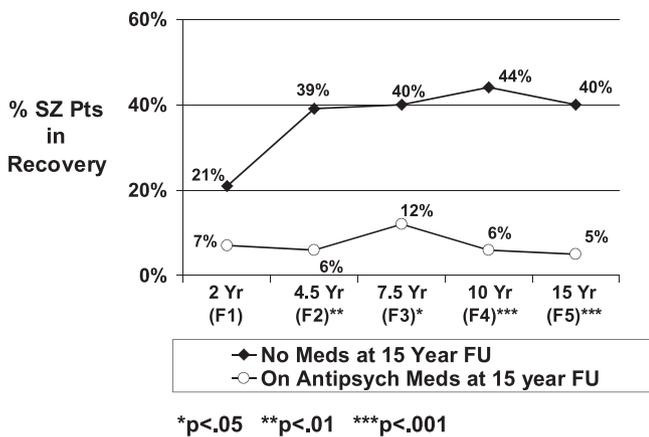


FIGURE 2. Schizophrenia patients who at the 15-year follow-up are on antipsychotic medications: Previous functioning of these patients.

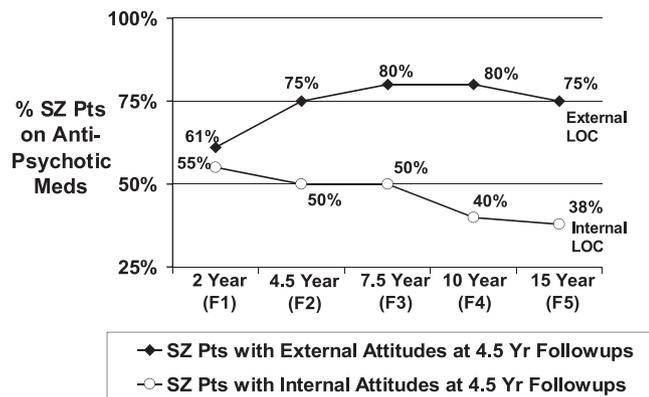


FIGURE 3. Schizophrenia patients with internal and external locus of control (LOC) at 4.5-year follow-ups: Percent patients later on antipsychotic medications.

follow-ups, to have had more negative self-esteem or self-images when they were compared over 10 years earlier ($t = 2.18, 31 df, p < .05$).

Earlier Prognostic Potential and Early Developmental Achievements of Schizophrenia Patients Not on Medications

Figure 4 compares the percent of schizophrenia patients with good prognostic features at index hospitalization (Vaillant-Stephens scale) on antipsychotics with those not on any medications, comparing these 2 medication groups at both the 4.5-year follow-ups and the 15-year follow-ups. Figure 5 reports the percent of these 2 medication groups with good versus poor premorbid developmental achievements (Zigler-Phillips scale). The results from Figure 4 indicate significantly more favorable prognostic scores (Vaillant-Stephens) at index hospitalization for schizophrenia patients later not on medications (versus those on antipsychotics) at both the 4.5-year follow-ups ($\chi^2 = 5.57, 1 df, p < .02$) and the 15-year follow-ups ($\chi^2 = 6.83, 1 df, p < .01$). The results from Figure 5 indicate more favorable premorbid developmental achievements for schizophrenia patients not on medications (versus those on antipsychotics) at the 4.5-year follow-ups ($\chi^2 = 3.18, 1 df, p < .10$) and the 15-year follow-ups ($\chi^2 = 3.97, 1 df, p < .05$).

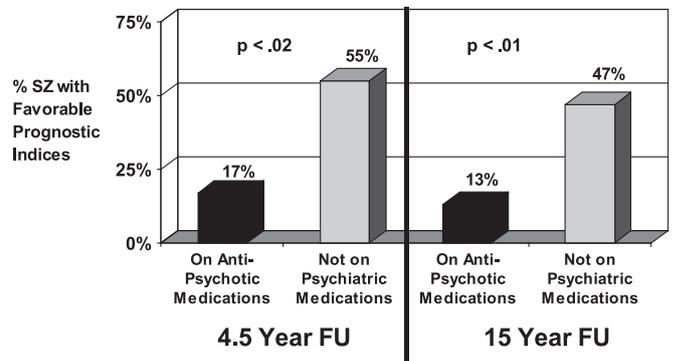


FIGURE 4. Prognostic indices (Vaillant-Stephens) as a later influence on medication treatment among schizophrenia patients (sz).

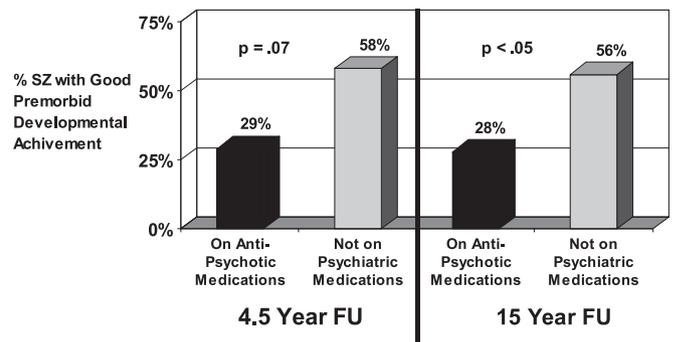


FIGURE 5. Premorbid developmental achievements as a later influence on medication treatment among schizophrenia patients (sz).

The results suggest that the subgroup of schizophrenia patients not on medications was different in terms of being a self-selected group having better earlier prognostic and developmental potential.

In addition, global outcome for the group of patients with schizophrenia who were on antipsychotics was compared with that for the off-medication schizophrenia patients with similar prognostic status. Starting with the 4.5-year follow-ups and extending to the 15-year follow-ups the off-medication subgroup tended to show better global outcomes at each follow-up.

Time Course and Outcome for Patients With Favorable Prognostic Indices

We conducted additional analysis of the medication course over time of the subsample of 10 schizophrenia patients who, at the 15-year follow-ups, were not on antipsychotics and also were in a period of recovery. At the 15-year follow-ups, 8 of these 10 schizophrenia patients were not on any psychiatric medications and the other 2 were on other medications, but not on antipsychotics. These 10 patients had removed themselves or been removed from antipsychotics at a relatively early period in their posthospital course. Thus, by the 2-year follow-ups 6 of these schizophrenia patients were not on antipsychotics, and remained off of them at all subsequent follow-ups. Another 2 were not on antipsychotics by the 4.5-year follow-ups, and the other 2 were not on antipsychotic medications by the 7.5-year follow-ups.

The current focus is on whether some or a subgroup of schizophrenia patients can show favorable outcomes after stopping their antipsychotics, and on characteristics of those who stay off antipsychotics for a sustained period. However, we also analyzed whether 2 of the main characteristics of the unmedicated patients are, in general, associated with more favorable global outcomes. The data indicate that both the Vaillant-Stephens prognostic index ($F = 12.04$, $df = 1.37$, $p < .001$), and the Zigler measure of premorbid developmental achievements ($F = 31.53$, $df = 1.41$, $p < .0001$) were predictors of significantly more favorable outcomes for the schizophrenia patients.

DISCUSSION

An important issue is which types of patients with schizophrenia, when studied on a longitudinal basis, are most likely to function adequately without antipsychotic medications. In general, modern-day medications for the severely mentally ill are a positive factor for many of these patients, especially those who remain in clinical outpatient settings; this has been firmly established in a large number of efficacy and effectiveness studies with first-generation antipsychotics and, more recently, second-generation antipsychotics, with the studies involving patients in clinical settings. Most of the many positive studies are based on an important population of patients, those involved in clinic treatment and clinic settings. However, after acute hospital treatment, when these patients leave the hospital, not all patients originally treated with antipsychotic medications continue on these medications.

Thus, although the majority of patients with schizophrenia were on antipsychotic medications, at each of the 5 follow-ups, over a third were not on antipsychotic medications. Although the focus of the current report is on the medication status of the patients at the 15-year follow-ups, the data indicate significantly better functioning for the patients not on antipsychotic medications at the 15-year follow-ups and also at earlier follow-ups for these patients extending back over the previous 10 years. It seems likely that some of these schizophrenia patients chose to leave the mental health caretaking system because their symptom level and functioning had improved.

A certain number of schizophrenia patients who go off antipsychotic medications and relapse are quickly brought to the attention of psychiatrists and other mental health workers when they return for treatment and/or rehospitalization; these relapsing patients are the ones from whom opinions by some about the absolute necessity of continual antipsychotic medications for all patients with schizophrenia are formed. The possible biases involved in limiting one's study to only this type of sample is discussed by Cohen and Cohen (1984).

The current results are similar in principle to earlier results reported from an important, landmark, report by Fenton and McGlashan (1987), but also involve continuous multifollow-up study of these patients and assessment with personality scales and other instruments. Unlike the Fenton and McGlashan study, it also involves prognostic and personality comparisons of patients on antipsychotics versus the combination of all schizophrenia patients not on medications, regardless of whether the latter patients had favorable or unfavorable outcomes.

It is possible that a lack of compliance with antipsychotic medication treatment may have reduced its effectiveness and lowered functioning for some schizophrenia patients. However, lack of compliance does not account for the relatively favorable outcomes of the untreated patients, especially select schizophrenia patients with favorable prognostic features, who experienced periods of recovery. Some of these schizophrenia patients eventually encounter (5–12 years later) further psychopathology and/or further disabilities.

Part of the reason that the current results do not fit some casual clinical observations is that many professionals in the mental health caretaking system are more closely in contact with those patients with schizophrenia and other types of psychotic disorders who are in treatment, either consistently or sporadically; the good and bad periods for these patients make a greater impression on us. We have less contact with patients not in treatment for a prolonged period and they are not included in medication versus placebo studies, so their outcomes are less likely to shape our views. However, the current results suggest that a number of other patients who do not immediately relapse while off medications, and especially those who disappear from the mental health caretaking system for a prolonged period, are less likely to come to the attention of professionals. As in many other areas of medicine, when one comes into contact with patients years after initial acute treatment, "sicker" people are more likely to

have been in continual treatment, and those who had symptom-free periods are less likely to be in treatment.

Looked at from a different viewpoint, the data suggest that schizophrenia patients with good prognostic features, with better premorbid developmental achievements and with more favorable personality characteristics are the subgroup more likely to stay off antipsychotics for a prolonged period.

Viewed as a group the total sample of patients with schizophrenia showed poorer outcomes than the other psychotic patients (Table 2). As shown in Table 2, in general, schizophrenia is a relatively poor outcome disorder compared with the outcomes of other disorders involving psychosis. However, the subgroup of schizophrenia patients with good prognostic characteristics who showed adequate outcomes for a number of years even without antipsychotics underscores that there is some heterogeneity of outcome in schizophrenia (Ciompi, 1984; Harding et al., 1987; Harrow et al., 2005a; Liberman, 2002) The heterogeneity of outcome is not unique to schizophrenia, and is found in many other major disorders.

Changes Over Time of Medication Status of Patients With Better Functioning

In regard to changes over time, the data indicate the strongest effect and the greatest likelihood of a number of factors of importance to emerge occurred after the first 2 years. Thus, by the 4.5- and 7.5-year follow-ups and at each follow-up thereafter, this trend toward better functioning for the patients not on antipsychotics and with more positive personality characteristics was stronger and statistically significant for this subgroup with more internal resources and positive attitudes about themselves.

Schizophrenia Patients Not on Antipsychotic Medications: Two Factors of Importance

As with other disorders, all schizophrenia patients are not alike. The view of "one treatment fits all" is not consonant with the current data or with clinical experience (Jobe and Harrow, 2005). Some patients have better internal resources, and there are other potential differences in personality style and attitudinal approaches. A number of researchers have pointed out the value of exploring predictors to identify schizophrenia patients who might function adequately without antipsychotics. Our data indicate 2 different types of factors that facilitate the better functioning of the patients with schizophrenia who were not on antipsychotics at the 15-year follow-ups.

The first set of factors concerns a trend for schizophrenia patients with favorable scores on the prognostic indices assessed years earlier (at index hospitalization), indicating their potential for better prognoses and better clinical courses, to not be on any antipsychotics many years later.

Viewed with the outlook that these indices tap a certain type of inner strength or a tendency to be less vulnerable to major psychopathology, the data on premorbid functioning and the prognostic data indicate one prominent factor is that the unmedicated patients were more likely to be more resilient patients with better prognostic potential, better developmental achievements, and more internal resources. The prospectively collected data in Figures 4 and 5 support the view

that the patients who were no longer medicated were different on these premorbid factors from those on antipsychotics. Although prognostic factors and premorbid developmental achievements are important influences on outcome, and were the strongest predictors, multiple other factors also are involved because the off-medication patients showed better global outcomes than the on-antipsychotic patients, even when subgroups with similar prognostic status were compared.

With regard to the other type of earlier influence we studied, the data indicate the value of constructive attitudinal and personality characteristics present years earlier before the 15-year follow-ups. Thus, the data indicate that patients with schizophrenia who were unmedicated at the 15-year follow-ups were more likely, over 10 years earlier, to have been patients who had (a) more internal attitudes on an LOC scale concerning the importance of their own efforts toward better functioning and (b) better self-esteem or better self-images. It is probable that for patients with a more internal attitude and better self-images at the 4.5-year follow-ups, some initial success in functioning contributed to their beliefs that their improved functioning was due to their own efforts and talents rather than to chance. This, in turn, could encourage and reinforce a more internal LOC, leading to increased personal efforts when faced with subsequent challenges, with the constructive attitudes and positive functioning exerting reciprocal positive influences on each other. Patients who are internally orientated and have better self-esteem are the types of patients who are more likely, if their functioning improves, to urge that they try functioning without medications and/or to choose to try functioning without any treatment at all. These data would fit with some reports and empirical studies on consumers who believe that schizophrenia patients who feel they have recovered are more likely to be those who have "taken responsibility for their lives" (Tooth et al., 2003, p 76).

Which Patients With Schizophrenia Can Profitably Stay Off Antipsychotic Medications?

Fenton and McGlashan (1987) note that it would be desirable to determine which patients with schizophrenia can profitably stay off antipsychotic medications. While identifying an important subgroup, they note that these factors could not be used to accurately predict which specific schizophrenia patients among those with favorable features would function well without medications. The premorbid factors they found seem to be effective predictors for many rather than all such schizophrenia patients. The difficulty of prediction can be seen when Vaillant (1978) and Stephens (1978) also noted that some, but not all, patients with favorable prognostic features function adequately (Jobe and Harrow, 2005).

Our data produced results that are similar in principle. Recommendations regarding the use of medications at various phases of illness are often based on a risk-benefit analysis involving, as in many other areas of modern medicine, the probability of success rather than certainty. The current data identify a clear subgroup of schizophrenia patients not being treated, a number of whom experienced periods of recovery, with the data indicating that on average, those patients not on any medications at the 15-year follow-ups had significantly better current and previous global adjustment than those on

antipsychotics (Fig. 2). There also has been some indication that as our patient sample is getting older, there may be some tendency for improvement among schizophrenia patients. Our overall analysis indicates that many schizophrenia patients not on antipsychotic medications played some role themselves in the decision for them to stop taking medication and leave treatment at a relatively early phase of their posthospital course. Thus, most of the subgroup of schizophrenia patients not on any medications who were in a period of recovery at the 15-year follow-ups had been taken off or removed themselves from antipsychotic medications over 10 years earlier by the 2-year or 4.5-year follow-ups.

After the acute phase, many schizophrenia patients are less symptomatic and function better, partly as a result of antipsychotics. We, as professionals, are closest to our treatments and are influenced by the positive effects on many patients of these treatments. However, other factors also influence our patients' subsequent symptom levels and outcomes. These include the extent or strength of their diathesis or constitutional predispositions toward schizophrenia, internal resources and cognitive skills, attitudes and personalities, and the not-totally-predictable external environmental events they will encounter in the future. Some tend to overlook the potential importance of these latter factors in influencing subsequent outcomes.

CONCLUSIONS

The data indicate that after the acute phase certain specific subgroups of patients with schizophrenia have an increased probability of going off antipsychotics for prolonged periods and opting out of the mental health caregiving system and indicate the characteristics of this particular subgroup are. Posthospital treatment is important for most patients with schizophrenia. The controlled trials data on clinic populations of patients suggest that among the patients with schizophrenia who stay in clinic treatment settings for years after the acute phase there is increased risk of relapse when going off antipsychotics. However, the current data suggest that for the select subgroup of patients with schizophrenia who are not in clinic settings, who have gone off antipsychotics and did not immediately relapse, and stayed off them for a period of time, a surprising number experienced periods of recovery and continued to function well for a considerable period without antipsychotics. Clearly, the present longitudinal data suggest that not all patients with schizophrenia need to use antipsychotic medications continuously throughout their lives.

It is not known how the off-medication schizophrenia patients experiencing periods of recovery, and those experiencing difficulties in functioning, would have been functioning had they been receiving medications, and from the present study one is not able to make definitive causal inferences about the treatment factors affecting outcome. However, knowledge by clinical workers of which factors are associated with greater chances of success can be helpful in treatment decisions for patients with schizophrenia who express an interest in going off antipsychotics.

The data, collected over a 15-year period, reveal factors that are protective and indicate which patients are more likely (but not certain) to function adequately if they choose to leave treatment. These factors, which were identified prospectively (e.g., the prognostic and developmental data were collected and scored many years earlier, at index hospitalization), and increase the probability of success when off antipsychotics, include 2 different prognostic indices and 2 different personality scales. For those schizophrenia patients who are functioning better for a period who, by themselves, show an interest in coming off antipsychotic medications and also show evidence of inner resources (or earlier favorable prognostic features and good developmental achievements), the data suggest that some or many will succeed for a period. Periods or intervals of recovery are dependent on multiple internal characteristics of the patient, and on external factors and treatment, rather than only one factor, and prediction can be made with moderate rather than perfect probability, as in most other areas of medicine and many areas of biology.

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