Defining Treatment Refractoriness in Schizophrenia

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At Issue

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Abstract

Addressing the need for research on the nature of refractoriness to antipsychotic drug therapy exhibited by a substantial minority of schizophrenic patients, Philip R.A. May and Sven Jonas Dencker instigated an international study group to discuss this problem, beginning with the International Congress of Neuropsychopharmacology in Göteborg, Sweden, in 1980. The study group subsequently met in Haar, Federal Republic of Germany, in 1985; in Banff, Canada, in 1986; and again in Telfs, Austria, in 1988. The study group set three objectives: (1) to clarify the concept of treatment resistance or refractoriness; (2) to suggest criteria for defining or rating the degree of treatment refractoriness; and (3) to explore the role of psychosocial and drug therapies in increasing the responsiveness of the treatment refractory patient. This position article represents a distillation of the study group's efforts to define treatment refractoriness in schizophrenia.

Despite innumerable positive reports on the efficacy of antipsychotic medication, there remain patients refractory to this form of therapy. While percentages vary depending upon the population studied, the general consensus is that from 5 to 25 percent of schizophrenic patients are partially or totally unresponsive to antipsychotic drug therapy (Davis 1976; Vaughn et al. 1984; Losonczy et al. 1986; Simpson and Levinson 1988). This does not include the approximately 15 percent of schizophrenic patients who improve with placebo treatment in double-blind studies of neuroleptic drugs (Cole et al. 1966; Hogarty et al. 1974). Despite the problems posed by the population of patients deemed unresponsive to antipsychotic drug therapy, research on the nature of treatment refractoriness has been scant (Dencker and Kulhanek 1988).

One study that revealed a large reservoir of chronic schizophrenic patients who were refractory to antipsychotic drugs was conducted with patients from Illinois State hospitals who had resisted many years of efforts at deinstitutionalization (Paul and Lentz 1977). After active and structured psychosocial therapies conducted over a period of 4½ years, more than 80 percent of these patients had their maintenance antipsychotic drugs discontinued despite showing significant improvement in psychopathology and personal functioning. Moreover, in a triple-blind study of interactions between neuroleptic medication and the structured therapies, investigators discovered that placebo treatment was actually associated with faster rates of patient improvement (Paul et al. 1972). The findings from this study must be viewed through the lens of its pre-*DSM-III* (American Psychiatric Association 1980) era when diagnostic

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criteria lacked rigor and many patients were incorrectly labeled schizophrenic. While the efficacy of highly structured, social learning therapies with refractory schizophrenic patients found by Paul and his colleagues has not been specifically replicated, other studies of behavior therapy with this patient population have yielded similar findings (Banzett et al. 1984; Glynn and Mueser 1986; Liberman and Weigand 1986; Wong et al. 1986). Moreover, older schizophrenic patients, if given the benefit of long-term psychosocial treatment, have been found to have much reduced requirements for maintenance antipsychotic drug therapy (Fenton and McGlashan 1987; Harding et al. 1987).

Several pharmacotherapy strategies have been employed to develop ways to overcome drug refractoriness in schizophrenia. Proponents of a "therapeutic window" for neuroleptic blood levels have generated data suggesting that large interindividual differences in absorption, transport, storage, and metabolism require a fine-grained analysis of steady-state plasma levels of drug and active metabolites (Bolwig-Hansen et al. 1982; Smith et al. 1984; Szukalski et al. 1986; Sramek et al. 1988; Van Putten et al. 1988, 1989; Marder et al. 1989). Other investigators have presented data suggesting that adding adjunctive drugs to conventional neuroleptics (e.g., lithium, propranolol, carbamazepine, benzodiazepines) may produce improved therapeutic outcomes in patients with poor response to neuroleptics alone (Csernansky et al. 1985; Kane 1987; Osser 1988). More recently, clozapine has been reported to achieve significant improvements in approximately one-third of schizophrenic patients who were first screened for refractoriness to standard neuroleptics (Kane et al. 1988; Marder and Van Putten 1988).

To spur on research and clinical advances on more effective treatment of refractory schizophrenic patients, consensus should be reached on how to define the varying degrees of resistance to conventional antipsychotic drug regimens. Thus, a systematic and standardized methodology is needed for rating the degree of treatment response and resistance in a schizophrenic patient who has received a conventional course of antipsychotic medication.

The construct of treatment resistance is a complex one because it assumes that patients have received an adequate neuroleptic dose of various types and routes of neuroleptic agents, alone or in combination, for an adequate period of time, before they are considered resistant or refractory. Moreover, careful assessment must eliminate as the reason for apparent treatment resistance (1) noncompliance, (2) excessive protein-binding of the neuroleptic with inadequate bioavailability, or (3) an inadequate or excessive dose resulting in the therapeutic window being missed or side effects outweighing therapeutic effects (Osser 1989). Thus, any definition of treatment resistance must specify the criteria for an adequate trial of conventional treatment. These criteria cannot be absolute since they may depend on how the classification of treatment resistance is to be used. For example, if treatment resistance is defined so as to recruit subjects for a trial of a new drug that has potentially hazardous side effects (e.g., clozapine), a higher threshold for defining the treatment-resistant patient may be required than when the alternative treatment is a form of behavior therapy (e.g., transfer to a token economy or social learning ward).

Because pharmacotherapy is never administered in a socioenvironmental vacuum, the quality and duration of the patient's psychosocial milieu must also contribute to the criteria used for defining treatment refractoriness. As noted above, highly structured behavior therapy can yield substantial improvements in apparently treatment-refractory patients, even without medication. Moreover, a host of well-controlled studies carried out during the past three decades has documented the interactions between schizophrenic patients' response to medication and the milieu in which they live (summarized in Falloon and Liberman 1983; Liberman et al. 1984). Generally, patients participating in neuroleptic drug trials while living in custodial environments have required higher doses to achieve less clinical improvement than have counterparts living in more active and structured units. Table 1 lists principles of psychosocial therapy that have emerged from past research as favoring an optimal response to treatment (Gunderson et al. 1983; Liberman and Mueser 1989). Before being certified as treatment refractory, schizophrenic patients might require lengthy (i.e., 1 to 2 years) exposure to optimal psychosocial treatment environments, if such were available and economically feasible.

Definition of Treatment Refractoriness

Treatment refractoriness is defined as continuing psychotic symptoms with substantial functional disability and/or behavioral deviances that persist in well-diagnosed persons with schizophrenia despite reasonable and customary pharmacological and psychosocial treatment that has been provided continuously for an ade-

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quate time period. In this definition, it is recommended that a conservative diagnosis of schizophrenia be employed that requires the criterion of continuous positive and characteristic symptoms of psychosis for at least 2 years, although some might argue that 1 year of unresponsiveness may be an adequate time period. Concomitant negative symptoms and disabling nonpsychotic symptoms also are usually present in the clinical picture of refractory schizophrenia. Two years was selected because that timeframe has been used in the literature to define chronicity; however, this duration also permits persisting schizophrenic symptoms to be differentiated from cases in which chronicity is marked by episodic remissions as well as from cases of nonschizophrenic psychoses having a prolonged course of active or residual symptomatology of up to 2 years.

In addition to persistent positive and negative symptoms of psychosis, associated functional disability in social, self-care, and occupational domains should be present for a patient to meet criteria for refractoriness. However, some patients with persistent psychotic symptoms may function with mild to moderate disabilities. Others may have little in measurable psychotic symptoms while exhibiting bizarre and disabling behavioral deviances and acting out. Behavioral deviances consist of low-frequency but socially intolerable actions that often disqualify a patient from community placement—for example, incontinence, aggression, self-injury, denudativeness, and firesetting. Thus, the graphic depiction in figure 1 shows the four interrelated dimensions that can be present for a patient to qualify for the designation of treatment refractoriness. While the four dimensions are interrelated, the

Table 1. Principles of effective psychosocial treatment for schizophrenia

- Psychosocial interventions, based on social learning principles, therapeutic community, and educational methods, need to be applied in a 24-hour, highly structured, consistent, and socially engineered environment.
- Target problems for psychosocial therapy can be—
  - Negative symptoms.
  - Functional deficits.
  - Deviant behavior that impedes adjustment in less restrictive environments.
  - Family dysfunctions and stress.
- Interventions must be directed at reducing behavioral deviances (e.g., excesses of maladaptive behavior) as well as strengthening adaptive abilities that will compensate for patient's deficits. Social skills training has been shown to be particularly valuable as a treatment modality.
- Interventions need to be designed to engage the thought-disordered and distractible patient's attention and learning capacities. This requires highly trained staff who are skilled in using prompts, reinforcers, and a positive relationship with patients.
- Staff must meet the challenge of establishing positive relationships with patients who may be very negativistic, regressed, rejecting, and apathetic. This often requires strategic and paradoxical interventions as well as a stable therapeutic team capable of engaging patients in a positive relationship with rapport, psychodynamic understanding, patience, and professionalism.
- Refractory schizophrenic patients have longstanding and overlearned symptoms and behavioral deficits and excesses that yield only slowly to changed environmental contingencies; hence, improvement may be measured in months and years of sustained and consistent treatment.
- Behavioral interventions should be titrated against the patient's tolerance for intensive environmental stimulation that requires therapy to—
  - Provide for periods of social withdrawal and modulation of social stimulation as well as for intervals in which to consolidate previous gains before undertaking further goals.
  - Aim for small, gradual, and incremental goals, with progress of any magnitude matched by abundant positive reinforcement.
- Patients should be involved as much as possible in the selecting, sequencing, and prioritizing treatment goals and in monitoring and reinforcing progress. This also requires the treatment team to educate the patient about the nature of his or

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Table 1. Principles of effective psychosocial treatment for schizophrenia—*Continued*

her illness and about the rationale for both drug and psychosocial therapy.

- Behavior therapy, including psychoeducational family therapy, has been documented as the psychosocial treatment of choice for schizophrenia; yet supportive group therapy and milieu therapy continue to provide benefits in comprehensive programs.
- In the presence of active and structured psychosocial therapy, the dosage needs for neuroleptic drugs may diminish.
- Durability and generalization of treatment effects require planned orchestration of the therapy and the aftercare environment. Staff should—
  - Use multiple exemplars for modeling adaptive behaviors that are the goals of treatment and employ multiple therapists to promote and reinforce therapeutic change.
  - Simulate the patient's natural or aftercare environment in the active treatment environment.
  - Conduct at least some of the treatment in the patient's natural environment.
  - Involve relatives and caregivers in psychosocial therapy so they will facilitate transfer of treatment effects.
  - Ensure that patients are given opportunities, encouragement, and reinforcement to utilize behavioral skills in their natural living and working environments.
  - Gradually fade the intensity and structure of therapy, using more intermittent sessions and reinforcement.
  - Teach patients a general problem-solving strategy.

Note.—The principles articulated in this table have emerged from disparate studies and represent a convergence of clinical and research wisdom. Future research should be driven by hypotheses that are developed from these principles and should be replicated at different institutions by different investigators to test the strength of the clinical implications.

nature and degree of intercorrelations are complex and nonlinear.

The pharmacological criterion for defining refractoriness requires at least three suitably long chemotherapeutic experiences in the preceding 2 years, using antipsychotic drug regimens from different chemical classes at daily dosages ≥ 1,000 mg of chlorpromazine. Each alternative drug should have been administered at a steady state for a period of at least 6 weeks, without significant symptomatic relief during any of these periods. If blood levels have not documented the bioavailability of the drug, depot long-acting neuroleptic drug administration should have been shown to offer no significant improvement. Just as inadequate dose and blood levels of antipsychotic drug must be excluded as a possible determinant of refractoriness, so must toxic and excessively high levels of drug (Van Putten et al. 1988, 1989; Marder et al. 1989).

Rating Degree of Treatment Refractoriness

A construct was selected that reflects a continuum of responsiveness-refractoriness of schizophrenic patients to treatment, while recognizing that dichotomous cutoff thresholds along the continuum might be chosen to operationalize "refractoriness" for particular studies and purposes. The use of a continuum in defining treatment refractoriness recognizes that a majority of persons with schizophrenia viewed as lacking responsiveness to antipsychotic medications are, in fact, suboptimal responders who show a modest degree of improvement with pharmacotherapy, but who persist with high levels of symptomatology and associated social disabilities (Kane et al. 1990; Osser and Albert 1990). The reliable measurement of the three dimensions included in the definition of refractoriness—treatment and clinical history, persistent psychotic symptoms, and associated social dysfunction and behavioral deviances—can define the magnitude of treatment resistance among schizophrenic patients and provide a basis for evaluating the efficacy of various innovative treatment strategies for dealing with patients who fail to respond to conventional therapy.

The Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), as expanded to 24 items for use with inpatients and outpatients by the University of California at Los Angeles Clinical Research Center for Schizophrenia (Lukoff et al. 1986) is recommended by the study group as a standard measure to evaluate positive and negative psychotic symptoms. The expanded BPRS is supplemented with operationalized anchor points for each item's scale levels and with standardized interview questions

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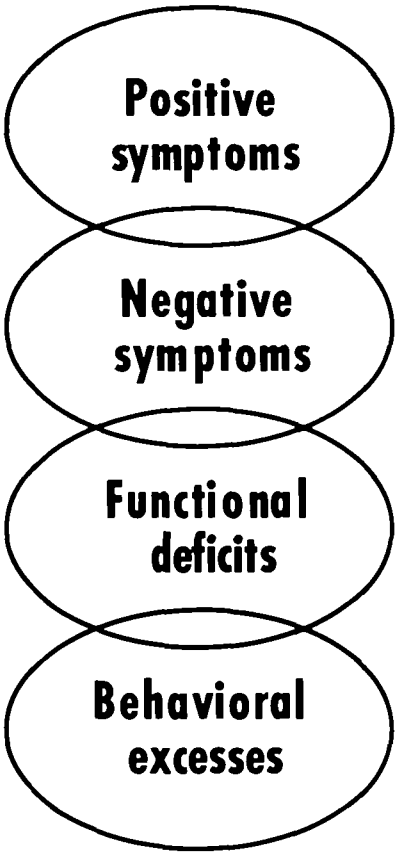
Figure 1. What are the symptoms, disabilities, and behavioral deviances that characterize treatment refractoriness?



Criteria for defining treatment refractoriness include positive and negative symptoms and associated social and behavioral disabilities that preclude independent community living. The interrelationships among the four domains are not always characterized by simple, linear functions as patients may show improvement in discrete aspects of social adjustment in the absence of symptomatic improvement while others may remain nonfunctional even when symptoms show improvement. In addition, criteria must be met for exposure to an adequate amount and duration of conventional neuroleptic drug therapy without sufficient improvement in symptoms and disabilities.

designed to promote the elicitation of accurate self-reporting of symptoms by patients. Other versions of the BPRS and its analogs can also be used for the purposes of determining whether a patient with schizophrenia meets the criteria for treatment refractoriness; for example, the Hillside Hospital adaptation of the BPRS (Woerner et al. 1988), the Positive and Negative Symptom Scale (PANSS; Kay et al. 1986), or the Scale for Assessing Negative Symptoms (SANS; Andreasen 1983) and the Scale for Assessing Positive Symptoms (SAPS; Andreasen 1984).

Delusions concerning somatic concerns, grandiosity, suspiciousness, and unusual thought content; hallucinations; and conceptual disorganization are all coded reliably on the BPRS. To qualify for treatment refractoriness, patients should be documented as having at least a 4 (moderate) on one or more of the psychosis scales of grandiosity, unusual thought content, suspiciousness, conceptual disorganization, and hallucinations. (Each symptom on the BPRS is rated on a scale of 1–7, where 1 = not present and 7 = extremely severe.) Negative symptoms—emotional withdrawal, motor retardation, uncooperativeness, self-neglect, and blunted affect—may also be present at a level of 4 or higher. More detailed rating of negative symptoms can be done using other validated scales such as the SANS or PANSS. However, treatment refractoriness to drug therapy should be defined more on the basis of the persistent positive psychotic symptoms than on the basis of negative symptoms because it is well established that conventional antipsychotic drugs have much greater effect on positive than on negative symptoms (Carpenter et al. 1985). In fact, patients may have their negative symptoms exacerbated by the pseudoparkinsonism and behavioral toxicity induced by neuroleptic drug therapy (Marder et al. 1987).

In rating the associated social and occupational deficits and behavioral deviances or acting out of psychotic symptoms, the clinician and the researcher have a number of assessment avenues available to them (Malm et al. 1981; Hurry et al. 1983; Wallace 1986). One particularly useful scale for pinpointing deficits in social and personal functioning is the Independent Living Skills Survey (ILSS; Wallace 1986). This survey, administered either by self-report questionnaire or through interview of informants, permits identification of up to nine domains in which a particular patient may function from autonomously to only with prompting and assistance or supervision. In addition, the survey documents the degree to which each functional deficiency represents a problem for the patient and his or her significant others. Figure 2 depicts the domains tapped by this instrument. Not only does the survey enable a clinician to determine the level of independence versus dependency exhibited by a patient, but its high degree of specificity also leads naturally to the formulation of operationally delineated treatment and rehabilitation goals.

Rather than arbitrarily define the level of social dysfunction necessary to determine treatment refractoriness from some rating scale, the study group advised a more functional criterion: the presence of either social deficits or behavioral excesses (e.g., aggression, incontinence, firesetting, self-injury) that singly or in combination conspire against the patient's successful placement and adaptation in an unsupervised and open community residential setting. Some exam-

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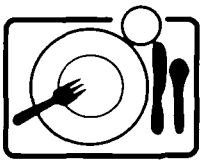
Figure 2. Independent Living Skills Survey



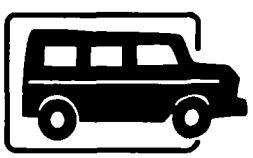
EATING
Eats at regular pace without bolting, dawdling (without prompting)

GROOMING
Bathes or showers using soap at least twice a week (without prompting)

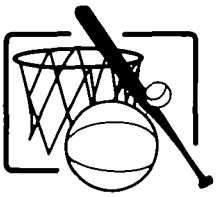
DOMESTIC ACTIVITIES
Keeps room clean (without prompting)

HEALTH
Reports physical problems appropriately, neither over nor under reporting

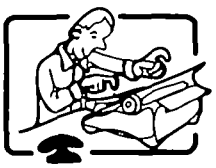
MONEY MANAGEMENT
Budgets money, planning how funds will be spent



TRANSPORTATION
Acts appropriately on busses, trains or airplanes (without prompting)



LEISURE
Works regularly on a hobby



JOB SKILLS
Contacts friends/peers/social worker/employment agencies for job leads (without prompting

SOCIAL RELATIONS
Interacts daily with family, friends or casual contacts in a congenial manner

INDEPENDENT LIVING SKILLS SURVEY

Scales-Rate for past month

1. Frequency of occurrence

N/O	0	1	2	3	4
No Opportunity	Never	Sometimes	Often	Usually	Always

2. Degree of behavioral problem or disturbance to others

0	1	2	3	4
Never	Occasionally	Sometimes	Frequently	Always

3. Global level of functioning

1	2	3	4	5	6	7	8	9	10	11
Not successful in adjusting to the demands of day-to-day life in the community										Extremely successful in adjusting to the demands of day-to-day life in the community

The Independent Living Skills Survey taps nine domains of functioning required for community adaptation. Ratings are made for the degree of independence (vs. required supervision and prompting) exercised by the patient and the degree to which deficits from each domain create problems for the patient's family, caregivers, or significant others.

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Table 2. Examples of schizophrenic patients who met criteria for treatment refractoriness

- A 33-year-old, single, never-employed male whose positive, psychotic symptoms had their onset at age 17. He has never been free of these psychotic symptoms, despite adequate trials of neuroleptic drugs. He has auditory hallucinations and persecutory and fantastic delusions that consistently rate 6 or 7 on the Brief Psychiatric Rating Scale (BPRS). His negative symptoms include anergia, amotivation, social withdrawal, and poverty of speech, all of which are rated "moderately severe" or "severe" on relevant BPRS items.

  He displays episodic aggression and has therefore been unplaceable in community facilities. He also has exhibited self-injurious behavior, burning himself intentionally with cigarettes. His functional deficits include poor grooming, refusal to make his bed or keep his personal belongings in order, inability to manage his money, and social isolation. When he is approached socially, he turns away, averts his gaze, and speaks inaudibly.
- A 38-year-old, single, woman who worked as a typist for 1 year before experiencing the onset of persecutory delusions, auditory hallucinations, and incoherence at the age of 19. Despite adequate doses of neuroleptics, her psychotic symptoms continue unabated.

  However, neuroleptic medication does reduce her acting-out behaviors such as aggression and denudativeness. Her functional deficits include poor grooming, provocative social behavior, continual complaining and whining, and refusal to participate in recreational activities.
- A 41-year-old, never-married male who has been continuously hospitalized for 6 years because of persisting positive and negative psychotic symptoms and incontinence. The latter prevents placement in a community facility. He has grandiose delusions and auditory hallucinations and is often so distractible that he cannot concentrate on simple tasks.

  Intermittently, but for only brief periods of months at a time, he has been able to regain earlier skills, such as drawing and piano playing. His memory is poor and he cannot keep track of his clothes or personal possessions, frequently losing his eyeglasses, wristwatch, and radio. He fails to count his change and is often exploited by others for his money.

ples of this criterion are given in the case vignettes in table 2.

The study group designed a global rating of the continuum of responsiveness or refractoriness to antipsychotic drug therapy. It was agreed that a rating scale keyed to ratings from the Clinical Global Impressions scale (CGI; Guy 1976), the BPRS, and the ILSS might serve a useful screening function for determining assignment of patients to treatment programs or research protocols. The 7-point scale is delineated in table 3.

Discussion

With the need to galvanize consensus among the research and practitioner communities regarding how conceptualization of treatment refractoriness in schizophrenia is defined, the study group has proposed an operational definition based on three major domains: treatment and clinical history, persistent psychotic symptoms, and associated social dysfunction and behavioral deviances that interfere with community adaptation. It is recognized that relying on the clinical history of a patient's purported exposure to adequate drug and psychosocial treatments may be limited by unreliable information. Moreover, complexities such as the patient's compliance with medication regimens, unique problems of drug absorption and metabolism, and side effects that obviate effective use of antipsychotic drugs may cloud the effort to define refractoriness. Hence, further screening for treatment responsiveness under well-controlled and defined therapy protocols may be required before a patient is determined to be "refractory" (Kane et al. 1988).

The study group's recommendations should provoke researchers and clinicians alike to undertake studies of patients who show suboptimal response to conventional neuroleptics and to clarify whether such patients are "apparently" or "truly" refractory. The use of operational criteria such as those presented in this article is increasingly important as new, atypical antipsychotic drugs—such as clozapine—become available for routine use. Having consensually agreed-upon criteria for "treatment refracto-

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Table 3. Rating Scale of Treatment Response and Resistance in Schizophrenia.

Level 1—**Clinical remission.** Rapid and substantial response when given antipsychotic medication in recommended dosage, but the patient might manifest some anhedonic traits and other negative symptoms. CGI: normal, not mentally ill. Any of the BPRS psychotic scale items score $\leq$ 2. Able to function without supervision.

Level 2—**Partial remission.** Rapid reduction of schizophrenic symptoms with mild signs of residual psychotic symptomatology. CGI: score of 2 = borderline mentally ill. None of the BPRS psychotic scale items score $\geq$ 3. Able to function with only occasional supervision in one domain of social and vocational activities.

Level 3—**Slight resistance.** Slow and incomplete symptom reduction and residual positive and negative symptoms have adverse effects on two or more areas of personal and social adjustment requiring occasional supervision. CGI: score of 3 = mildly ill. Not more than one BPRS psychotic scale item score $\geq$ 4.

Level 4—**Moderate resistance.** Some symptom reduction, but persistent and obvious symptoms adversely affect four or more areas of personal and social adjustment requiring frequent supervision. CGI: score of 4 = moderately ill. Two of the BPRS psychotic scale items scores = 4. Total BPRS score adds to at least 45 on the 18-item version and at least 60 on the 24-item expanded BPRS.

Level 5—**Severe resistance.** Some symptom reduction, but persistent symptoms adversely affect six or more areas of personal and social adjustment requiring frequent supervision. CGI: score of 5 = markedly ill. One BPRS psychotic scale item score = 5, or at least 3 of the items = 4. Total BPRS score of at least 50 on the 18-item version and at least 67 on the 24-item expanded version.

Level 6—**Refractory.** Slight or no obvious symptom reduction, and persistent positive and negative symptoms that markedly disrupt all areas of personal and social adjustment. CGI: score of 6 = severely ill. At least one BPRS psychotic scale item score = 6, or two items score $\geq$ 5. The total BPRS scores are at least as high as in level 5.

Level 7—**Severely refractory.** No symptom reduction, with high levels of positive and negative psychotic symptoms associated with behavior observed to be helpless, disturbing, or dangerous. All areas of personal and social adjustment are seriously impaired and require constant supervision. CGI: score of 7 = among the most extremely ill patients. At least one BPRS psychotic scale item score = 7. Total BPRS scores are at least as high as level 5.

Note:—The scale levels consist of an index of values from the Clinical Global Impressions scale (CGI), the psychotic items from the Brief Psychiatric Rating Scale (BPRS), and a determination of independent functioning from a scale such as the Independent Living Skills Survey. "Rapid" reduction of symptoms is defined by relief in the first 6 weeks of treatment. To permit initial treatments to have their effect, no patient should be classified as Level 5 or higher before 2 years of persisting symptoms and disability have elapsed following the first admission to hospital. For convenience, the Global Rating Scale can be collapsed into three levels: 1 and 2 reflect "remission"; 3 and 4 reflect "suboptimal response"; and 5, 6, and 7 reflect "treatment refractory."

riness" will permit comparisons across facilities and countries in evaluating the risk-benefit ratio of new treatment agents, alone or in combination with specified psychosocial milieus and programs.

Consensus on defining refractoriness can also have a salutary effect on research into the heterogeneity and biological bases of schizophrenia. It is likely that patients who respond to neuroleptics and those who do not respond reflect variations in the nature or causes of their schizophrenic disorders. At this point in the understanding of the heterogeneity of schizophrenia, the study group felt that a multidimensional and continuum-based method of operationally defining refractoriness would be more heuristic than a dichotomous method.

The primary needs of clinicians and researchers for methods to plan treatment and clinical trials led the study group to construct a classification that may permit criteria to be set for referring patients to intensive programs of social learning and rehabilitation, as well as to controlled trials of novel and adjunctive antipsychotic drugs. Preliminary efforts in the United States, Sweden, and Germany to use the criteria identified in this article suggest the potential for acceptable interrater reliability.

The proposed rating system can also be used for assessing the treatment needs of schizophrenic patients, since levels are based on an integrated assessment of social functioning and symptom expression evidenced at a particular time. Levels 1 and 2, "remission," might indicate no need for a formal rehabilitation program. Levels 3 and 4 indicate responsiveness to a learning-based rehabilitation program. Level 5 suggests the need for a continuous, individually oriented strategy; for intensive trials of atypical or adjunctive antipsychot-

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ics; and for a team approach to case management. Levels 6 and 7 clearly indicate longer-term hospitalization with empirical trials of untried pharmacological or psychosocial treatments. It is hoped that the wider-scale testing of the constructs, criteria, and instruments described in this article will lead to further research and development aimed at fostering clearly demarcated, operationalized, and measurable criteria, thereby making the assessment of treatment refractoriness replicable and useful in research and clinical practice.

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