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After completing this CME activity, physicians practicing clinical psychiatry should be able to:

- Understand differences in patients' antipsychotic response patterns in terms of the biological heterogeneity of the schizophrenia syndrome

Statement of Need and Purpose

Antipsychotic response varies across the spectrum of schizophrenia and schizophrenia-related disorders. This CME activity is designed to address the needs of physicians who have requested information on the rationale for such differences in response among patients with such disorders. There are no prerequisites for participation in this CME activity.

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Heterogeneity of Response to Antipsychotics From Multiple Disorders in the Schizophrenia Spectrum

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Background: Antipsychotic response after the initiation of neuroleptic treatment shows wide variation in schizophrenic patient populations. In this overview, the authors suggest that the variance in antipsychotic drug response within schizophrenia can be reduced by resolving the schizophrenias into several discrete "endophenotypes," each with different etiologic underpinnings.

Method: Studies relating differences in the relative speed or completeness of antipsychotic response to differences in distribution of 2 biological markers with possible etiologic significance are reviewed. Such studies had assessed recently hospitalized, neuroleptic-free patients undergoing exacerbation of nonaffective psychotic disorders. Prior to initiation of neuroleptic, the cohort of patients had been assessed for the quantity of the dopamine metabolite homovanillic acid in plasma (pHVA) and had undergone the first of 2 magnetic resonance imaging (MRI) studies for analyses of ventricle volumes. A second MRI was subsequently performed during a period of (partial) remission to determine within-patient stability of ventricular volumes. These selected studies assessed the distribution of pHVA and distribution of rates of ventricular change, with non-normal distributions resolved by K-means clustering. The speed and completeness of neuroleptic-induced antipsychotic response were related to 3 clusters of patients delineated by modal distributions of pHVA and of apparent rates of ventricular change.

Results: At least 3 unique "endophenotypes" of the "group of the schizophrenias" can be defined with respect to speed and completeness of antipsychotic response. Each endophenotype appears to show at least one unique biological feature that differentiates it from a normal comparison group. A rapidly responsive psychosis was associated with excessive production of dopamine, as identifiable by elevation of pHVA and a "good-prognosis" course. A delayed-response psychosis had low-to-normal pHVA, clinically demonstrated persistent negative symptoms, and was associated with an excessive rate of change in ventricle volume between exacerbations of psychosis and (partial) remissions. Finally, a nonresponsive psychosis could be characterized as having both low-to-normal pHVA and rate of change of ventricle volumes similar to that of controls. Additional studies revealed that each of the endophenotypes had high rates of the psychoses in family members. The good-prognosis course of the rapidly responsive group of studied patients was also found in their family members who had psychotic disorders. Similarly, the prominent negative symptoms of the delayed-response probands were reflected as a prominent trait in their family members also afflicted with psychosis. The endophenotypes tended to "breed true" in terms of prognosis and negative symptoms.

Conclusion: Major differences in antipsychotic response patterns appear to be associated with patient and family characteristics that may be related to differences in the etiology and consequent pathophysiology of illness.

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The fortuitous discovery in the French asylums during the 1950s that the antihistamine chlorpromazine had unusual antipsychotic properties for patients with psychoses[1] heralded several revolutions in psychiatry. Clinically, it provided relief from hallucinations and delusions for a substantial number of patients burdened with psychosis, allowing many patients at least partial access to rehabilitative therapies. Scientifically, together with the parallel discoveries of the antidepressants, it prompted a conceptual revision in psychiatry. It led to the conclusion that a substantial number of psychiatric disor-

ders are fundamentally biological and resulted in a reinvestment in the medical model in psychiatry.

Despite 40 years of research into schizophrenia, our understanding remains quite limited with respect to how such drugs produce or induce antipsychotic effects in most psychotic patients. Between-patient differences in response patterns,[2] and, sometimes, within-subject inconsistency of response patterns[3] after initiation of neuroleptics, remain poorly understood. The relatively recent appreciation that the schizophrenic psychoses themselves may be etiologically heterogeneous[4,5] and that antipsychotic effects may be induced by different mechanisms (different pharmacodynamics) in different psychotic conditions have provided new directions for exploring such treatment-response heterogeneity.

This integrative overview is grounded in observations first reported in 1988[2] which demonstrated that speed of antipsychotic response in a group of schizophrenic-like patients is trimodally distributed. Three subgroups of schizophrenic patients were defined, whose time course to antipsychotic response following initiation of a neuroleptic suggested 3 pharmacodynamically distinct mechanisms of action of the neuroleptic: (1) a direct effect blocking a putative excess in synaptic dopamine; (2) an indirect effect with a delayed time course, suggesting that dopamine blockade initiated a series of other linked processes which, after several weeks, eventually resulted in an antipsychotic response; and (3) a noneffect with failure of antipsychotic response following similar neuroleptic-induced dopamine receptor blockade.[2] It was further suggested that each of these patterns of response provided a differential "signal" pointing to different underlying biological processes. The purpose of this review is to (1) confirm with an expanded number of schizophrenic-like patients initial data related to differential speed and completeness of antipsychotic response and (2) integrate these 3 clinical response patterns with evidence from the recent literature on these same patients, which suggests differing underlying biopathology in each of these schizophrenic-like psychotic subtypes.

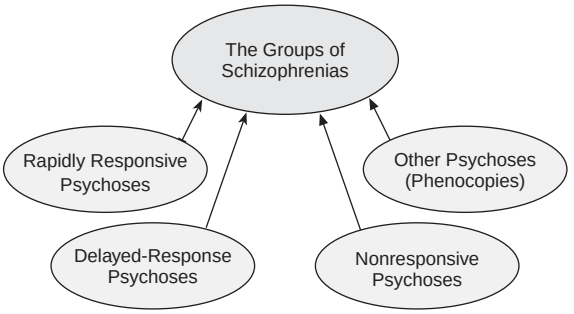
We argue that present evidence suggests that several different disorders/diseases with associated different response patterns (different "endophenotypes") are nested within the commonly defined "schizophrenia syndrome."

METHOD

Eight previously published articles from our laboratory describe (1) rates and completeness of reduction of "positive" symptoms of psychosis following neuroleptic initiation, (2) patterns of premorbid and residual "negative" symptoms in patients and in their family members, and (3) studies of potentially relevant biological markers. These domains are integrated in the present article. In these studies of recently admitted, consenting patients (drug-free for at least 2 weeks), positive psychotic symptoms and the time course of their reduction were assessed at drug-free baseline and during neuroleptic treatment by the "S" (psychosis) subset of scores from the Brief Psychiatric Rating Scale (BPRS)[6] and/or the Schedule for the Assessment of Positive Symptoms (SAPS).[7] Negative symptoms were monitored premorbidly by a modification of the Phillips Scale described in the Comprehensive Assessment of Symptoms and History (CASH)[8] and during the study by the Schedule for the Assessment of Negative Symptoms (SANS).[9] Following structured assessments according to the CASH, patients were diagnosed according to the DSM-IV[10] with disorders of the schizophrenia spectrum: schizophrenia, schizoaffective disorders, schizophreniform disorder, or psychosis not otherwise specified. The drug-free patients also underwent studies of the primary metabolite of dopamine in plasma, plasma homovanillic acid (pHVA) (3 samples were drawn, each at 7:00 a.m.), with the mean calculated, and underwent the first of 2 magnetic resonance imaging (MRI) volumetric assessments of cerebral ventricles. A second MRI volumetric assessment permitted the assessment of volume changes associated with treatment. Each of the following distributions were assessed for normality: (1) the number of days until treatment response criteria were met, (2) the quantitative baseline drug-free pHVA, and (3) the change in ventricle volume between acute exacerbation and subsequent (partial) remission. The non-normal distributions of pHVA and change in ventricle volume were each resolved into bimodal distributions using K-means clustering. First- and second-degree family members of patients also were assessed for life history of psychiatric disturbances using the CASH,[8] the DSM-IV,[10] and the Structured Clinical Interview for DSM-III-R Personality Disorders,[11] and current symptoms were recorded using the SAPS[7] and SANS[9] to determine whether symptom patterns "breed true" within pedigrees. Differences in rate and completeness of drug-treatment response were assessed by repeated measures analysis of variance. Details of all the methods are found in the original publications.[2,4,5,12,13]

Herein we review recent data that suggest that 3 subgroups of schizophrenia spectrum psychoses exist with respect to rapidity of antipsychotic response. We relate each of these 3 response subgroups to variations in biological findings from the same patients, biological varia-

Figure 1. The Putative Endophenotypes That Make up the Schizophrenia Syndrome



tions that may be associated with etiologic underpinnings of the different patterns of drug response and of the disease(s). The working integrated conceptual framework is featured in Figure 1. We suggest that much of the within-syndrome variance, including the heterogeneity of antipsychotic response, can be reduced by the reformulation of schizophrenia not as a single disease, but as a clinical syndrome associated with a series of distinct endophenotypes. We review and attempt to integrate data which suggest that each clinical endophenotype is the consequence of a unique, etiologically distinct process. Each process leads to the expression of a relatively common syndrome, diagnosable using the DSM-IV as disorders of the schizophrenia spectrum.

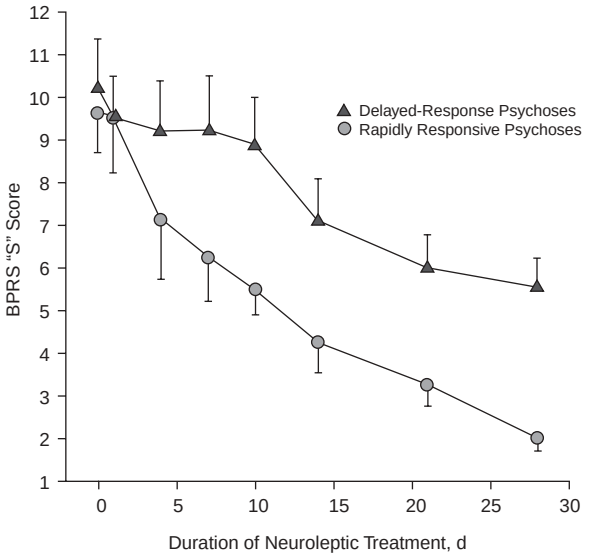
RESULTS AND COMMENTARY

The assessments and analyses noted above suggest that data variance found in the familial psychoses can be reduced by separating the patients' illnesses into at least 3 endophenotypes based first on the distributions of pHVA and second on the assessment of the residual patients with respect to the distribution of rate of change of cerebral ventricles. Each of these putative endophenotypes appears to have a relatively unique response pattern following the introduction of a neuroleptic.

Rapidly Responsive Psychosis

The distribution of pHVA in 32 schizophrenic-spectrum patients differed significantly from normal levels ($p < .033$), but fit a 2-cluster model ($F = 134.4$). One cluster of patients ($N = 17$) was found to have a mean ± SD pHVA of 53.6 ± 12.5 pmol/mL, while another cluster ($N = 15$) had a pHVA of 115.1 ± 16.4 pmol/mL.[4]

Figure 2. Changes in Brief Psychiatric Rating Scale (BPRS) "S" (Psychosis) Score During the First 28 Days of Neuroleptic Treatment in Psychotic Patients With High Plasma Homovanillic Acid Levels (pHVA) (Rapidly Responsive Psychoses) and in Patients With Normal-to-Low pHVA[a]



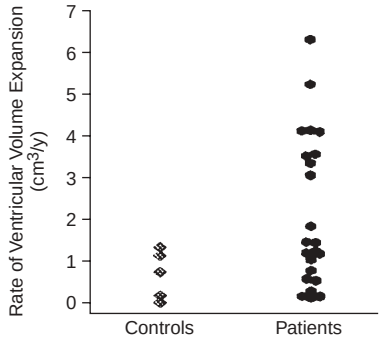
[a]Data from Garver et al.[4]

From chart reviews and longitudinal illness course information provided from the CASH, the high-pHVA patients appeared to have an episodic psychosis, with sustained between-episode periods of minimal symptoms, a history of good interpersonal relationships, little overall interepisode impairment in functioning,[4] and smaller third ventricles,[14] as compared with the lower pHVA psychoses (all $p < .045$). Direct interview of 35 first-degree family members of 8 of the high-pHVA probands demonstrated an 8.6% lifetime risk of a similar psychosis.[4,12]

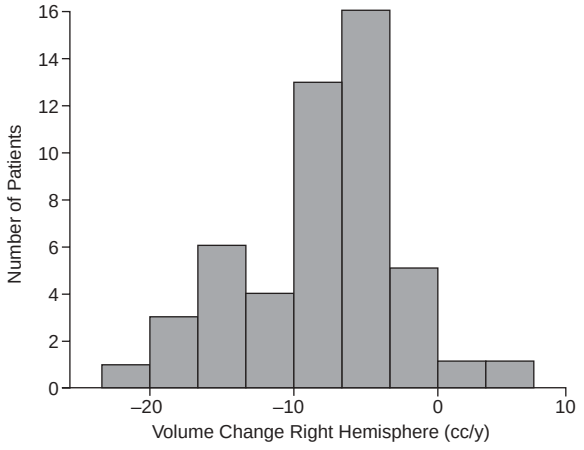
The antipsychotic effects of neuroleptic treatment (haloperidol, 10 mg/day) were quite dramatic in the high-pHVA psychotic patients. As contrasted to a group of patients with lower pHVA ($N = 9$), the high-pHVA patients ($N = 8$) had a significantly greater reduction of psychosis scores early in the course of treatment. By day 4 after the initiation of haloperidol, the high-pHVA psychotic patients had already shown reduction of baseline psychosis scores by > 30%. By day 7 and thereafter, as contrasted to the low-pHVA patients, there was significantly greater improvement ($p < .021$) at all timepoints despite comparable plasma haloperidol levels. At 28 days of treatment, high-pHVA patients had achieved a mean ± SD reduction

Figure 3. Rate of Ventricle and Brain Volume Change in Patients With Delayed-Response or Nonresponsive Psychosis

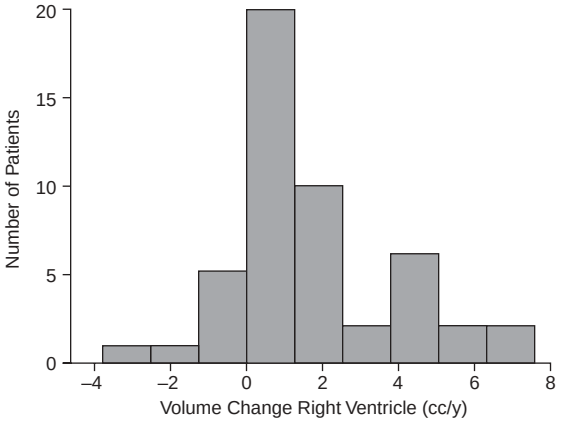
A. Bimodal Distribution of Ventricle Expansion in Delayed Responders and Nonresponders (patients without elevated pHVA; N = 22) and in Controls (N = 5)[a]



B. Bimodal Distribution of Change/Year in Right Hemisphere Volume (N = 50)[b]

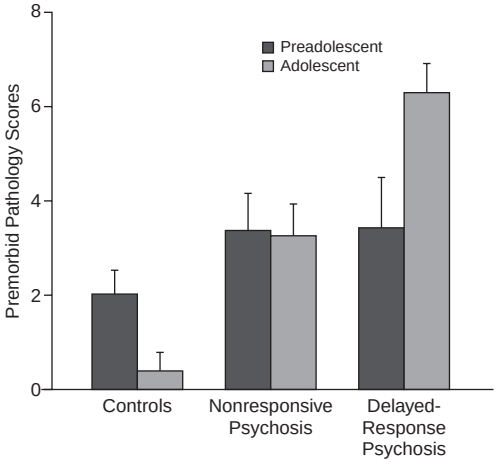


C. Bimodal Distribution of Change/Year in Right Ventricle Volume (N = 50)[b]



[a]Data from Garver et al.[5]
[b]Data from DeLisi et al.,[16] reanalyzed by Garver et al.[17]

Figure 4. Premorbid Adjustment (modified Phillips Scale) During Preadolescence and Adolescence in Controls, Stable Brain (nonresponsive) Psychosis, and Unstable Brain (delayed-response) Psychosis[a]



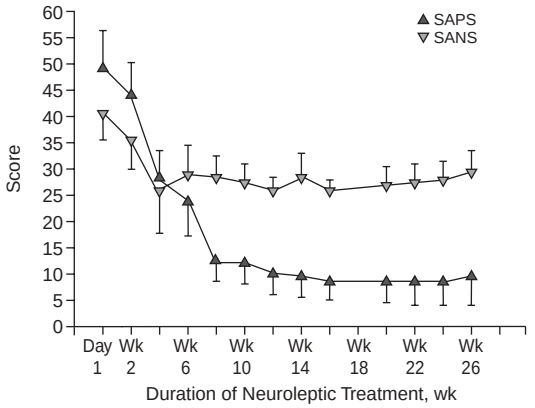
[a]Data from Garver et al.[5]

of 76.8% ± 13.3% in baseline BPRS "S" scores, while lower-pHVA patients showed 50.5% ± 12.2% improvement ($p = .001$)[4] (Figure 2). The rapidity of antipsychotic response was similar to that reported previously in a cohort of 15 patients.[2]

Delayed-Response Psychosis

The advent of serial cerebroventricular imaging enabled a further differentiation of the nondopamine psychoses into additional subtypes or separate disorders. Recent serial studies of the ventricle-brain ratio (VBR)[14] and the volume of cerebroventricles (Figure 3A and 3C)[15] and brain (Figure 3B)[16,17] have reported that some schizophrenic-like patients show instability of brain and ventricle volumes from times of acute exacerbation to subsequent times of (partial) remission. In a cohort of 22 subjects, rates of brain or ventricular change between scans appeared to differ from that expected from a normal (Gaussian) distribution ($p < .01$), but were resolved by K-means clustering (SYSTAT for Windows[18]) into 2 clusters, indicative of 2 patient groups: 20% to 40% of patients evidence rate of brain and ventricular change > 3 times that of controls and other psychotic patients (Figure 3).[5,17] The process of excessive ventricular and brain change did not appear to be limited to a single phase of the illness, since it was present at and following the first episode (Figure 3B and 3C),[16,17] was associated with subsequent episodes throughout

Figure 5. Neuroleptic Response During 6 Months of Neuroleptic Treatment With Respect to Positive Symptoms and Negative Symptoms in Patients With Delayed-Response Psychoses With Unstable Brain and Ventricle Volumes[a]



[a]Data from Garver et al.[5] Abbreviations: SANS = Schedule for the Assessment of Negative Symptoms, SAPS = Schedule for the Assessment of Positive Symptoms.

middle age (Figure 3A),[5,15] and has also been reported in patients aged in their late 60s and 70s,[19] where it is accompanied by profound negative symptoms and dementia (praecox dementia).[20]

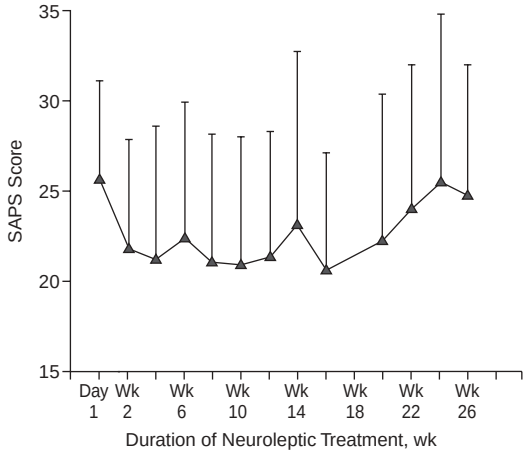
Such patients with psychosis with unstable brain and ventricle volumes were recently reported as having a prodrome of progressive withdrawal from interests and peer relationships from preadolescence through young adulthood[5] (Figure 4), a withdrawal that subsequently is punctuated by episodes of psychosis. Beginning with the withdrawal patterns seen during preadolescence and adolescence, the negative "trait-like" symptoms of these patients with unstable ventricle volume persist throughout the subsequent course of illness. Figure 5 shows the change of negative symptoms (SANS), or lack thereof, in such patients during course of treatment with ≈ 7 mg/day of haloperidol.

Beginning in week 3 of neuroleptic treatment and continuing to week 10 of treatment there was a steady, although delayed, antipsychotic response demonstrated by the reduction of SAPS scores in 8 patients with unstable ventricle volume[5] (Figure 5). This time course was similar to that in a group of 27 delayed-response patients reported in another cohort of patients[4] (Figure 2). In contrast, the course of negative symptom improvement was limited to the initial 4-week period of reduction of positive (SAPS) symptoms. Thereafter, SANS scores reflected persistent trait impairment, previously noted as developing during the prepsychotic phase of the illness. Such persistent and progressive negative symptoms appear to be a hallmark of the disease process characterized clinically by delayed antipsychotic response and unstable ventricle and brain volumes. The prominence of negative symptoms in patients also appears to be replicated as a distinct familial pattern in affected pedigree members of probands with delayed-response psychosis.[13] Later in the course of the disease, in patients aged 60 to 80 years, many schizophrenic-like patients with such instability of ventricles and brain have been reported to have lost interest in self-care, require continuous caregivers, and evidence an emerging dementia (praecox dementia), a dementia that at postmortem examination does not manifest the hallmarks (plaques and tangles) of Alzheimer's disease.[19,20]

Critical questions concerning the etiology of the ventricle-brain instability of delayed-response psychosis remain. If the etiology of the disorder were known, it is possible or even likely that specific interventions to prevent or to arrest this apparently active process could be devised. For example, if the ventricle-brain changes were due to inflammatory processes associated with inadequate production of neurotrophins or defective neurotrophins, delivery of such substances to an affected brain might arrest further progression. If such changes were associated with failure of detoxification of metabolism-induced peroxidases, antioxidants might be important in treatment. The underlying nature of the instability of ventricle-brain volumes and the development of focused interventional procedures remain the subject of investigation.

In the meantime, the use of D_2 receptor antagonists, albeit in an indirect and delayed manner not yet understood, ameliorates the acute psychotic decompensations associated with delayed-response psychosis with unstable brain and ventricle volumes and may provide some prophylactic effects on its progression.[21] Such D_2 blockade appears to set into motion a cascade of effects that results in partial reduction of the positive psychotic features (hallucinations, delusions, and thought disorder) of this syndrome over a time period of 2 to 10 weeks (instead of 4–7 days, as in dopamine psychosis[4]). This delayed period until antipsychotic response suggests that relevant mechanisms of action may include the sequential activation of multiple pathways, including gene activation and transcription, translation of new proteins, and/or the evolution of new or strengthened synaptic connections. The putative partial protection from poor outcome occasioned by early (vs. delayed) initiation of neuroleptics may be due to partial interruption of an ongoing process that underlies both

Figure 6. Neuroleptic Response in Patients With Nonresponsive Psychoses With Stable Brain and Ventricle Volumes[a]



[a]Data from Garver et al.[5] Abbreviation: SAPS = Schedule for the Assessment of Positive Symptoms.

positive and negative symptomatology. Wyatt[21] has reported that prompt diagnosis of schizophrenia and prompt treatment result in less morbidity than when diagnosis and/or initiation of D_2-blockade treatment has been delayed. Although initial, partial reduction of negative symptoms may parallel the partial reduction of positive symptoms, further reduction of negative symptoms stalls, revealing a negative-symptom or avolitional "trait-like" defect characteristic of the delayed-response disorder with unstable brain and ventricle volumes (see Figure 5).

Nonresponsive Psychoses

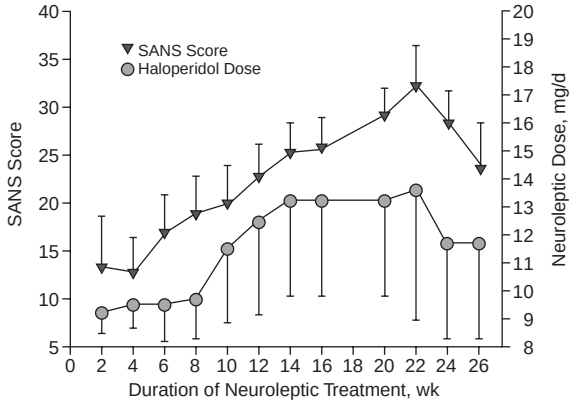
A substantial number of psychotic patients have neither rapid response following initiation of antipsychotics with evidence of excess dopamine production nor delay in response to treatment with evidence of brain and ventricular instability. Among this "residual" group of patients, single, cross-sectional brain and ventricular volumes have been found to be highly variable: some were grossly indistinguishable from controls, others showed evidence of substantial anatomic abnormalities of volume and cytoarchitecture.[5] However, serial anatomic studies showed no evidence of volumetric changes in excess of those found in controls. Probably the most viable explanation for these observations, especially in those patients with large ventricles, has focused on anomalies of brain development and, more particularly, on anomalies as a consequence of defective early neuronal migration and circuitry development.[22]

Conventional, classical antipsychotic drugs have been the mainstay for treatment of these nonresponsive psychoses, as for the other types of schizophrenia. However, their effectiveness in the treatment of such patients may be marginal at best. Reports of the relative ineffectiveness of antipsychotic drugs in the treatment of first-episode teenaged psychotic patients who have large cerebral ventricles[23] suggest that such patients may either have a very malignant atrophic process or, more likely, have an anatomic anomaly of brain, presumably associated with partial failure of brain neurodevelopment. It is clear that even such neuroleptic-nonresponsive patients have periods of relative remissions and exacerbations, the latter often being associated with physical and especially psychological stressors. Such fluctuations of the positive symptoms of the disorders are often associated with life changes, such as the loss of stabilizing persons or stabilizing living situations, and the use of substances, particularly stimulants such as cocaine. Use of cocaine and other drugs of abuse has previously been reported to be more prevalent in these nonresponsive psychoses with stable brain and ventricle volumes than in delayed-response psychoses with unstable brain and ventricle volumes.[15]

Initiation of neuroleptic treatment in patients with such stable brain and ventricle volume psychoses (with normal-to-low pHVA) results in an early partial reduction of the acute exacerbation of symptoms occasioned by acute stressors. A 15% to 20% reduction of positive psychotic symptoms was common in the first days of treatment, but thereafter, further antipsychotic effects of neuroleptic treatment were minimal (Figure 6).[5] Except for relieving the exacerbation of ongoing psychotic symptoms associated with the acute stressors, such nonresponsive psychoses retain a core of schizophrenic symptoms that are not readily amenable to further reduction by antipsychotic drugs despite increased drug doses.

However, it is quite likely that nonresponsive patients and their families receive substantial comfort by the use of neuroleptic drugs despite the continuation of active, unabated psychosis. As noted previously, and in contrast to the delayed-response patients, most nonresponsive patients have relatively intact affect when free of medications. Except for paranoid isolation with interruption of peer relationships, these patients do not present with prominent negative symptoms. Open-label dose increases of neuroleptic drugs in such patients in an effort to (unsuccessfully) reduce positive psychotic symptoms was found to be accompanied by the emergence of negative symptoms as monitored by the SANS. The effects of such dose escalation from an initial dose of 9.0 mg/day of halo-

Figure 7. Change in Negative Symptoms in Patients With Nonresponsive Psychoses With Stable Brain and Ventricle Volumes in Relation to Open Increase of Haloperidol Dose[a]



[a]Data from Garver et al.[5] Abbreviation: SANS = Schedule for the Assessment of Negative Sypmtoms.

peridol to 14.0 mg/day of haloperidol in these patients was associated with increasing global detachment (Figure 7).[5] At higher doses of neuroleptic treatment, patients appear to be less interested in work, relationships, and recreation, but are less bothered by the continued presence of voices, persecutors, passivity, and other bizarre experiences, although such experiences persist. To the relief of clinicians and family, the patients became more docile. With subsequent reduction of such negative symptoms, greater experience of psychotic pain returned. The dilemma in the treatment of such patients is often the dilemma of reducing the patient's pain versus reducing feeling and attachment by the drug induction of negative symptoms.

DISCUSSION, SYNTHESIS, AND SUMMARY

Heterogeneity of treatment response associated with conventional neuroleptic treatment in the schizophrenic-like psychoses appears to be associated with clusters of other illness characteristics (Table 1).

A very rapid and relatively complete response following initiation of neuroleptic appears to be associated with a form of the illness (rapidly responsive) characterized by an overproduction and excess availability of synaptic dopamine and an unusually good prognosis.

Perhaps we understand best the critical mechanism of action of the conventional neuroleptics (D_2 receptor blockers) associated with antipsychotic effects in this subgroup of psychotic patients who present with such evidence of excessive activity of central dopamine systems.[24] This group of good-prognosis schizophrenic-like patients has previously been identified by several investigators on the basis of elevated plasma concentrations of the primary metabolite of dopamine, pHVA.[25–27] There appears to be an overproduction (likely the consequence of failure of feedback control) of dopamine synthesis and release, which putatively spills into synapses, bombarding and triggering excessive activity of the associated dopamine receptors. In the face of already high synaptic levels of dopamine, physiologic or psychological stress further augments dopamine release.[28] The consequence is a partially "reactive" psychosis in subjects already predisposed by failure of mechanisms that ordinarily restrain synaptic dopamine.

Table 1. Characteristics of Response Subtypes of the Schizophrenias[a]

Subtype	Defining Features	Clinical Course	Evidence
Rapid response	Elevated pHVA, normal ventricle size	Good prognosis for patient and family	Garver et al,[2] Garver et al,[4] Sautter et al,[12] Kaplan et al[14]
Delayed response	Normal-to-low pHVA, unstable ventricle	Negative symptoms in patient and family	Garver et al,[2] Garver et al,[4] Garver et al,[5] Sautter et al,[12] Davis et al,[19] Pruohit et al[20]
No response	Normal-to-low pHVA, stable ventricle	Persistent psychosis	Garver et al,[2] Garver et al,[5] Filbey et al[13]

[a]Abbreviation: pHVA = plasma homovanillic acid level.

In such rapidly responsive dopamine psychoses, blockade of D_2 receptors by conventional D_2 antipsychotics appears to rapidly compensate for the excess synaptic dopamine and provides almost immediate relief from hallucinations, turmoil, and associated disruption of cognitive processes. D_2 antagonists impede access of the excess synaptic dopamine to postsynaptic D_2 receptors. Relief of psychotic turmoil and hallucinations and restoration of cognitive coherence begins within a few hours of D_2 antagonist initiation, with the patient substantially improved in the first few days of treatment. Depending on the duration of the episode, well-formed delusional "gestalts" may be much more persistent and require weeks to months to extinguish.

Aid in identifying such patients also comes from examination of the course of psychotic illness in the patient and in his or her pedigree, as well as the patient's history of previous response. A similar good-prognosis psychotic disorder is often found in other affected members of the patient's pedigree. Laboratory diagnosis by excess pHVA

is often unavailable and is likely to be useful only when the patient has been free of neuroleptic drugs for > 2 weeks.

A second moderately responsive psychotic illness, characterized by trait-like negative symptoms in both the drug-free and neuroleptic-treated state and by a slow evolution of greater latency and incompleteness of antipsychotic response during subsequent trials of neuroleptics,[3] appears to be associated with an instability of ventricle-brain volumes and, perhaps, with progression of brain atrophy.[15–17] It is possible that the progression of this as yet poorly understood process can be retarded both anatomically and clinically by early and regular use of neuroleptic medication.[21] It is likely, although not yet clearly demonstrated, that the atypical antipsychotics (especially clozapine) have ameliorating effects far into illness progression. Future work with these delayed-response psychoses with unstable brain and ventricle volumes needs to focus on the mechanisms underlying such instability, so that future treatment intervention can be directed more specifically toward the offending deficiencies (or excesses) responsible for the process, rather than relying on the indirect effects of simple D_2 blockade on the cascade of relevant events.

A third, poorly responsive series of psychotic illnesses may arise as the consequence of failure of neuroblast proliferation and/or migration, and failure of establishing coherent homeostatic circuitry within the central nervous system. The delayed emergence of prominent psychotic symptoms until late adolescence may be due to the protection offered by the juvenile pattern of redundant synaptic connections and circuitry, which diminishes during adolescence as a consequence of physiologic pruning.[29]

It is possible that both genetic and nongenetic forms of these nonresponsive neurodevelopmental psychoses exist. The genetic forms may be the consequence of multiple additive gene irregularities. Nongenetic forms (or partially nongenetic forms) may be the consequence of viruses[30] or malnutrition[31] on fetal development. The pain of such nonresponsive psychoses may be partially alleviated by stress reduction and supportive interventions through individual psychosocial engineering. The use of conventional antipsychotics, although providing little relief of hallucinations, delusions, and cognitive disturbances, may yet relieve pain associated with these positive symptoms via induction of negative symptomatology, partially dissociating the patient from the discomfort of both hallucinations and delusions, but also, unfortunately, from interests and relationships. Better treatment strategies are clearly needed for the nonresponsive psychoses. Partial arrest of the physiologic pruning process (as by steady delivery of neurotrophic-like substances to the brain to partially prevent physiologic synaptic pruning) might be a possible alternative to prevent the emergence of psychosis, if the potential for psychosis could be identified early. It is also not unthinkable that deficient circuitry can now be constructed from pleopotential, as yet undifferentiated cells still present and active within the brain.

The reconceptualization of schizophrenia as not one disorder, but a series of disorders, and the clustering of data distributions so as to delineate several relatively distinct endophenotypes may permit considerable reduction of the variance found in virtually all parameters described within the schizophrenic-like psychoses. Of special relevance presently is the treatment-response heterogeneity observed across the spectrum of schizophrenic illnesses. This novel manner of conceptualizing the heterogeneity of schizophrenia and antipsychotic response in the schizophrenias is based on a series of relatively small data sets over various domains, each of which needs be confirmed in other laboratories. Also of considerable interest is the potential association of each of the putative endophenotypes of schizophrenia noted herein with one or more of the multiple genomic susceptibility regions that are being described in pedigrees multiplex for schizophrenia.[32]

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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Instructions

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1. Three endophenotypes of the schizophrenias have been shown to:
   a. Each link at distinct unique genomic sites
   b. Have different family patterns of illness
   c. Respond to antipsychotic drugs similarly
   d. Have identical symptom patterns

2. Breeding true is associated with:
   a. Resistance to the use of artificial insemination
   b. Characteristic clinical features found in both patient and family members
   c. Random, as contrasted to selective, breeding
   d. Selection of the fittest in reproductive choice

3. Differences in antipsychotic response patterns are thought to be due primarily to:
   a. Different underlying biopathologies within the schizophrenia spectrum
   b. Different pharmacokinetics of drug absorption and metabolism
   c. Different concentrations of antipsychotic at the D_2 receptor
   d. Altered linkage between D_2 receptors and second messenger systems

4. Rapid antipsychotic response following the initiation of haloperidol treatment is associated with:
   a. Sensitization from previous treatment with conventional antipsychotics
   b. Family history of anxiety disorders
   c. Drug-free homovanillic acid elevation in plasma
   d. Enlarged cerebral ventricles

5. Negative symptoms are associated with:
   a. An excess of dopamine synthesis and release in cortical areas
   b. Abnormalities of early cellular migration during fetal development
   c. Unstable brain-ventricle volumes during psychosis exacerbation and remission
   d. Greater interpersonal and vocational challenges during rehabilitation from psychotic episodes

6. Delay of 2 to 5 weeks in onset of antipsychotic effects in the unstable-brain psychosis suggests:
   a. A larger lipid compartment exists in the unstable-brain psychosis, resulting in delayed steady-state antipsychotic concentrations for ameliorative effects.
   b. D_2 blockade is but a first step in a long chain of biological activations that ultimately result in antipsychotic effects.
   c. Initial compliance with medication is poorer in patients with volumetrically unstable brains.
   d. Peripheral protein binding, until fully saturated at 2 to 5 weeks, makes free drug relatively unavailable to cross the blood-brain barrier to elicit antipsychotic effects.

7. Development of the unstable-brain (delayed responsive) psychosis can often be detected in adolescence by:
   a. Extremes of sexual activity
   b. Family history of depressive spectrum disorders
   c. Assessment of plasma homovanillic acid (pHVA)
   d. Emergence of negative symptoms

Answers to the June 2000 CME posttest

1. a 2. c 3. d 4. b 5. a 6. c 7. b

Circle the one correct answer for each question.

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