Cognitive Functioning in Late-Life Schizophrenia: Its Importance and Implications for Overall Outcome

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Cognitive impairment is an intrinsic feature of schizophrenia and a discriminating factor between patients who require high and low levels of community support. Although it was long believed that positive and disorganized symptoms of schizophrenia "burned out" over time and only negative or deficit symptoms would be detected in late life, several recent studies have suggested that this conception is not fully accurate. However, patients who are unable to care for themselves and suffer from deficits in adaptive life functioning often have negative symptoms as well as severe cognitive impairment. The strong correlation with cognitive function, even when the severity of negative symptoms is considered, suggests that interventions aimed at improvement of adaptive outcome may be targeted at enhancement of cognition. These interventions may include atypical neuroleptic medications and augmentation strategies directly targeting cognition with specific agents that may not affect the positive or negative symptoms of the illness. *(J Clin Psychiatry 1999;60[suppl 13]:10–16)*

Cognitive impairment is now recognized as an important feature of schizophrenia. For the past 50 years, it has been recognized that patients with schizophrenia commonly perform poorly on a wide range of cognitive tests.[1] Patients with more severe cognitive impairments are more likely to have more severe negative symptoms[2] and deficits in adaptive functioning.[3] Overall outcome is also correlated with cognitive impairments—patients with a chronic course of illness are more likely to perform worse on cognitive tests than patients with more episodic illnesses.[4] This relationship also is present on a longitudinal, predictive basis in that more severe cognitive impairment early in the course of illness predicts a more adverse outcome over time.[5]

Impairments in cognitive functioning are commonly believed to be consequences of other aspects of the illness, including severe hallucinations or delusions, poor motivation, or iatrogenic effects of treatment. These factors are actually of considerably less importance in terms of cognitive functioning than would be expected at first glance. The potential causal role of positive symptoms is undermined by the finding that cognitive impairments are found to be unchanged in severity after the remission of positive symptoms following an acute episode.[6] Thus, the severity of positive symptoms is uncorrelated with the severity of cognitive impairments within individual patients. Since severity of positive symptoms has repeatedly been found to be uncorrelated with the severity of most cognitive impairments in large samples of patients with schizophrenia,[7,8] hallucinations and delusions are uncorrelated with cognitive functioning within as well as across patients.

Lack of motivation is a poor explanation for cognitive impairments in schizophrenia, because of the well-known variation in different aspects of cognitive functioning in schizophrenia.[9,10] If cognitive impairments were being produced by a global factor such as poor motivation, there is no explanation for why some cognitive tests are performed at levels consistent with the patient's level of premorbid functioning and the results of others are three to five standard deviations lower.[11] The notion of identification of differential deficits, known for years to be a desirable methodological goal,[12] would be implausible if poor motivation caused all cognitive impairment.

Similarly, somatic treatments in schizophrenia are unlikely to be the main cause of cognitive deficits. First, cognitive deficits were noted historically before somatic treatments for schizophrenia were developed.[1,13] Second, cognitive impairment is common and can be severe in neuroleptic-naive patients.[14] Third, typical neuroleptic medication has been demonstrated repeatedly to have little or no effect on the majority of aspects of cognitive functioning in schizophrenia, other than improving a limited set of attentional functions.[15] Anticholinergic medications co-administered with typical neuroleptics have been shown to worsen various aspects of memory functioning,[16] but patients who are not treated with anticholinergics also have memory deficits.[17] Finally, the grossly invasive treatments of decades ago, including frontal leukotomy[18] and insulin coma therapy,[7] have been shown to have little

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adverse effect, if any, on cognition. Thus, cognitive impairment is an intrinsic part of schizophrenia, is endogenous to the illness, and is not completely accounted for by correlates of schizophrenia or its treatment.

GENERAL OUTCOME OF SCHIZOPHRENIA IN LATE LIFE

Schizophrenia has been long noted for its variability in outcome, with a tendency toward negative outcome dominating. Only about one third of patients who meet diagnostic criteria for schizophrenia are able to resume adaptive functioning with any success, and as many as one third are chronically impaired and largely dependent on others for care on a lifelong basis.[19] Comprehensive studies suggest a wide variance in overall outcome.[20] Many patients live in the community throughout their lives and are occasionally readmitted for short-term hospital stays associated with symptomatic exacerbations.[21] Hospital-based studies have suggested that large numbers of geriatric patients with schizophrenia still reside in chronic psychiatric hospitals and function at a low level.[7,22] These patients often have a relatively early age at onset, severe negative symptoms, poor adaptive functioning (both before and after the onset of initial symptoms), and severe cognitive impairments. Although some of these patients may be discharged from the hospital, many long-stay patients are simply referred to nursing home care.[23,24] Among the characteristics of patients who are difficult to discharge in late life are belligerent and hostile behaviors,[23,25] including both verbal and behavioral aggressiveness.

In contrast to hospital-based studies, which tend to paint a fairly negative picture of outcome in the disorder, one comprehensive study has suggested that many individuals with an early diagnosis of schizophrenia are eventually discharged from the institution and live in the community for decades with modest-to-no residual symptoms. The Vermont longitudinal study[26,27] suggested that many individuals with a diagnosis of schizophrenia in early adulthood are residing in the community, with modest-to-adequate adaptive, occupational, and interpersonal functions. Since this study sample was drawn from a rural state, which generally provides different levels of support and intactness of the community than urban areas, the applicability of this study to patients from urban and suburban catchment areas is unclear. A recent study of community-dwelling geriatric schizophrenic patients[28] living in the nearby state of New Hampshire found that there was considerably more impairment in adaptive functioning and clinical symptoms than was reported in the Vermont study. Many of the New Hampshire patients required considerable assistance to remain in the community. Interestingly, cognitive impairment was a strong discriminator of patients who required high and low levels of support to sustain independent living.

CLINICAL SYMPTOMS IN LATE-LIFE SCHIZOPHRENIA

Before returning to the main topic of this article, cognitive functioning, more background information on late-life schizophrenia may be helpful. Cognitive impairments do not exist in a vacuum, and the relationship between cognitive functions and other aspects of the illness is important. Since late-life schizophrenia is diverse in its presentations, a brief overview of the symptoms and overall adaptive outcomes of the illness may be informative.

Clinical symptoms have been studied in both early- and late-onset patients with late-life schizophrenia. For years, clinical lore held that positive and disorganized symptoms "burned out" and only negative or deficit symptoms would be detected in late life, even in long-stay institutionalized patients.[29] Several recent studies have suggested that this conception is not fully accurate. In a large-scale study of chronically institutionalized schizophrenic patients stratified into seven groups designated by 10-year age groups from 25 to more than 85 years,[7] negative symptoms manifested an increase in severity over the age ranges studied, while positive symptoms decreased. The severity scores for negative symptoms in the older population were elevated compared with those seen in typical younger patients. The severity of positive symptoms, however, was such that even the oldest of the patients studied manifested positive symptom severity scores at the 40th percentile for the standardization sample for the rating scale used (the Positive and Negative Syndrome Scale [PANSS][30]). The severity of negative symptoms in the geriatric patients in this sample was found to increase slightly at a 1-year follow-up of the sample, with no statistically significant decrease in positive symptoms.[31] This result is in contrast to studies of younger chronic schizophrenic patients,[32–34] in which negative symptoms failed to worsen in severity at similar follow-up intervals.

In a comparative study of late-onset, acutely ill patients and early-onset, chronic patients with schizophrenia, paranoid symptoms were significantly more common in the late-onset cases.[21] In addition, late-onset patients were more likely to have better lifelong functioning, including marriage and a stable work history. A previous study[35] suggested that the deficit syndrome was present in approximately 30% of older patients with schizophrenia; this prevalence was probably not elevated from that seen in younger patients. Finally, White et al.[36] used confirmatory factor analysis to compare the structure of symptoms in poor-outcome geriatric schizophrenic patients, divided on the basis of their level of cognitive dysfunction, with that in younger poor-outcome patients. No differences in the factor structure of clinical symptoms were found between older and younger patients or between the geriatric patients who varied in their level of cognitive impairment. The authors concluded that since schizophrenic cognitive

impairment did not affect the structure of symptoms, it may be an intrinsic aspect of poor-outcome schizophrenia.

ADAPTIVE IMPAIRMENT IN LATE-LIFE SCHIZOPHRENIA

One of the principal sources of negative outcome in schizophrenia is a deficit in adaptive life functioning.[4,37,38] Many schizophrenic patients manifest severe and persistent disability and become dependent on others for their care because they are unable to care for themselves. Some of these impairments are present more often in patients with the negative symptoms[39] of schizophrenia as well as in patients with more severe cognitive impairment.[5] Patients who are dependent on others for their care are typically not more seriously affected by the positive symptoms of the disorder.[40] Previous behavioral interventions in schizophrenia have often focused on remediation of these deficits in adaptive life functions,[41–43] but there have been some recent suggestions that pharmacologic interventions should also be targeted at these types of deficits.[44] Furthermore, deficits in cognitive functioning appear to act as a rate limiter for acquisition of new instrumental and social skills in studies of younger patients with chronic schizophrenia.[45]

Limited information is available on adaptive functioning deficits in geriatric patients with schizophrenia. The available information suggests that the range of adaptive functioning is quite wide and that the level of care received by the patient is often correlated with adaptive skill. Kincaid et al.[46] studied 339 geriatric chronically hospitalized inpatients with schizophrenia and found that clinical ratings of self-care and personal hygiene accounted for 9% of the variance in global ratings of severity of overall functional, cognitive, and behavioral impairment. Harvey et al.[47] developed the Social Adaptive Functioning Evaluation (SAFE) scale, which was designed to evaluate overall adaptive dysfunction in geriatric institutionalized patients. They reported that total scores on the measure were strongly associated with the overall severity of cognitive impairment, as measured by the Mini-Mental State Examination or MMSE. In addition, the overall level of impairment was quite high in their population. For example, very severe impairments were found for neatness and maintenance, money management, orientation and mobility, communication skills, and friendships, while impairments at a level that was considered severe were found on nine other measures of social, instrumental, and self-care skills. When a sample of 140 patients was followed prospectively for up to 3 years,[47] it was found that deficits in the general areas of impulse control and self-care were quite predictive of discharge and placement. Patients with poor impulse control were likely to remain hospitalized, while patients with better self-care were more likely to be discharged to a community setting than to a nursing home. Social functioning did not discriminate between three different placement outcomes: remaining hospitalized, being referred to the community, or being transferred to a nursing home. In a later study of these patients, cognitive impairment, as measured by the global score on a composite neuropsychological battery, was strongly correlated with both social and instrumental skills deficits but less strongly correlated with deficits in impulse control.[3] In a study of more than 800 geriatric psychiatric patients followed for 3 years during a period of downsizing a psychiatric hospital, White et al.[36] found that the presence of severe adaptive deficits was less strongly correlated with discharge from chronic care than the presence of hostile and belligerent behaviors. In patients who were discharged, however, severe deficits in adaptive functioning were more common in patients referred to a nursing home than in those discharged to the community. Thus, a high prevalence of adaptive deficit is seen in geriatric patients with chronic schizophrenia and, like in younger patients, there is preliminary evidence that those patients with more severe adaptive deficits are more likely to be cognitively impaired.

COGNITIVE FUNCTIONING IN LATE-LIFE SCHIZOPHRENIA

Cognitive impairment is a common symptom in schizophrenia, being present across the entire course of the illness.[11,14] In fact, cognitive impairments—specifically deficits in academic functioning—relative to classmates can be identified in preschizophrenic individuals as early as the first grade.[48] Cognitive impairment appears to be stable within patients over time and across various follow-up intervals as well as to correlate with poor outcome.[49] It should also be noted that there are many changes in cognitive functioning associated with aging in the normal population. While the domain of aging-related changes is enormous and beyond the scope of this article, several general points can be made. Major aging-related changes occur in motor speed and in memory functions, while the level of change in long-term memory and ability to access and utilize previously learned material is much more modest. As a consequence, baseline functioning can be estimated from performance on tests of old learning such as reading and vocabulary, because of the minimal aging-related changes in these areas. For a complete review of aging and neuropsychology, the reader is referred to Albert and Moss.[50] Since schizophrenic patients at their first episode often score two to three standard deviations below normal comparison groups[14] or standardization samples on certain critical cognitive measures, the possibility of detecting cognitive decline with aging is reduced because of floor effects. At the same time, it should be noted that the types of cognitive operations that change with normal aging (new learning and recall, concentration and attention, psychomotor and visuomotor speed) are the deficits most commonly noted in schizophrenic patients early in life. Thus, aging-related changes are likely to maximally im-

pact those functions most impaired in schizophrenia patients earlier in life.

In younger schizophrenic patients, the typical assessment of cognitive functioning has used assessment either with clinical neuropsychological tests or with experimental measures of attention and memory. Across these studies, significant impairments have been found in learning and memory, attention, and executive functioning (see Gold and Harvey[11] for a review of these findings in younger patients), with lesser impairment noted in most other cognitive functions.[10] As noted by Green,[45] these three domains of cognitive functioning are also specifically related to poor outcome and poor response to rehabilitation-based interventions. In older schizophrenic patients, prominent cognitive impairments resembling dementia have also been reported. For example, in the Davidson et al.[7] study, over 60% of the geriatric chronic schizophrenic patients would have met DSM-III-R criteria for dementia in addition to schizophrenia. Similar findings were reported by Arnold et al.[49] in a separate sample. In contrast, in a sample of patients with better outcomes, as many as 33% of patients with schizophrenia would be considered neuropsychologically "normal."[51] As demonstrated below, one of the issues that has been addressed in research on cognitive functioning is a comparison of the cognitive performance profiles of geriatric patients with schizophrenia, both early- and late-onset, with the cognitive impairments seen in degenerative dementing conditions such as Alzheimer's disease (AD). Spurred by preliminary reports of an elevated prevalence of AD in postmortem brain specimens from patients who have a hospital chart diagnosis of schizophrenia,[52] a number of studies have compared the cognitive profiles of patients with these two disorders.

Studies of global estimates of cognitive functioning in patients with late-life schizophrenia have suggested that as many as 60% of geriatric chronically hospitalized patients with schizophrenia have MMSE scores in the range suggestive of dementia. Davidson et al.[7] used a cross-sectional design to compare MMSE scores in chronically hospitalized patients ranging in age from 25 to 95. There was a consistent linear relationship between MMSE scores and age: the mean MMSE score of patients who were 25 to 35 years was 27 ("questionable impairment") and the mean MMSE of 85- to 95-year-olds was only 9.6 ("severe dementia"). Even when low levels of premorbid education and age are considered, these scores are extremely low. There was a cross-sectional difference of 3 MMSE points per decade over the age-span of the patients studied. In contrast, MMSE scores in AD change an average of 3 points per year.[53] When the geriatric patients who were still in the hospital were followed up 1 and 2 years later,[54] there was no measurable change in MMSE scores for the sample as a whole, the intraclass correlation coefficient (ICC) was over 0.85 at each assessment, and 1-month stability of the MMSE score was found to be over 0.90 (ICC). When the sample of patients in the Davidson et al. study were compared with similar-age, long-stay patients from the United Kingdom, there were no statistical differences in their MMSE scores.[55] In addition, MMSE scores of chronic schizophrenic patients in other U.S. hospitals are strikingly similar across institutions.[50]

These data suggest that globally estimated cognitive functions appear to manifest age-related differences, although MMSE scores do not decline at a rate consistent with a degenerative dementia such as AD.[53] Further evidence for dissimilarity to AD was provided by Harvey et al.,[56] who used a battery of neuropsychological tests, which was developed to assess the nature and progression of cognitive impairments in AD, to study cognitive function in geriatric patients who were chronically ill with schizophrenia. At a 1-year follow-up, none of these cognitive functions showed evidence of decline. In addition, the profile of impairment was quite different from that seen in AD. A delayed recall memory deficit is the first reliable sign of mild AD,[57] but this deficit fails to progress over time and is uncorrelated with overall MMSE scores.[53] In the Harvey et al. study,[56] delayed recall deficits were correlated with MMSE scores more strongly than with any other measure. Further evidence of the dissimilarity of cognitive performance profiles in AD and geriatric schizophrenia is provided by the results of a cross-sectional study comparing late- and early-onset geriatric schizophrenic patients, nongeriatric schizophrenic patients, patients with AD, and normal controls on an expanded version of the Halstead-Reitan Neuropsychological Test Battery.[58] Patients with AD were found to perform worse than all schizophrenic patients on a measure of delayed recall, with the schizophrenic patients performing worse than those with AD on several other summary measures. A similar result was obtained by Davidson et al.,[17] who compared schizophrenic and AD patients who were matched on global cognitive impairment as measured by MMSE scores. Patients with AD were more impaired on delayed recall and less impaired on verbal and visuomotor skills than schizophrenic patients who had similar MMSE scores. No differences in rate of learning were detected. Both studies suggest that schizophrenic patients are differentially impaired compared with patients with AD, and both were careful to rule out alternative causes of cognitive impairment in their samples.

The results of these studies, combined with prospective studies of postmortem characteristics of geriatric schizophrenic patients that failed to find evidence of AD-related neuropathology in the majority of cognitively impaired patients with schizophrenia,[50,59,60] can be interpreted to conclusively demonstrate that the profound cognitive impairments seen in geriatric long-stay schizophrenic patients are not always due to degenerative dementia. What is considerably less clear, then, are the characteristics of cognitive impairment in geriatric schizophrenic patients and any possible differences between late- and early-onset

cases, as well as the associations between outcome and cognitive impairments. In the Heaton et al. study,[58] no differences in global neuropsychological summary scores were found between similar-aged early- and late-onset geriatric schizophrenic patients, and no cognitive performance differences were found as a function of age in the schizophrenic sample. Similarly, Hyde et al.[61] reported no age-related differences in cognitive functions in a cross-sectional study of schizophrenic patients ranging in age from the 20s to the late 60s. In contrast, several other studies of a large sample of extremely chronic institutionalized patients have found major age-related differences both in global indices of cognitive functions[7] and in specific neuropsychological measures.[62,63]

There is a clear correlation between overall outcome status and cognitive functioning in late-life patients with schizophrenia. When Jeste et al.[21] examined late-onset patients with schizophrenia whose overall adaptive functioning had been adequate over their entire life and compared them with early-onset patients with an overall adequate adaptive outcome, it was found that there were minimal differences in their cognitive performance. Both samples of patients were more impaired than similarly aged patients with affective disorders. In contrast, when very poor-outcome affective patients who had a 10 or more year consecutive stay in chronic psychiatric care were compared with a similar group of patients with schizophrenia, there were no differences between poor-outcome affective disorder and schizophrenic patients.[64] Thus, outcome appears to be strongly related to cognitive deficit, regardless of specific psychiatric diagnosis.

In terms of the specific characteristics of cognitive impairments seen in geriatric schizophrenic patients, Harvey et al.[65] compared geriatric chronic schizophrenic patients with either absent-to-mild or moderate cognitive impairments, defined by global ratings of a general clinical severity measure for dementia, on a battery of memory tests that have been demonstrated in brain-injured populations to be differentially sensitive to dysfunctions in the temporal and frontal lobes. They found that there were large differences in memory performance associated with global cognitive impairments and that patients, regardless of their level of cognitive impairment, tended to manifest patterns of performance consistent with either a temporal-lobe or frontal-lobe memory deficit. Paulsen et al.[66] also performed a comprehensive neuropsychological evaluation of profiles of memory impairment in schizophrenic patients, dividing their geriatric patients on the basis of cortical, subcortical, or unimpaired profiles. Cortical profiles include deficits in learning, recall, and recognition memory, while subcortical profiles include preserved recognition memory and increased benefits from cuing and encoding assistance. They found about one third of the patients manifested an unimpaired profile, and half manifested a subcortical profile. Only 15% of the patients manifested a cortical pattern of impairment. These results are consistent with the findings of Harvey et al.,[65] who found that recognition memory performance did not vary across patients who differed considerably in their global level of cognitive impairment. When the Paulsen et al. memory study was expanded to include a full neuropsychological assessment, the rate of unimpairment in cognitive functions was somewhat consistent, at less than one third of the patients.[51] In a study of verbal fluency performance, geriatric chronically hospitalized schizophrenic patients were found to be more impaired on phonemic fluency than younger chronic patients, with no age-related differences in category-based fluency when education differences between these two samples were considered.[63] Both groups of patients performed at least 2 to 3 standard deviations below the age- and education-corrected mean on category fluency and 1.5 to 2 standard deviations below the mean on phonemic fluency. An additional finding of some importance is that estimates of premorbid intellectual attainment (i.e., the Wide-Range Achievement Test-Revised [WRAT-R][67] reading subtest) were correlated with overall cognitive status in geriatric patients but not nongeriatric patients. This suggests a possible bias effect that should be considered in later studies, as the WRAT-R or other similar tests are often employed as estimates of premorbid cognitive status in studies of cognitive functions in younger schizophrenic patients.[68]

In an examination of the long-term effects of psychosurgery in chronic schizophrenia, Harvey et al.[18] studied 72 chronically hospitalized schizophrenic patients on a neuropsychological battery, comparing patients who had experienced a leukotomy with a control sample matched for age, education, and overall cognitive status. Consistent with earlier studies of patients leukotomized at younger ages (see Joschko[69] for a review), no major differences in cognitive functioning were found. These data suggest that a frontal lobe lesion that may disconnect the cortex and striatum does not interact with aging in chronic schizophrenia to produce even greater cognitive impairment, although there are some interpretive problems with the results. The geriatric chronic schizophrenic patients without leukotomy performed so poorly on tests sensitive to frontal lobe lesions, including the Wisconsin Card Sorting Test,[70] that it would be almost statistically impossible for the leukotomized patients to perform more poorly and reveal a differential performance deficit.

The results of these studies highlight the problem in studying cognitive performance in schizophrenic patients across wide ranges of age, chronicity, and severity of illness. Some of the inconsistent results may simply be the consequence of subject selection processes. The subjects in the studies conducted by Heaton and colleagues[10,51,58,66] were largely outpatients residing in the community, in contrast to the subjects my colleagues and I studied, who had been continuously hospitalized for decades. Since more

severe cognitive impairment is a powerful correlate of poor outcome in younger schizophrenic patients, as it is in other neuropsychiatric conditions,[71] there is no reason to expect that extremely poor-outcome geriatric patients would not also have more severe impairments than those patients who are functioning adaptively in community. In the Hyde et al. study,[61] relatively poor-outcome patients were studied, but younger and older patients were matched in WRAT-R scores in order to equalize premorbid intellectual functioning. As noted above, if WRAT-R scores are correlated with cognitive impairment in geriatric patients, matching on this variable would create a sample of geriatric patients who are preselected for reduced levels of cognitive impairment.

The previous research has revealed several important cohort effects when younger and older chronically hospitalized patients are compared. Geriatric chronic patients are consistently found to have a later age of first psychiatric admission and lower levels of formal education than younger patients.[7,50] These differences have the potential of obscuring the interpretation of differences in cognitive functioning between the samples, because education and onset age have both been previously demonstrated to influence performance on cognitive tests. Performance differences between early- and late-onset patients have the potential of being influenced by the correlates of chronic schizophrenia, including treatment and lifelong histories of social isolation, ostracism, and failure.

COGNITIVE FUNCTIONING, NEGATIVE SYMPTOMS, AND ADAPTIVE DEFICIT

The main finding associated with the study of cognitive functioning in late-life schizophrenia is that there is little evidence for the development of types of cognitive impairments that are qualitatively different from those seen in younger schizophrenic patients. While some studies find no age-related differences in cognitive performance, others do, with the principal variation between the studies being the nature of subject samples. The primary change appears to be a worsening of memory performance, in line with expected changes associated with normal aging, although this worsening still does not lead to performance as poor as that seen in Alzheimer's disease. The association between extremely poor outcome and profound cognitive impairment leads to interpretive problems because of the very long length of institutional stay and extensive treatment experienced by these patients. Since only a subset of these patients manifest age disorientation or other profound cognitive impairments, it is not possible that all aspects of their impairment are caused by institutional stay. Assuming that institutional stay and its correlates (e.g., medication treatment) have the potential to cause some cognitive impairments seen in geriatric chronically institutionalized patients, the variability across patients in level of impairment suggests that there may be individual differences in factors that predict vulnerability to these effects. Identification of these factors is a useful target for later research. As noted above, the strong correlation between cognitive functioning and adaptive outcome, even when the severity of negative symptoms is considered, suggests that interventions aimed at improvement of adaptive outcome may be targeted at enhancement of cognition. As noted elsewhere in this supplement, atypical neuroleptic medications may be useful in this area, as may be augmentation strategies directly targeting cognition with specific agents that may not affect the positive or negative symptoms of the illness.

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

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