Associations Between Cognitive Impairment and Tardive Dyskinesia: Another Perspective

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The extended administration of neuroleptics, especially those of high potency, is the essential etiologic factor in the development of tardive dyskinesia (TD). Schizophrenic patients, almost all of whom receive neuroleptics to reduce psychotic symptoms, are therefore at risk for the development of TD. In this review of the literature, we propose that neuroleptic use is not the sole risk factor for the emergence of TD. Rather, we attempt to demonstrate that impairments of cognitive function play a role in the development of TD. Furthermore, we show that this idea has explanatory value for understanding higher rates of TD in the elderly. *(J Clin Psychiatry 1999;60[suppl 13]:17–21)*

Extrapyramidal side effects (EPS) and tardive dyskinesia (TD) are major concerns in the treatment of psychotic disorders with neuroleptics. EPS are a set of symptoms that involve acute dystonic reactions, cogwheel rigidity, tremor, bradykinesia, and restlessness. These symptoms usually result from acute dysfunction of the extrapyramidal motor system induced by the dopaminergic blockade of neuroleptics. TD is a movement disorder characterized by rapid, involuntary, arrhythmic, choreiform movements or dystonic posturing of the orofacial region, jaw, limbs, and trunk that appear after extended neuroleptic exposure.[1] The development of TD, after only months or many years of neuroleptic treatment, often leads to patient noncompliance with medication regimens, resulting in functional decompensation, increasingly psychotic behavior, and possible rehospitalization. Epidemiologic data suggest that neuroleptic drugs are the essential etiologic factor in the development of TD, although individuals are not equally vulnerable to the development of this disorder.[2]

TD may be the result of chronic high neuroleptic doses that "overwhelm" the neural networks subserving motor control.[3] This has been modeled in studies in which vacuous chewing movements (VCM), a surrogate measure of TD in rats, were induced by chronic administration of neuroleptic agents that, among other neurobiological effects, result in D_2 blockade. However, Gunne et al.[3] demonstrated that lesions of the frontal cortex markedly increase the frequency of VCMs in rats after haloperidol treatment. It is believed that such a lesion dysregulates the striatum and, in the presence of neuroleptics, produces higher rates of abnormal movement. In this review, we will consider a factor primarily related to cortical function: cognitive impairment and its relation to TD. While most researchers suggest that TD makes the development of severe cognitive impairments in schizophrenic patients more likely, we believe there is compelling evidence that cognitive impairment, in and of itself, is a risk factor for the development of TD. In this view, cognitive impairment serves as a surrogate measure for cortical dysfunction; neuropsychological tests used to assess cognitive function thus indirectly measure the likelihood of striatal dysregulation.[4–7] In this selective review, we will present evidence that impaired cognition is indeed a risk factor for TD. Before doing so, we will first provide a short summary of the "classic" risk factors.

RISK FACTORS: THE USUAL SUSPECTS

While the incidence of TD in young patients (average age of 28 years) is approximately 5% after the first year of neuroleptic treatment, age increases the risk of TD.[2] There is an interaction between age and length of neuroleptic exposure, with the prevalence increasing dramatically in older people. Jeste et al.[8] found the cumulative annual incidence of TD among patients (over the age of 45) to be 26%. The higher prevalence may result from elderly patients' increased sensitivity to the side effects of neuroleptic medications. After 266 neuroleptically naive patients (average age of 77 years, with a range of 55–101) received low doses of antipsychotic medication (starting average daily dose in CPZ equivalents was 80 mg) for an average period of 43 weeks, 31% of the subjects developed TD.[9]

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Not every person who receives neuroleptic treatment develops TD. In addition to the role of age, the 2 most significant predictors are the duration of neuroleptic exposure and total lifetime neuroleptic intake.[8] A less clearly defined factor is gender. Yassa and Jeste,[10] in a meta-analysis, found the incidence of TD to be significantly higher in women (26.6%) than in men (21.6%). In addition, they found that women had more severe forms of TD than men did. However, the increased incidence could be due to age since women generally have a longer life expectancy and increasing age raises the risk of TD development. Other significant risk factors include a history of alcohol abuse/dependence and tremors or subtle movement disorders at initial assessment.[8] Paulsen et al.[11] suggested that subtypes of TD, namely orofacial (defined by involuntary movements of the mouth and face) and limb-truncal (involuntary movements occurring in the trunk or the limbs), may have different predisposing factors. A history of alcohol abuse or dependence was associated with only orofacial TD, while evidence of a tremor was a significant predictor of only limb-truncal TD.

Treatment with anticholinergic medications, in conjunction with typical neuroleptics, is also associated with an increased risk of TD.[8] Many patients receive anticholinergic medications during the course of their treatment in order to control EPS. Parenthetically, anticholinergic medications affect cognition as measured by neuropsychological testing, independent of antipsychotic medications.[12–14] According to Kane et al.,[15] anticholinergic medications in vulnerable patients may also aggravate movement disorders that had not previously reached a level of severity such that they would be measurable on a scale of movement disorders. Alternately, anticholinergic medications may be a moderating variable that lies between EPS and the development of TD.

RISK FACTORS: AN UNUSUAL SUSPECT

Recent studies identifying differences between the cognitive function of schizophrenic patients with TD versus schizophrenic patients without TD provide surprising and compelling evidence that cognitive impairment is a risk factor for TD (reference 16 and J.E. Kleinman, T.E. Goldberg, B. Elvevaag, et al., unpublished data, 1997). Given that prefrontal cortex dysfunction may play a role in the cognitive deficits found in schizophrenia,[17] it follows that the pathophysiology of the prefrontal cortex associated with schizophrenia might also predispose a patient to the development of TD, as based on the work of Gunne et al.[3]

Waddington and Youssef[18] have often proposed a contrasting view of the relationship between cognitive dysfunction and TD. In a study that investigated TD and cognitive function in chronic schizophrenic patients using a longitudinal design, it was found that the level of cognitive function in patients who demonstrated symptoms of TD at baseline (N = 7) did not deteriorate over the course of the 10-year study. Patients whose TD emerged at 5-year testing (N = 6) showed worsening of their measures of cognitive ability at the 5-year time-point, as compared with baseline measures, but did not show additional decline at 10 years. However, the conclusion that TD and cognitive decline result from the same pathophysiologic process because of the apparent synchrony of their emergence is problematic. Group sizes were very small, the patients were elderly, they were not screened for subtle or occult neurologic events, such as subcortical infarcts, and the measure of cognitive function was very limited in scope (an abbreviated 10-question mental status test).

In contradistinction, findings from a large study of schizophrenic patients with TD raise the question (though they do not definitively provide an answer) whether cognitive deficits are a consequence or a precursor to TD. Paulsen et al.[16] found that schizophrenic patients with TD perform more poorly on neuropsychological tests than schizophrenic patients without TD. The non-TD group had the least neuropsychological impairment and the moderate-to-severe TD group had the greatest degree of impairment. The mild-TD group scored between the non-TD and the moderate-to-severe TD groups. Critically, all groups had the same neurocognitive impairment profile. This is important because TD is thought to be caused by basal ganglia dysfunction and as such it would have been predicted that patients with TD would have had a distinct profile of cognitive impairment. At the very least, this study indicates that schizophrenic patients with TD have more severe cognitive impairments in every test, consistent with the view that cognitive impairment is a risk factor for the emergence of TD.

Gold et al.[19] found no global neuropsychological differences in their sample of 27 schizophrenic patients with TD and 27 schizophrenic patients without TD based on an extensive battery of cognitive function tests including Weschsler Adult Intelligence Scale-Revised IQ Test, Weschsler Memory Scale, Halstead Reitan Battery, and Wisconsin Card Sort Test (WCST). Although no global differences were found, the patients with TD generally performed worse on many of the measures.

A recent study reexamined the cognitive deficits in patients experiencing different types of TD to determine whether specific areas of function were affected by the subtype of TD (J.E. Kleinman, T.E. Goldberg, B. Elvevaag, et al., unpublished data, 1997). Patients with orofacial TD performed disproportionately worse on the WCST, considered to be a measure of dorsolateral prefrontal cortex function. Patients experiencing limb-truncal TD did not demonstrate marked deficits on the WCST, but performed poorly on putative measures of posterior (sensorimotor or parietal) cortex (Boston Naming Test and dominant hand finger-tapping). Given the aforementioned animal model of TD, we hypothesize that pathology of the prefrontal cor-

tex in schizophrenics might predispose patients to the development of orofacial movements during exposure to neuroleptics. Indeed, those schizophrenic patients with this subtype of TD had significantly lower levels of performance on a putative test of prefrontal cortex function, the WCST. By analogy, damage to sensorimotor cortex might lead to trunk and limb dyskinesias or dystonias (the sensorimotor region of cortex innervates the putamen). For example, in Parkinson's disease, there is a dopamine depletion in the putamen; therefore, increased dyskinesias and dystonias are observed. The group of schizophrenics with limb-truncal movement disorders performed at significantly lower levels on tests widely considered to be dependent on sensorimotor/parietal cortex functions, e.g., finger tapping and visual confrontation naming.

In the most important study to date, Pappadopulos et al.[20] assessed a large sample of first-episode schizophrenic patients. More severe cognitive impairments were found at initial assessment in the group of patients who developed TD over the course of treatment, as compared to their counterparts who did not develop TD.[20] Crucially, the group in whom TD emerged did not undergo further cognitive deterioration; they simply started at a lower level. This finding provides compelling support for the argument that cognitive impairment is a risk factor for the development of TD. It also provides strong evidence against the view that TD is a risk factor in the development of cognitive impairment.

ATYPICAL NEUROLEPTICS AND TD

Generally, the recommended treatment of TD is to discontinue neuroleptic medication. This may reduce TD symptoms, although some residual involuntary movements may continue even after neuroleptic treatment ends. Sometimes, discontinuation does not lead to a decrease in symptoms at all, and the TD proves to be essentially irreversible.[16] Pari passu, termination of neuroleptic treatment often leads to the exacerbation of psychotic symptoms.

Atypical neuroleptic medication may prevent the development of TD, or at least minimize its emergence. Atypical drugs that have been approved for use in the United States include clozapine, risperidone, quetiapine, and olanzapine. They differ from typical neuroleptics in their effects on a variety of neurotransmitter systems. For example, risperidone antagonizes both serotonin 5-HT_2 and dopamine D_2 receptors, as opposed to many typical high-potency neuroleptics that are primarily D_2 antagonists.[21] The unique pharmacologic profiles of atypical neuroleptics may, in an as of yet undetermined mechanism, prevent the development of TD. Alternatively, the relatively lower affinity of some atypical neuroleptics for D_2 receptors may prevent the development of TD (S. Kapur, oral communication, March 1997).

Additionally, it has been shown that receiving clozapine may actually reduce TD symptoms and prevent "withdrawal dyskinesia" when medication is discontinued.[22] Kane et al.[15] found that clozapine-treated patients had a lower incidence of TD than the comparison group treated with high-potency typical neuroleptic drugs. Similarly, Gerlach and Peacock[23] found a reduction in tardive dyskinesia after 5 years of clozapine treatment. This is an important finding because clozapine is often administered to treatment-refractory patients who also tend to have severe cognitive impairment. In our view, this is the very group at highest risk for the development of TD. Clozapine has also been found to reduce symptoms of TD, as well as EPS, in elderly populations.[24] Frankenburg and Kalunian[24] in their sample of 8 patients found a reduction in patients' TD symptoms after initiating treatment with clozapine.

Recent studies have also been conducted to examine the effects of olanzapine and risperidone on TD. Administration of the former, because of its pharmacologic profile showing more pronounced 5-HT and muscarinic antagonism than D_2 antagonism, would be expected to result in TD less often than a typical neuroleptic.[25] In a study by Street et al.,[25] patients were found to have significantly less long-term treatment-emergent dyskinetic symptoms (as measured by the Abnormal Involuntary Movement Scale [AIMS]) than a parallel group taking haloperidol.[25] Risperidone, because of its combined D_2 and 5-HT_2 receptor antagonism, may also be associated with fewer EPS.[2] If the relationship between EPS and the later emergence of TD is indeed correct, then risperidone treatment should produce fewer cases of TD. One study of risperidone in an elderly subject group (over the age of 60) found that 4 of 11 patients experienced a decrease in EPS and TD symptoms while receiving risperidone, although these findings are problematic due to the variability of treatment duration (1 to 35 days) and the fact that 3 patients discontinued the study (due to nonresponse or side effects).[26]

CLINICAL IMPLICATIONS FOR THE ELDERLY

Volumetric brain changes associated with aging are often characterized by a loss of cortical volume seen most profoundly in the frontal lobe.[27,28] Volume loss in the frontal cortex is especially deleterious vis-à-vis TD because prefrontal cortex projections have a modulatory function on the striatum.[29] Cognitive impairment associated with aging may be a result, in part, of this atrophic process. Specifically, the loss of frontal cortex could result in the decreases observed in working memory and other executive functions including free recall in memory tests.[30] Decreased cognitive function, as discussed above, is associated with an increased incidence of TD. Additionally, there is a decrease in the number of specific D_2 dopamine binding sites in the striatum,[31,32] further increasing the probability that D_2 blockade by neuroleptics will result in TD.

NEUROLEPTIC DOSAGES IN THE ELDERLY: "GO SLOW AND STAY LOW"

Without neuroleptic treatment, psychiatric symptoms are likely to recur, especially in major psychotic disorders.[33] Therefore, neuroleptics should be prescribed to control psychiatric symptoms, but, in order to limit the risk of TD, doses should start at lower levels than would be used with a younger patient. Devanand et al.[34] found that elderly patients suffering from Alzheimer's disease could not tolerate a dose of more than 5 mg per day of haloperidol, due to the development of EPS. The mean daily dose, at the end of the 8-week active medication phase, was 2.44 mg (SD = 1.4). Effective doses in the elderly may be as low as one third of the amount used for a younger patient.[35] Besides using low dosages of typical neuroleptics, another option is the use of novel antipsychotics (such as risperidone and olanzapine) that have a reduced risk of TD and other adverse side effects, including cognitive impairment.

CONCLUSIONS

We have presented evidence that cognitive impairments, as measured by neuropsychological tests that in turn are surrogate measures of cortical function, are not merely associated with TD, but appear to be a predisposing factor. Whether this relationship indicates a primarily causal relationship or is only one of many risk factors is not known. Does a certain level of cognitive impairment preordain the development of TD or do cognitive deficits make the development of TD more likely to occur? Based on the evidence with first-break patients, we suggest that cognitive deficits reflect underlying cerebral dysfunction, which, in interactions with typical neuroleptic treatment, leads to the rapid development of TD. Although there does not appear to be a specific basal ganglia "profile" for TD, there does seem to be an indication of regional cortical dysfunction such that deficits identified by "frontal lobe" tests may place patients at higher risk for orofacial TD. The clinical implications of the relationship between cognitive impairment and the development of TD are clear. Practitioners need to be especially cautious in administering high-potency typical neuroleptics to individuals with diminished cognitive capacity, as well as elderly patients who are increasingly susceptible to TD due to the effects of aging on cortical integrity.

Drug names: clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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

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