Effects of Clozapine Therapy in Schizophrenic Individuals at Risk for Tardive Dyskinesia

Daniel E. Casey, M.D.

Neuroleptics were the first modern class of pharmacotherapeutic agents available for the treatment of schizophrenia. Although they were effective in reducing florid psychotic symptoms, up to 90% of treated individuals subsequently developed extrapyramidal symptoms (EPS) (akathisia, dystonia, or parkinsonism), and about 20% developed tardive dyskinesia (TD). When clozapine became commercially available for treatment-resistant and treatment-intolerant (i.e., prone to EPS and TD) schizophrenic individuals, it became apparent that an antipsychotic need not induce motor side effects to be efficacious in reducing the symptomatology of schizophrenia. Sociodemographic, behavioral, and clinical predictors of TD are useful in identifying a subset of schizophrenic individuals who would benefit from treatment with clozapine, the prototype atypical antipsychotic whose efficacy and motor side effect profile are superior to those of chlorpromazine. This favorable motor side effect profile of clozapine contributes to improved patient outcomes by reducing noncompliance, substance abuse, and suicide, resulting in improved quality of life and savings on health care costs.

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The advent of chlorpromazine in the 1950s marked a beginning in the modern pharmacotherapy of schizophrenia. Other similar neuroleptics became available within 3 decades,[1] and while some were more potent than others, these neuroleptics were, by and large, interchangeable because of a common mechanism of action that centered on D_2-receptor antagonism.[2] Neuroleptics were efficacious in reducing the florid aspects of psychosis (i.e., hallucinations, delusions),[1] but because D_2-receptor binding occurred primarily in areas of the brain controlling movement,[3] clinical experience would show these agents to be associated with an array of distressing motor symptoms, collectively termed *extrapyramidal syndrome* (EPS), which includes akathisia, dystonia, and parkinsonism (Table 1).[4]

EPS occurs in up to 90% of schizophrenic patients treated with neuroleptics.[2] Chronic neuroleptic use predisposes the schizophrenic individual to tardive dyskinesia (TD), a potentially severe and irreversible CNS condition. The relationship between EPS and TD is complex. Conceptually, TD lies along a continuum with drug-induced parkinsonism, akathisia, and dystonia.

The definition of an antipsychotic was modified with the emergence of clozapine, whereby therapeutic efficacy and EPS and TD liability are now distinguishable. Clozapine exhibits superior efficacy over conventional antipsychotics in reducing both positive and negative symptoms and yet has a highly favorable EPS and TD profile.[5] Furthermore, clozapine is efficacious in 30% to 61% of schizophrenic individuals who do not appreciably respond to other neuroleptics.[6]

Sociodemographic, behavioral, and clinical predictors of TD are useful in identifying a subset of schizophrenic individuals who would benefit from clozapine treatment. Motor and mental side effects associated with neuroleptic treatment have been associated with increased morbidity in schizophrenia. Identifying individuals prone to EPS and TD would qualify patients for clozapine treatment and facilitate a therapeutic regimen that has been shown to improve the schizophrenic patient's ability to function on many levels.[7] The risk factors for developing TD and the evidence for the efficacy of clozapine among the treatment-intolerant (i.e., prone to EPS and TD) schizophrenic population are discussed.

TARDIVE DYSKINESIA

TD affects as many as 15% to 20% of predisposed patients.[8] It is characterized by orofacial or trunk-limb involuntary movement.[2,9] Orofacial symptoms include chewing, vermicular tongue movements, lip sucking, tongue protrusion, lateral jaw movements, brow wrinkling, and blepharospasm.[9] Trunk-limb involuntary movements in-

From the Mental Illness Research, Education & Clinical Center, Veterans Administration Medical Center, and the Oregon Health Sciences University, Portland.

Supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation.

Reprint requests to: Daniel E. Casey, M.D., Mental Health Division (116A), VA Medical Center, 3710 SW U.S. Veterans Hospital Road, Portland, OR 97201.

Table 1. Acute Extrapyramidal Syndromes*

Syndrome	Mental Symptoms	Motor Symptoms	Distinguish From Psychiatric Symptoms	Idiopathic Syndromes
Akathisia	Restless, unable to relax, poor concentration, irritable	Pacing, rocking, shifting foot to foot	Severe agitation, psychotic decompensation	Restless-legs syndrome
Dystonia	Fear, anxiety	Briefly sustained or fixed abnormal postures of the eyes, tongue, face, neck, limbs, trunk	Manipulation, hysteria, seizures, catatonia	Focal or segmental dystonia
Parkinsonism	Bradyphrenia, cognitive impairment	Tremor, rigidity, bradykinesia (akinesia), facial masking, decreased arm swing	Negative symptoms of psychosis, depression	Parkinson's syndrome

*Adapted from Casey.[50]

Table 2. Risk Factors for Tardive Dyskinesia

Genetics
Race
Age
Female sex
EPS
Organic brain disorders
Affective disorder
Diabetes mellitus
Substance abuse
Cognitive dysfunction
Illness severity
Cumulative duration of exposure to typical neuroleptics

clude choreoathetoid dyskinesias of the toes and fingers ("piano playing") as well as athetoid movements in the head, hips, shoulders, and neck. Trunk-limb dyskinesias can result in gait disturbances and a rocking/swaying orientation.[2,8] The diaphragmatic musculature can also be involved, leading to respiratory abnormalities, sometimes accompanied by coughing and grunting sounds.

The pathophysiology underlying TD is not fully understood.[2,8,10–14] The prevailing view had been that chronic blockade of dopamine receptors by neuroleptics leads to up-regulation in their number or binding affinity in the nigrostriatal pathway, creating a supersensitive state that culminates in TD.[2] However, attempts to identify a neurologic substrate for TD, be it at the radiologic, light-microscopic, biochemical, or endocrine level, have not shown consistent differences between patients with and without TD. Thus the supersensitivity hypothesis has not been confirmed in patients, and the cause of TD remains unknown.

Risk Factors for TD

Consistent with the multifactorial nature of both schizophrenia and TD is a heterogeneous array of risk factors that have emerged for the latter condition (Table 2).

Genetics. In some schizophrenic individuals, genetics may contribute to a predisposition to TD. Approximately 5% to 10% of European whites lack the hepatic cytochrome P450 enzyme CYP2D6, which is pivotal in the catabolism of neuroleptic agents. In a study of 100 schizophrenic patients in Scotland, Andreassen and colleagues[15] identified 10 patients (10%) with genetic variability at the CYP2D6 allele and termed them poor metabolizers. Among patients who were poor metabolizers, 51% exhibited TD, 38% parkinsonism, and 15% akathisia. When these data were correlated with the CYP2D6 overall results, there was no significant difference in the frequency of the poor-metabolizer group compared with patients without the motor side effects. However, there was a tendency toward more severe and higher rates of TD at 3-year follow-up in the poor-metabolizer group.

Further evidence supporting a hereditary mechanism derives from work by Steen's group,[16] who found genetic variation in the dopamine D_3 (*DRD3*) receptor gene (allele 2) in schizophrenia. The investigators documented an elevated frequency in homozygosity at the *DRD3* Ser9Gly variant (allele 2) in patients with TD chronically treated with neuroleptics: 22% to 24% of patients were homozygous for the altered allele, compared with only 4% to 6% of patients with no or fluctuating TD. Additional studies with twins and other cohorts will give further insights into the genetic contributions to TD.

Race. A higher incidence of TD has been found in blacks than in whites.[17] On the other hand, Asian patients have shown a lower risk of acquiring TD compared with North American, European, or African patients.[18] Whether such differences are attributable to a racial-genetic or environmental disparity or other unknown treatment factors is unresolved.

Age. Advancing age is a risk factor for TD—the older the patients, the more likely they are to exhibit TD.[19] Although the appearance of TD was often attributed to long-term exposure to neuroleptic drugs, Saltz and colleagues[20] observed that TD occurred early in treatment in 31% of elderly patients (mean age = 77 years) receiving neuroleptics for the first time. Advancing age would tend to be consistent with the free-radical hypothesis in TD,[11] whereby the formation of free-radical cytotoxic species from catecholamines is cumulative and may be expected to increase with age. However, there is no direct evidence yet that this process accounts specifically for TD or for unique neuroleptic effects.

Gender. There may be a correlation between age and gender, in which TD is more prevalent in older women than in older men. A meta-analysis of studies on the prevalence of TD in schizophrenia indicated that the mean ages of women were significantly higher than for men—a 5- to 10-year difference.[18] In the age groups 51 to 70 years and above 70 years, the prevalence of TD was significantly higher in women than in men. Severe TD also occurred more frequently in women (3.1%) than in men (1.3%).[18]

Further evidence of a correlation between age and gender and TD risk has been advanced. In a study by Smith and coworkers,[21] women exhibited a linear rise in TD severity with age, whereas men showed a curvilinear (inverted U-shape) rise, with middle-aged men most susceptible.

EPS. The development of EPS appears to be a strong risk factor for TD. In a longitudinal study involving a cohort of 169 schizophrenic outpatients treated with neuroleptics, the prevalence of TD increased 2-fold (from 22% to 44%) over the 5-year study interval. If somewhat more liberal research criteria are used, the prevalence rises to 58%. Neuroleptic-induced parkinsonism proved to be the best prognostic feature in the emergence of TD.[22] Saltz et al.[20] also showed that patients with EPS had a higher risk of developing TD.

Withdrawal-emergent dyskinesia is another neuroleptic-related motor dysfunction that may be a predictor of TD.[23] Withdrawal-emergent dyskinesia is characterized by moderate abnormal movements, but not frank TD, that evolve during withdrawal of neuroleptics in some schizophrenic patients. Schizophrenic patients with withdrawal-emergent dyskinesia show characteristics intermediate between those of patients with TD (persistent TD) and those without this manifestation (non-TD), which is consistent with the continuum model for movement disorders in which those patients destined to develop TD might show the early manifestation of withdrawal-emergent dyskinesia.[23] Patients with such neuroleptic-induced motor side effects are candidates for treatment with clozapine, an antipsychotic with an efficacy profile superior to that of neuroleptics, yet without the prevalence and severity of associated movement disorders.

Organic brain disorder. Schizophrenic patients with a poor prognosis typically exhibit more pronounced structural brain abnormalities that may correlate with greater TD liability. Investigators attempting to characterize a neuropathologic substrate for TD have utilized magnetic resonance imaging. Mion et al.[24] demonstrated that, although volumes of the putamen, globus pallidus, and lateral ventricle were unaltered, the volume of the caudate nucleus was decidedly and significantly diminished in patients with TD compared with schizophrenic patients without TD and with normal controls. The exact nature of this phenomenon and its relationship to neuroleptic-induced TD remain a matter of ongoing inquiry; however, the authors did propose that the decreased caudate-nuclei volumes might constitute the structural substrate necessary for the establishment of TD with continued neuroleptic therapy.[24] Preexisting organic CNS impairment, such as mental retardation or dementia, might augment the expression of drug-related dysfunctions.[2]

Diagnoses. Affective disorders have correlated with an increased incidence in TD. Numerous reports indicate that patients who present with mood disorders are predisposed to TD, especially those with unipolar depression.[12,25,26]

Schizophrenic individuals diagnosed with diabetes mellitus are also predisposed to TD.[19]

Substance abuse. Substance abuse has also been identified as a putative risk factor for development of TD.[27–30] Dixon and colleagues[29] showed that alcohol abuse was related to a significantly higher incidence of TD among hospitalized schizophrenic patients, hypothesizing that alcohol might have an additive adverse effect when combined with neuroleptics.

Yassa et al.[27] found a higher prevalence of TD among smokers (54%) than nonsmokers (26%) ($p < .001$). Smoking appears to enhance hepatic biotransformation of neuroleptic agents, such that smokers need substantially higher doses of these medications, which might indirectly predispose them to TD.[27] On the other hand, these smoking patients may not have abnormally high blood or brain drug levels because of the enhanced hepatic biotransformation.

Thus far, clozapine has shown the strongest evidence for reducing substance abuse among schizophrenic individuals.[31–34] This beneficial effect will enhance both the therapeutic effectiveness of clozapine as well as improve the quality of life in patients who decrease or discontinue substance abuse.

Cognitive dysfunction. TD has been associated with compromised cognitive function.[35–37] Using the Conceptual Level Analogy Test (CLAT), Wegner et al.[35] reported that patients with TD showed cognitive impairment that predated the onset of motor manifestations. However, it remains unclear if these are cause-effect relationships or indicators of some preexisting vulnerabilities.

Illness severity. Illness severity,[22,38] increased levels of negative symptomatology,[22] and greater deficits on the childhood Premorbid Adjustment Scale (PAS),[38] all associated with inherent neurobiological dysfunction, appear to predispose patients to TD. In a longitudinal study of 118 patients having their first psychotic episode, Chakos and coworkers[38] found that increased antipsychotic drug dose and poor response to treatment of the index episode were significant risk factors for time-to-emergence of TD. These findings indicate that individuals who are more severely ill and less responsive to treatment are predisposed to TD.

Duration of neuroleptic exposure. Prospective studies have shown an incidence of new TD cases of approximately 3% to 5% per year of neuroleptic treatment.[39,40] The duration of neuroleptic exposure correlates with illness severity, which is itself a risk factor for TD.

CLOZAPINE THERAPY FOR TREATMENT-RESISTANT AND TREATMENT-INTOLERANT SCHIZOPHRENIC INDIVIDUALS

A multicenter trial comparing the efficacy of chlorpromazine with that of clozapine established the superiority of clozapine in reducing symptomatology in treatment-resistant schizophrenia.[41] Clozapine is also indicated for schizophrenic patients who are intolerant of the motor side effects of neuroleptics.[42]

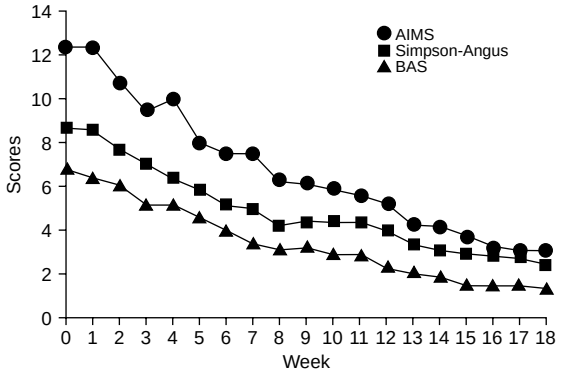
In a multicenter study including 151 hospitalized schizophrenic patients experiencing EPS or TD who were randomly treated with clozapine or chlorpromazine, the majority of patients who discontinued chlorpromazine did so because of EPS, whereas only 8% of those receiving clozapine did so for EPS.[43]

An open-label, 18-week trial with clozapine was recently conducted in 20 chronic schizophrenic patients with TD, parkinsonism, or chronic akathisia.[44] The improvement rates for TD (74%), parkinsonism (69%), and chronic akathisia (78%) after 18 weeks of treatment with clozapine are shown in Figure 1. These included a statistically significant improvement in scores on the Abnormal Involuntary Movement Scale and Simpson-Angus Rating Scale for Extrapyramidal Side Effects at week 5 and a significant reduction on the Barnes Rating Scale for Drug-Induced Akathisia at week 6 ($p < .0001$ for each).[44]

In a unique retrospective and prospective study by Peacock and coworkers,[45] 100 patients receiving long-term neuroleptic monotherapy (flupenthixol, 9 mg/day; perphenazine, 24 mg/day; and zuclopenthixol, 20 mg/day) and 100 patients receiving clozapine (median dosage = 400 mg/day) were evaluated for EPS and other side effects. Total prior duration of neuroleptic treatment was similar in the two cohorts (approximately 14 years).

On the basis of the St. Hans Rating Scale for EPS, 33% of patients receiving clozapine showed features of parkinsonism (mainly hypokinesia), compared with 61% of controls, despite its anticholinergic properties. Tremor was observed in 3% of patients in the clozapine group, compared with 11% of controls, and rigidity in 0% of patients in the clozapine group, compared with 19% of controls. Psychic akathisia emerged in 14% of patients in the clozapine group, compared with 40% of controls, whereas motor akathisia was seen in 7% and 29% of these patient groups, respectively. Each of the foregoing changes was statistically significant in favor of clozapine. Moreover, there was a significantly lower prevalence of TD in the clozapine group, even though at baseline there were more patients in that group than in the control group ($p < .05$). This effect emerged because of both a lower induction of new cases ($p < .001$) and a tendency toward greater disappearance of TD in the clozapine group compared with the control group ($p = .07$). Finally, patients in the clozapine group exhibited less neuroleptic-induced emotional apathy and depression than those in the control group.[45] These more recent results are consistent with findings in earlier reviews of clozapine and motor adverse effects.[5]

Figure 1. Mean Weekly Scores for the AIMS, Simpson-Angus, and BAS During 18 Weeks of Clozapine Treatment*†



*Reproduced with permission from Spivak et al (1997).[44]
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Rating Scale for Drug-Induced Akathisia, Simpson-Angus = Simpson-Angus Rating Scale for Extrapyramidal Side Effects.
†Differences between study onset and the 18-week follow-up for all 3 scales were statistically significant at a level of $p < .0001$.

AKATHISIA: A RISK FACTOR FOR INCREASED MORBIDITY IN SCHIZOPHRENIA

Akathisia has been associated with hostile behavior, including assaults, homicide, and suicide; medication refusal and noncompliance; and psychotic exacerbation. Because of the central importance of this phenomenon and the widely divergent prevalence rates, Chengappa's group[46] assessed the prevalence of akathisia in 29 patients taking stable dosages of clozapine. Only 2 patients (6.8%) receiving clozapine were rated to have akathisia by the Barnes Rating Scale for Drug-Induced Akathisia. Moreover, only 4 (28.6%) of the 14 patients with a history of moderate-to-severe TD while taking classic neuroleptics continued to manifest these symptoms while receiving clozapine; conversely, 10 (71.4%) of the 14 patients had no evidence of TD while receiving clozapine. There have been isolated reports of TD among patients receiving clozapine; however, because of prior neuroleptic use, the relationship of TD to clozapine has not been established.

CLOZAPINE PHARMACOLOGY IN TD

The pharmacology of clozapine in TD was investigated by Lieberman and coworkers.[47] Unlike robust though transient rises in the dopamine end-metabolite homovanillic acid (HVA) in the cerebrospinal fluid (CSF) found in previous studies, clozapine had no demonstrable effect on plasma HVA and showed only a mild rise in CSF

HVA, mainly in women.[47] This may be due to a relatively weak effect of clozapine on nigrostriatal dopamine neurons—which collectively account for a substantial fraction of dopamine metabolism—producing no compelling changes in HVA in plasma or CSF.

There were no significant changes in CSF 5-hydroxyindoleacetic acid, the terminal metabolite of serotonin. However, a dramatic elevation in CSF norepinephrine was observed after clozapine administration, indicating potent α-adrenergic receptor blockade.

Of the new atypical antipsychotic agents, clozapine has the most favorable profile with respect to EPS and TD liability.[48] In a prospective study of 28 schizophrenic or schizoaffective patients with no history of TD who had inadequate response to or intolerable adverse effects with conventional neuroleptics for at least 1 year, only 2 patients receiving clozapine exhibited mild TD on at least 2 consecutive occasions 3 months apart. Whether these cases were actually caused by clozapine was equivocal, in that TD may have been present at baseline; however, these cases might also have represented dyskinetic movements related to the progression of underlying chronic schizophrenia.

OTHER ATYPICAL ANTIPSYCHOTICS

Atypical antipsychotics are unlike typical antipsychotics in that it is possible to separate therapeutic doses from motor side effects with the newer generation agents. Before the prototype atypical antipsychotic clozapine, neuroleptics were interchangeable, and it was held that an appropriate therapeutic dose was achieved at a level that also produced EPS.[49] The risk for EPS is greater when more than 80% of D_2 receptors in the striatum are blocked,[49] which usually occurs at therapeutic doses of conventional neuroleptics. The others that were developed after clozapine all have lesser propensity to induce EPS, relative to typical antipsychotics.[49,50] However, because of varying pharmacologic profiles, some atypical antipsychotics have a better motor side effect profile than others.[51,52]

Because risperidone and olanzapine have been commercially available for extended periods, there are relatively more efficacy studies on these atypical antipsychotics than on the more recent ones such as quetiapine, sertindole, and ziprasidone.

At dosages of 6 mg/day, risperidone is more efficacious than haloperidol and has low potential for EPS.[53,54] However, a dose-related rise in Extrapyramidal Symptom Rating Scale scores has been observed at dosages of risperidone between 6 mg/day and 16 mg/day.[51] A few case reports of withdrawal-emergent dyskinesia and TD have also been associated with reduction in risperidone dose,[55,56] but the true risk of TD with risperidone is unknown. Olanzapine is an effective antipsychotic with EPS rates that do not appear to be significantly different from those of placebo.[57] A recent prospective study of olanzapine and haloperidol responders showed a favorably low TD rate in the olanzapine group.[58] However, more studies are needed to fully assess the EPS and TD profile of olanzapine and the other new-generation antipsychotics.

Table 3. Clozapine Pharmacoeconomic Studies

Author/Year of Study	Description of Study Results
Rosenheck et al[62] 1997	Estimated an annual per-capita cost savings of approximately $2000 associated with improved compliance and fewer EPS/TD episodes requiring hospitalization in clozapine group.
Reid et al[63] 1994	Estimated per-capita savings of $33,000 at year 1.5, $41,500 at year 2, and $50,250 at year 2.5 associated with dramatic declines in hospitalizations (bed-days) among patients treated with clozapine.
Meltzer et al[64] 1993	Estimated per-capita savings of $8700 per year in clozapine-treated patients, when comparing cost for 2 years before and 2 years during clozapine therapy.
Honigfeld and Patin[65] 1990	Calculated per-capita savings by the second year of study of $20,000 because of diminished rehospitalization rates and costs associated with clozapine, compared with typical neuroleptics.
Revicki et al[66] 1990	Estimated per-capita savings of $9000 at first year after index date and over $30,000 in second year for hospital costs associated with clozapine, compared with conventional neuroleptics.

COST-EFFECTIVENESS

Although neuroleptic agents provide relief from psychotic symptoms of schizophrenia, the motor side effects (EPS, TD) associated with such treatment contribute to the current morbidity of this mental illness. Noncompliance, substance abuse, and suicide have been linked to treatment intolerance.[59–61] Such increase in morbidity results in exacerbations of psychotic symptoms, relapse, and medical emergencies that lead to increases in hospitalization and utilization of health care resources. Numerous studies have shown that the superior efficacy of clozapine (vs. chlorpromazine) without the distressing motor side effects has led to cost savings (Table 3).[62–66]

CONCLUSIONS

With the typical neuroleptics, EPS afflicts up to 90% of patients and TD afflicts approximately 20% to 25%. Risk factors for TD, which can be irreversible, include a number of clinically relevant parameters that can be used to decrease the occurrence of TD. Numerous studies have shown that aside from its superior efficacy in reducing psychotic symptoms (vs. chlorpromazine), clozapine is associated with far less liability for EPS and TD. The favorable profile regarding motor and mental EPS with

clozapine treatment contributes to the improved psychiatric well-being, enhanced compliance, and reduction in treatment-induced morbidity associated with schizophrenia, resulting in a net reduction in health care cost.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), sertindole (Serlect).

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