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Focus on Lower Risk of Tardive Dyskinesia with Atypical Antipsychotics

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Background. *Tardive dyskinesia (TD) is one of the most serious iatrogenic neurological complications of the first-generation antipsychotics. Identifying the risk factors for TD is important to minimize the risk of this potentially irreversible movement disorder in susceptible populations.*

Methods. *A Medline search was conducted for the literature on risk factors for TD with the first-generation antipsychotics, as well as the emerging literature of the lower risk of TD with the second-generation antipsychotics.*

Results. *Several demographic, phenomenological, comorbidities and treatment variables have been reported to be associated with higher risk of TD. On the other hand, significantly lower rates of TD have been reported with the second-generation atypical antipsychotics, even in high risk groups such as the elderly.*

Conclusions. *The use of the second-generation antipsychotics as first-line treatment of psychosis appears to have lowered the overall prevalence of acute movement disorders as well as TD, and have led them to become the standard of care in part because of their safer extrapyramidal profiles.*

Keywords Comorbidities, Extrapyramidal symptoms, Risk factors, Tardive dyskinesia

INTRODUCTION

Tardive dyskinesia (TD) is one of the most serious adverse effects of the first-generation antipsychotics, also known as neuroleptics (1,2). Despite extensive research, the pathogenesis and treatment of TD remain unknown, but its link to neuroleptic therapy is well established. Persons who develop *acute* extrapyramidal symptoms (EPS) with neuroleptic treatment appear to be at much higher risk for developing TD than those who do not (3). It is therefore expected that the second-generation antipsychotics (also known as novel or atypical antipsychotics), which produce far less acute EPS, are much less likely to be associated with late-onset movement disorders such as TD.

Many risk factors for TD have been reported (see Table 1). Understanding the risk factors that predispose acute EPS in a given patient can significantly help the clinician avoid long-term EPS syndromes such as TD. The risk factors for acute EPS and TD are also relevant for the atypical antipsychotics; although some of them (clozapine and quetiapine) do not differ from placebo along their entire dose range (4,5), other atypicals have a progressively higher EPS rate at higher doses, as reflected in their package insert (5) and labeling.

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DEMOGRAPHIC RISK FACTORS

Aging

Many studies have shown that age is a risk factor for developing TD (6,7), and that the increased risk with age is not due to longer duration of neuroleptic exposure. It should be noted that the aging process can trigger movement disorders, either spontaneous or due to medical conditions, even without previous neuroleptic exposure (8,9). However, recent longitudinal studies in geriatric populations (10,11) show TD incidence rates of 26% to 31% after only 1 year of exposure to conventional antipsychotics. These studies represent strong evidence that aging per se, and not coincidental movement disorders, is a risk factor for the high neuroleptic-related TD rates in the elderly. Of note is that the 1-year incidence rate of TD with novel antipsychotics in the elderly is only 2.5%, which is 10-fold

Table 1 Risk Factors for EPS and TD

Demographic Factors
• Age
• Gender
• Ethnicity
Clinical Factors
• Diagnosis of mood disorder
• Early age of onset
• Negative symptom cluster
• Cognitive dysfunction
Comorbidities
• Psychiatric: alcoholism, mental retardation, etc.
• Neurologic: epilepsy, brain trauma, etc.
• Medical: diabetes
Biological Factors
• Morphological brain abnormalities
• Postmortem neuropathology (gliosis)
• Basal ganglia iron deposits
Treatment Factors
• Duration of antipsychotic treatment
• Cumulative dose
• Drug holidays
• Anticholinergic use
• Depot formulation

lower than the rate observed among patients receiving the older conventional antipsychotics (12,13).

Children

Children are also at higher risk for TD when treated with neuroleptics. Campbell et al. (14) reported a TD rate of 22% after only 30 months in 36 children receiving haloperidol. Others have reported even higher rates of 41% and 48% (15,16).

Gender

A greater prevalence of TD has been repeatedly observed in females. A review of 13 studies (17) reported a higher vulnerability to TD in females compared to males, with an odds ratio of 1.69. Some researchers attribute the higher TD risk in neuroleptic-treated women to estrogen effects on dopamine pathways in the nigrostriatal tract (18) but no definitive research exists in this area. However, some evidence suggests that men and women may have similar rates of TD until about 64 years of age, after which women significantly outpace men (19).

Ethnicity

Several studies indicate ethnic differences in susceptibility to EPS, including TD. These ethnic differences are probably due to both pharmacodynamic and pharmacokinetic factors (20,21). Functionally significant genetic polymorphisms exist in most of the oxidative enzymes (cytochromes) (22), which can lead to very large variations in the activity of these enzymes in any population. For example, cytochrome P450 2D6 has been found to have over 20 mutations that inactivate, impair, or accelerate its function (23), and most of the mutant alleles are ethnically specific.

African American persons have been reported to have a higher risk for TD (24). This higher risk may be due in part to an increased prevalence of low metabolizers in this population. Additionally, compared to Caucasian persons, this ethnic group has often been exposed to higher doses of oral neuroleptics and to a higher rate of parenteral depot neuroleptics, all of which may lead to increased TD rates (25,26). It should be noted that misdiagnosis of bipolar disorder, panic attacks, or obsessive-compulsive disorder (OCD) as schizophrenia appears to have contributed to higher use of neuroleptics in African Americans (27,28).

Asian Americans and Hispanic persons have also been reported to be more sensitive to the motor side effects of neuroleptics than Caucasian persons, and they generally need lower doses of antipsychotics (29,30). Other studies have failed to replicate these findings (31). However, sufficient evidence suggests that for some ethnic groups, the newer atypical antipsychotics, with their lower propensity to cause EPS and TD, should be used as first-line treatment.

DIAGNOSTIC AND CLINICAL RISK FACTORS

Mood Disorders

A substantial body of literature suggests that patients with mood disorders and schizophrenia are at higher risk for TD (32–34) than acute EPS (35). Family history may also be associated with increased risk of TD (36), while lithium coadministration may decrease that risk (37). Given the high frequency of antipsychotic usage in bipolar disorder, the use of atypicals with the lowest EPS rates should be given priority consideration in the treatment of mood disorders.

Schizophrenia

Some studies, including those of Kraepelin and Bleuler, have described choreiform movements resembling TD in medication-naive schizophrenic patients (38). The rate of naturally occurring spontaneous movements in schizophrenia is about 5%, and patients exhibiting such movements may be misdiagnosed as having TD (39).

Clinical Features

Certain clinical parameters, such as early onset of psychosis, presence of negative symptoms, and cognitive impairment have been associated with increased TD risk (40). Such clinical features tend to cluster together in some patients.

COMORBIDITY FACTORS

The presence of comorbid psychiatric or neurologic pathology appears to contribute to the higher risk of TD in patients receiving neuroleptics (41). These comorbid conditions include alcoholism, mental retardation, brain trauma, autism, encephalitis, and epilepsy. In addition, some medical comorbidities, such as diabetes, have been associated with higher TD risk as well (42). The use of the atypical class of antipsychotics in psychotic patients with neuropsychiatric comorbidities should lower the risk of TD. On the other hand, some atypicals, such as clozapine and olanzapine, have been reported to increase the risk of diabetes (43) but to date there have been no studies to establish whether new-onset diabetes increases the risk for EPS or TD in patients receiving maintenance antipsychotic drugs.

BIOLOGICAL RISK FACTORS

Certain biological features have been reported to increase the risk of TD. These include structural brain abnormalities such as enlarged lateral cerebral ventricles (44), presence of gliosis in the midbrain and brainstem, and degeneration in the substantia nigra (45), iron deposition in the basal ganglia and substantia nigra (46), or inflated neurons in the cerebellar dentate nucleus without neuronal loss (47). The literature in this area of research is not well replicated and therefore is not reliable.

TREATMENT VARIABLES

Acute EPS

In two separate prospective studies (3,48), acute EPS appeared to predict the development of future TD, with a 3-fold risk rate. Some investigators postulated that acute movement disorders such as dyskinesia, dystonia, and akathisia may be more likely to predict future TD than bradykinesia or rigidity.

Drug Holidays

Although drug holidays were recommended in the 1970s to reduce the cumulative exposure to neuroleptics (which supposedly would reduce the TD risk) (49), subsequent studies demonstrated that periodic interruptions in neuroleptic treatment may actually increase the risk of TD (50). While one study reported that continuous neuroleptic therapy was associated with improvement in TD (51), a previous study that found TD to be 3 times higher in continuously treated patients compared with those medicated only when the early signs of relapse emerged (52). These conflicting reports reflect the inconsistent findings that plague the field of TD research.

Anticholinergic Drugs

Many researchers observed that the concomitant use of anticholinergic drugs can worsen TD symptoms and that stopping anticholinergics may lead to improvement in TD symptoms (53–55). However, an examination of the hypothesis that chronic anticholinergic administration with neuroleptics increases the risk for TD failed to show such an association (56), and another review similarly found no evidence linking antiparkinsonian medication use with TD risk (57). One possible confounding variable in the allegedly increased risk for TD with anticholinergic drugs is that these drugs are given to patients who develop acute EPS with neuroleptics. As mentioned earlier, acute EPS is itself a risk factor for subsequent TD. Thus, the link between anticholinergic use and TD may be spurious, since the increased susceptibility to TD may be related to the pathophysiology of EPS symptoms rather than to the effect of added anticholinergics.

Lithium Copharmacy

There are limited data regarding the effects of coadministration of lithium with neuroleptics on the risk of TD. Kane et al. (3) reported that lithium reduced the incidence of TD in a sample of patients receiving neuroleptics. Aside from some animal data suggesting that chronic lithium treatment may reduce dopamine receptor supersensitivity (58), there are no other studies examining this issue.

Drug Dose and Duration

The issue of dosage, cumulative dose, and duration of treatment with neuroleptics as risk factors for the development of TD is too complex to dissect. One reason is that there is a subset of patients who appear to be immune from developing either acute EPS or TD, regardless of dosage and duration of treatment. Another reason is that since prospective studies in this area have proven to be very difficult to conduct in real-world settings, most of the studies are cross-sectional (1). Yet another reason may be that most chronic patients received excessive doses, resulting in a failure to detect a dose-response relationship in many studies (24,25). Finally, another confounder for this area of research is that elderly patients are at high risk of TD even when they receive very low doses of neuroleptics (40,59). Patients' age may have eliminated the possibility of finding a correlation in the various published studies because different samples had various proportions of young and old patients. Thus, only studies that focused on TD in the first new year of neuroleptic treatment detected a direct and significant relationship between TD and antipsychotic dose and duration of treatment.

Atypical versus Conventional Antipsychotics

For the past several decades, TD has been one of the most serious iatrogenic brain disorders caused by the first-generation antipsychotics. Casey (60) reported that up to 75% of patients treated with conventional antipsychotic medications will experience EPS. A comparison of several prospective studies of the incidence of TD by Kane (61) showed that the average yearly risk of developing TD from conventional antipsychotic drug use is 5.3% per year over the first 5 to 8 years of treatment. Carried forward for 8 years, the risk for developing TD while taking conventional antipsychotics is over 40%.

Although research has failed to identify an effective treatment for TD, much has been learned about its risk factors, as discussed earlier in this article. The advent of a new generation of atypical antipsychotics has been a major breakthrough in reducing the development of TD in patients who need long-term antipsychotic treatment. A key benefit from the reduced incidence of acute EPS and TD with atypical antipsychotics is enhanced patient adherence to treatment that leads to better compliance and improvement in outcomes for those with psychiatric disorders requiring lifelong antipsychotic therapy (62).

The use of the term *atypical antipsychotics* refers to the substantial decrease in EPS associated with these agents as compared to the conventional antipsychotics. The "proof of the pudding" of atypicality is best inferred by studying these agents in the populations at the highest risk of developing EPS. Patients suffering from Parkinson Disease (PD) represent the population most vulnerable to EPS side effects. In a review of studies of atypical antipsychotics in the EPS-vulnerable patients, Friedman concluded that while low levels of EPS were reported with each of the atypical antipsychotics in low doses, quetiapine proved to be the atypical antipsychotic most suitable for use in PD patients (63) who develop psychosis while receiving dopamine agonist therapy for PD. Because quetiapine does not require blood monitoring for agranulocytosis as does L-dopa and it is better tolerated by PD patients than clozapine, it is generally used as a first line treatment for psychosis with PD patients.

Dolder and Jeste (2003) studied typical versus atypical antipsychotics in a population at very high risk of developing TD, that is, middle-aged and older adults with pre-existing borderline dyskinesia (64). They found that among patients at a very high risk for worsening TD, the use of atypical antipsychotics was associated with a significantly lower risk of developing definitive TD compared with conventional antipsychotics ($P < 0.001$). While Dolder and Jeste were able to show a significantly lower risk of TD with atypical antipsychotics as compared to conventional antipsychotics, their sample size was not powered enough to make meaningful comparisons of TD risk among the atypicals studied (olanzapine, quetiapine, and risperidone). In an examination of short-term clinical data derived from drug development trials of atypical antipsychotics, Kane (2001) compared the overall incidence of EPS among placebo, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone (61). All of the atypicals were compared to placebo and all but ziprasidone were compared to haloperidol. These clinical trial data show that the percentages of patients using antiparkinsonian medication in the atypical groups (olanzapine = 20%, quetiapine = 12%, and risperidone = 28%) were considerably lower than those in the haloperidol groups (68%, 42%, 47%, respectively). These same data demonstrated that of the patients receiving placebo, approximately 11% to 18% required antiparkinsonian drugs. The author believes that this finding is likely attributable to the fact that patients entering such trials have usually received prior long-term treatment with conventional neuroleptics. The nonstriatal dopamine receptor selectivity and the very low EPS profile of atypical antipsychotics are probably key factors in minimizing TD, in light of the evidence that acute EPS is a major predictor of TD risk.

CONCLUSIONS

Wider use of atypical antipsychotics could very well make TD a relatively rare adverse event and lessen the need for physicians to address the numerous risk factors for neuroleptic-induced TD. Several studies have ranked the atypical antipsychotics based on their risk of inducing acute EPS as well as TD, from lowest risk to high risk: clozapine < quetiapine < aripiprazole < olanzapine = ziprasidone < risperidone (65). In addition to the broader efficacy of atypical antipsychotics, the minimization of acute (EPS) and long-term movement disorders (TD) clearly dictates that the older neuroleptics no longer be used as first-line pharmacotherapy for psychotic disorders.

REFERENCES

1. Jeste DV, Wyatt RJ: *Understanding and Treating Tardive Dyskinesia.* New York: Guilford Press, 1982
2. *Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association*. Washington, DC: The American Psychiatric Association, 1992
3. Kane JM, Woerner M, Borenstein M, Wegner J, Lieberman J: Integrating incidence and prevalence of tardive dyskinesia. *Psychopharmacol Bull* 1986; 22:254–258
4. Meltzer HY: The mechanism of action of clozapine in relation to its clinical advantages. In: HY, Meltzer ed. *Novel Antipsychotic Drugs.* New York: Raven Press, 1992:1–13
5. Arvanitis LA, Miller BG: Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: A comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. *Biol Psychiatry* 1997; 42:233–246
6. Kane JM, Smith JM: Tardive dyskinesia: Prevalence and risk factors, 1959 to 1979. *Arch Gen Psychiatry* 1982; 39:473–481
7. Smith JM, Baldessarini RJ: Changes in prevalence, severity, and recovery in tardive dyskinesia with age. *Arch Gen Psychiatry* 1980; 37:1368–1373

8. Blowers AJ, Borison RL, Blowers CM, Bicknell DJ: Abnormal involuntary movements in the elderly. *Br J Psychiatry* 1981; 139:363–364
9. Molsa PK, Martilla RJ, Rinne UK: Extrapyramidal symptoms in dementia. *Neurology* 1984; 34:1114–1116
10. Jeste DV, Caligiuri MP, Paulsen JS, et al.: Risk of tardive dyskinesia in older patients. A prospective longitudinal study of 266 outpatients. *Arch Gen Psychiatry* 1995; 52:756–765
11. Woerner MG, Alvir JM, Saltz BL, Lieberman JA, Kane JM: Prospective study of tardive dyskinesia in the elderly: Rates and risk factors. *Am J Psychiatry* 1998; 155:1521–1528
12. Jeste DV, Okamoto A, Napolitano J, Kane JM, Martinez RA: Low incidence of persistent tardive dyskinesia in elderly patients with dementia treated with risperidone. *Am J Psychiatry* 2000; 157:1150–1155
13. Jeste DV: Low TD rate with quetiapine in the elderly. Paper presented at Philadelphia, PA Institute for Psychiatric Services, October 25–29, 2000
14. Campbell M, Grega DM, Green WH, Bennett WG: Neuroleptic-induced dyskinesias in children. *Clin Neuropharmacol* 1983; 6:207–222
15. Polizos P, Engelhardt DM, Hoffman SP, Waizer J: Neurological consequences of psychotropic drug withdrawal in schizophrenic children. *J Autism Child Schizophr* 1973; 3:247–253
16. Engelhardt DM, Polizos P, Waizer J: CNS consequences of psychotropic drug withdrawal in autistic children: A follow-up report. *Psychopharmacol Bull* 1975; 11:6–7
17. Smith JM, Dunn DD: Sex differences in the prevalence of severe tardive dyskinesia. *Am J Psychiatry* 1979; 136:1080–1082
18. Hruska RE: Sex hormone exposure and non-reproductive behavior. *Int J Ment Health* 1985; 14:112–134
19. Richardson MA, Pass R, Craig TJ, Vickers E: Factors influencing the prevalence and severity of tardive dyskinesia. *Psychopharmacol Bull* 1984; 20:33–38
20. Kalow W: *Pharmacogenetics of Drug Metabolism.* New York: Pergamon, 1992
21. Webber WW: *Pharmacogenetics.* New York: Oxford University Press, 1997
22. Lin K-M, Poland RE: Ethnicity, culture, and psychopharmacology. In: FE, Bloom, DI, Kupfer eds. *Psychopharmacology: The Fourth Generation of Progress.* New York: Raven Press, 1995:1907–1917
23. Daly AK, Brockmoller J, Broly F, et al.: Nomenclature for human CYP2D6 alleles. *Pharmacogenetics* 1996; 6:193–201
24. Morgenstern H, Glazer WM: Identifying risk factors for tardive dyskinesia among long-term outpatients maintained with neuroleptic medications. Results of the Yale Tardive Dyskinesia Study. *Arch Gen Psychiatry*. 1993; 50:723–733
25. Glazer WM, Morgenstern H, Doucette J: Race and tardive dyskinesia among outpatients at a CMHC. *Hosp Community Psychiatry* 1994; 45:38–42
26. Swartz JR, Burgoyne K, Smith M, Gadasally R, Ananth J, Ananth K: Tardive dyskinesia and ethnicity: review of the literature. *Ann Clin Psychiatry* 1997; 9:53–55
27. Littlewood R: Psychiatric diagnosis and racial bias: empirical and interpretative approaches. *Soc Sci Med* 1992; 34:141–149
28. Lawson WB: Issues in pharmacotherapy for African Americans. In: P, Ruiz ed. *Ethnicity and Psychopharmacology.* Washington, DC: American Psychiatric Press, 2000:37–53
29. Lin KM, Finder E: Neuroleptic dosage for Asians. *Am J Psychiatry* 1983; 140:490–491
30. Ruiz S, Chu P, Sramek J, Rotavu E, Herrera J: Neuroleptic dosing in Asian and Hispanic outpatients with schizophrenia. *Mt Sinai J Med* 1996; 63:306–309
31. Sramek JJ, Sayles MA, Simpson GM: Neuroleptic dosage for Asians: A failure to replicate. *Am J Psychiatry* 1986; 143:535–536
32. Davis KL, Berger PA, Hollister LE: Tardive dyskinesia and depressive illness. *Psychopharmacol Commun* 1976; 2:125–130
33. Mukherjee S, Rosen AM, Caracci G, Shukla S: Persistent tardive dyskinesia in bipolar patients. *Arch Gen Psychiatry* 1986; 43:342–346
34. Casey DE: Affective disorders and tardive dyskinesia. *Encephale* 1988; 14:221–226
35. Nasrallah HA, Churchill CM, Hamdan-Allan GA: Higher frequency of neuroleptic-induced dystonia in mania than in schizophrenia. *Am J Psychiatry* 1988; 145:1455–1456
36. Wegner JT, Catalano F, Gibralter J, Kane JM: Schizophrenics with tardive dyskinesia. Neuropsychological deficit and family psychopathology. *Arch Gen Psychiatry* 1985; 42:860–865
37. Kane JM, Woerner M, Borenstein M, Wegner J, Lieberman J: Integrating incidence and prevalence of tardive dyskinesia. *Psychopharmacol Bull* 1986; 22:254–258
38. Barnes TRE, Liddle PF: Tardive dyskinesia: Implications for schizophrenia? In: AA, Schiff, M, Roth, HL, Freeman eds. *Schizophrenia: New Pharmacological and Clinical Development.* London: Royal Society of Medicine Services, 1985:81–87
39. Owens DG, Johnstone EC, Frith CD: Spontaneous involuntary disorders of movement: Their prevalence, severity, and distribution in chronic schizophrenics with and without treatment with neuroleptics. *Arch Gen Psychiatry* 1982; 39:452–461
40. Waddington JL, Youssef HA: Late onset involuntary movements in chronic schizophrenia: Relationship of "tardive" dyskinesia to intellectual impairment and negative symptoms. *Br J Psychiatry* 1986; 149:616–620
41. Yassa R, Nair V, Schwartz G: Tardive dyskinesia and the primary psychiatric diagnosis. *Psychosomatics* 1984; 25:135–138
42. Woerner MG, Saltz BL, Kane JM, Lieberman JA, Alvir JM: Diabetes and development of tardive dyskinesia. *Am J Psychiatry* 1993; 150:966–968
43. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity: Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27:596–601
44. Waddington JL: Schizophrenia, affective psychoses, and other disorders treated with neuroleptic drugs: The enigma of tardive dyskinesia, its neurobiological determinants, and the conflict of paradigms. *Int Rev Neurobiol* 1989; 31:297–353
45. Christensen E, Moller JE, Faurbye A: Neuropathological investigation of 28 brains from patients with dyskinesia. *Acta Psychiatr Scand* 1970; 46:14–23
46. Campbell WG, Raskind MA, Gordon T, Shaw CM: Iron pigment in the brain of a man with tardive dyskinesia. *Am J Psychiatry* 1985; 142:364–365
47. Arai N, Amano N, Iseki E, et al.: Tardive dyskinesia with inflated neurons of the cerebellar dentate nucleus. Case reports and morphometric study. *Acta Neuropathol* (Berl) 1987; 73:38–42
48. Saltz BL, Woerner MG, Kane JM, et al.: Prospective study of tardive dyskinesia incidence in the elderly. *JAMA* 1991; 266:2402–2406
49. American College of Neuropsychopharmacology — Food and Drug Administration Task Force: Schiele BC, Gallant D, Simpson G,

et al.: Neurologic syndromes associated with antipsychotic-drug use. *N Engl J Med* 1973; 289:20–23
50. Goldman MB, Luchins DJ: Intermittent neuroleptic therapy and tardive dyskinesia: A literature review. *Hosp Community Psychiatry* 1984; 35:1215–1219
51. Gardos G, Cole JO, Haskell D, Marby D, Paine SS, Moore P: The natural history of tardive dyskinesia. *J Clin Psychopharmacol* 1988; 8:31S–37S
52. Carpenter WT Jr, Heinrichs DW, Hanlon TE: A comparative trial of pharmacologic strategies in schizophrenia. *Am J Psychiatry* 1987; 144:1466–1470
53. Klawans HL, Rubovits R: Effect of cholinergic and anticholinergic agents on tardive dyskinesia. *J Neurol Neurosurg Psych* 1974; 37:941–947
54. Jus A, Gautier J, Villeneuve A, et al.: Chronology of combined neuroleptics and antiparkinsonian administration. *Am J Psychiatry* 1977; 134:1157
55. Greil W, Haag H, Rossnagl G, Ruther E: Effect of anticholinergics on tardive dyskinesia. A controlled discontinuation study. *Br J Psychiatry* 1984; 145:304–310
56. Klawans HL, Goetz CG, Perlik S: Tardive dyskinesia: Review and update. *Am J Psychiatry* 1980; 137:900–908
57. Gardos G, Cole JO: Tardive dyskinesia and anticholinergic drugs. *Am J Psychiatry* 1983; 140:200–202
58. Pert A, Rosenblatt JE, Sivit C, Pert CB, Bunney WE Jr.: Long-term treatment with lithium prevents the development of dopamine receptor supersensitivity. *Science* 1978; 201:171–173
59. Barnes TR, Kidger T, Gore SM: Tardive dyskinesia: A 3-year follow-up study. *Psychol Med* 1983; 13:71–81
60. Casey DE: Side effects of new antipsychotic agents. *J Clin Psychiatry* 1996; 57:40–45
61. Kane JM: Extrapyramidal side effects are unacceptable. *Eur Neuropsychopharmacol* 2001; 11(suppl 4):S397–S403
62. Gerlach J: Improving outcome in schizophrenia: the potential importance of EPS and neuroleptic dysphoria. *Ann Clin Psychiatry* 2002; 14:47–57
63. Friedman JH: Atypical antipsychotics in the EPS-vulnerable patient. *Psychoneuroendocrinology* 2003; 28(suppl 1):39–51
64. Dolder CR, Jeste DV: Incidence of tardive dyskinesia with typical versus atypical antipsychotics in very high risk patients. *Biol Psychiatry* 2003; 53:1142–1145
65. Correll CU, Leucht S, Kane JM: Lower risk for tardive dyskinesia associated with second-generation antipsychotics: A systematic review of 1-year studies. *Am J Psychiatry* 2004; 161:414–425