0271-0749/00/2002-0188/0
Journal of Clinical Psychopharmacology
Copyright © 2000 by Lippincott Williams & Wilkins, Inc.

Vol. 20, No. 1
Printed in U.S.A.

# Tardive Dyskinesia Associated With Higher Mortality in Psychiatric Patients: Results of a Meta-Analysis of Seven Independent Studies

JAVIER BALLESTEROS, MD*†, ASUNCIÓN GONZÁLEZ-PINTO, PHD*, AND ANTONIO BULBENA, MD, MSC(CANTAB)†‡

*Department of Neuroscience, University of the Basque Country, Leioa, Vizcaya; †Institute of Psychiatric Research, Aita-Menni Psychiatric Hospital, Arrasate-Mondragón, Guipúzcoa; ‡Department of Psychiatry, Hospital del Mar, Barcelona, Spain*

**This article reports a meta-analysis of seven independent studies on the association of tardive dyskinesia with all-cause mortality in psychiatric patients. Most of the studies included provide either small sample sizes or follow-up periods too short to reach a substantive conclusion on their own. In the meta-analysis, the overall odds ratio (OR) was significant when calculated either by the fixed-effects model (OR = 1.4, 95% confidence interval [CI] = 1.2–1.7, $p < 0.005$) or the random-effects model (OR = 1.4, 95% CI = 1.1–1.8, $p < 0.005$). There was no overall heterogeneity ($Q$ test = 8.1, $df = 7$, $p = 0.32$). The overall estimate changed within study designs (OR = 1.4, $p = 0.002$ in three prospective controlled studies; OR = 2.2, $p = 0.02$ in two prospective uncontrolled studies; and OR = 0.9, $p = 0.80$ in two retrospective controlled studies). It was modified upward when the two most influential studies (one prospective and one retrospective) were removed from the overview (OR = 2.2, 95% CI = 1.4–3.5, $p = 0.001$; $Q$ test = 0.81, $df = 4$, $p = 0.94$). The conclusion of the meta-analysis was that tardive dyskinesia must be considered a weak risk factor in terms of mortality. It remains to be elucidated whether it is a risk factor on its own or just a surrogate for any unknown organic liability. (J Clin Psychopharmacol 2000;20:188–194)**

THE DEVELOPMENT OF abnormal involuntary movements affecting the facial muscles, tongue, jaw, trunk, or extremities that appear after exposure to neuroleptic medications is called tardive dyskinesia (TD) (DSM-IV). These abnormal movements are not uniquely associated with neuroleptics because they also appear in neuroleptic-naive patients.[1] However, it is estimated that more than 50% of TD cases are caused by long-term neuroleptic exposure.[2] The risk of developing TD seems to increase with the cumulative exposure to neuroleptics, and the highest TD incidence rates have been reported within the first 2 years of exposure.[3,4] It has also been reported that the 5-year risk for developing TD among psychiatric patients exposed to neuroleptics is in the range of 17% to 42%.[5]

Beyond the obvious impact TD has on the quality of life of psychiatric patients,[6] its potential as a life-threatening condition has also been stressed.[7] However, data on this key issue are scarce and contradictory. Soon after the index article was published,[8] two negative reports appeared.[9,10] Subsequently, two more articles provided evidence on the association between TD and increased mortality,[11,12] whereas another two presented inconclusive results.[13,14] It is worth noting that most of these studies were based on either small sample sizes[8–10,12,14] or too short of a follow-up period (i.e., <5 years)[9,10,13,14] to reach a substantive conclusion on their own. In an attempt to more reliably estimate the association between TD and all-cause mortality, a quantitative overview of published data was undertaken.

## Methods

Articles dealing with the stated objective were identified through searches of several computerized databases: MEDLINE (1966 through September 1998), Dissertation Abstracts (1992 through July 1998), ERIC (1982 through March 1998), PsycLIT (1993 through June 1998), and all of the editions of Current Contents (July 1995 through September 1998). A less to more inclusive hierarchical text search was used with the key words "dyskinesia," "tardive dyskinesia," and "(dyskinesia or tardive dyski-

Received November 9, 1998; accepted after revision May 5, 1999.
Address requests for reprints to: Javier Ballesteros, MD, University of the Basque Country, Medical School, Department of Neuroscience, Campus de Leioa s/n, E-48940 Leioa, Spain. Address e-mail to: onpbaroj@lg.ehu.es.

nesia) and mortality." After checking the titles and abstracts and retrieving the original articles, their secondary references were checked again until no further original articles were obtained. Because there was a small number of retrieved studies, no inclusion or exclusion criteria were established *a priori*. A coding scheme was developed to categorize the characteristics of the studies. For each retrieved article, the methods section was carefully checked to extract its main methodologic issues: study design (prospective vs. retrospective), TD criteria, control for possible confounding variables, and length of follow-up. In the context of this meta-analysis, the studies were classified as prospective versus retrospective and controlled versus uncontrolled. We defined as prospective those studies for which the sampling design was based on the exposure factor (TD), whereas we distinguished those studies with sampling based on the outcome (mortality) as retrospective. For the criterion of controlled versus uncontrolled studies, we assessed the adjustment for possible confounding variables that might hinder the primary relationship being studied. The studies were classified as controlled if any procedure, either by design or statistical analysis, was reported to control for important confounding factors such as age, sex, or psychiatric diagnosis.

Eight articles were retrieved for the meta-analysis.[8–15] One study[15] was excluded because it was published in Japanese and the translation was not available. In addition to that reason, this study was coauthored by several investigators who also published two further studies dealing specifically with TD and mortality.[12, 14] Another study[14] was not retrieved by the computerized search, but was obtained from an external consultant.

Because of the different designs, sampling procedures, and length of follow-up recorded in the studies, the odds ratio (OR) was selected as the relative-risk measure for quantifying the effect of exposure (presence or absence of TD) on the outcome (number of patients who died over the follow-up period). For each independent study, data were extracted to conform to a two-by-two table. The studies were then individually reanalyzed to obtain an estimate of the OR; its 95% confidence intervals (95% CI) were estimated by the Cornfield method.[16] In one study,[14] the iterative calculations for computing the Cornfield limits failed to give an upper estimate, and the Woolf method was then used.[16] The study of McClelland and associates[11] reports regression coefficients associated with several stages of TD severity. In that case, an overall weighted mean coefficient was estimated by the use of the general variance method[17] and then transformed to OR and 95% CI.

The overall OR was calculated either by the general variance method, with study weights proportional to the precision of each study, which implies a fixed-effects model, or by the random-effects model.[17] The heterogeneity between studies was tested by an omnibus $Q$ test.[17] Heterogeneity sources were also assessed by a procedure similar to the analysis-of-variance method, as described by Hedges.[18] Post hoc influence or sensitivity analysis was calculated by leaving out studies from the meta-analysis according to their influence on the overall results. All statistical analyses were performed with Stata Statistical Software[19] by using a programmed routine.[20]

## Results

### *Summary of studies included in the meta-analysis*

Table 1 shows a summary of the seven studies from four countries included in the meta-analysis. Most of the studies came from inpatient samples with a main diagnosis of schizophrenia or affective disorders, but some researchers also included organic disorders in their study populations.[8–11] The assessment and diagnosis of TD were done on clinical grounds in two studies,[8, 11] whereas in the other five,[9, 10, 12–14] a standardized scale, the Abnormal Involuntary Movement Scale,[21] was used. The follow-up time was in the range of 16 months[9] to 15 years.[11] Only three studies reported results over a period of 5 or more years.[8, 11, 12] According to the axes for study classification previously defined, three articles reported a prospective controlled design[8, 11, 14] and two described a retrospective controlled design.[9, 10] Two articles were classified as prospective uncontrolled designs.[12, 13] In their original results only three studies reported statistically significant differences in mortality between TD patients and controls;[8, 11, 12] and these were also the studies with a longer follow-up since the time of exposure ascertainment.

### *Overall results*

Table 2 and Figure 1 show the individual and combined analyses for the four-fold tables extracted from the original reports. Most studies contributed to the meta-analysis with a single two-by-two table, but the study by McClelland and colleagues[11] yielded two data sets: one for functional disorders and another for organic disorders. Apart from the study by Kucharski and associates,[9] all individual OR were above unity, but only two data sets gave statistically significant results. The combined OR indicated a significant relationship between TD exposure and all-cause mortality when calculated either by the fixed-effects model (OR = 1.40, $p < 0.005$) or the random-effects model (OR = 1.43, $p < 0.005$) (see Table 2).

As Table 3 shows, there was no evidence of heterogeneity either by the overall $Q$ statistic or the between- and within-studies $Q$ statistics; thus, the overall OR calculated by the fixed-effects model was homogeneously

TABLE 1. Summary of reviewed studies of tardive dyskinesia and all-cause mortality[a]

| Reference (yr) | Setting (country) | TD Assessment and Diagnosis | Study Design (N) | Length of Follow-Up | Variables Controlled | Main Conclusions Reported |
|---|---|---|---|---|---|---|
| Mehta and associates (1978)[8] | State mental hospital (USA) | Signs of oral dyskinesia assessed by three fully trained psychiatrists | Prospective: 35 matched pairs (TD/control patients) at study inception | 5 yr | Age, sex, and primary diagnosis (schizophrenia or affective psychosis; psychosis associated with organic brain syndromes; mental retardation) | TD is associated with shorter life span ($p = 0.046$) |
| Kucharski and associates (1979)[9] | Psychiatric hospital (USA) | At least a rating of 2.5 on any of the AIMS items rated by two independent examiners | Retrospective: 16 matched pairs (deceased/living patients) looking backward to the AIMS score | 16–18 mo | Age, sex, diagnosis (schizophrenia; organic brain syndrome; mental retardation), and neuroleptic dosage | No differences are found either in total AIMS mean score (3.41 for deceased vs. 5.25 for living subjects) or in TD prevalence (25% for deceased vs. 43.7% for living subjects) |
| Yassa and associates (1984)[10] | A convenience sample assembling inpatients, outpatients, and a population with affective disorders from former studies on TD prevalence (USA) | A minimum score of 2 in any of the AIMS items | Retrospective: 18 matched pairs (deceased/living patients) looking backwards to the AIMS score | Not reported; it is estimated as 3–4 yr | Age, sex, diagnosis (schizophrenia; manic-depressive illness; mental retardation with psychosis), and duration of illness | No differences are found either in TD prevalence (10 over 18 for deceased; 8 over 18 for living patients) or in total AIMS mean score (3.2 for deceased vs. 2.5 for living patients |
| McClelland and associates (1986)[11] | Psychiatric hospital (UK) | Clinical diagnosis of facial dyskinesia for three severity grades: | Prospective: cohorts assembled from a prevalence study on | 15 yr | Sex (all females); age at cohort inception and psychiatric diagnosis | Moderate and severe TD are associated with shorter |

| | | | | | | |
|---|---|---|---|---|---|---|
| McClelland and associates (1986)[11] | Psychiatric hospital (UK) | Clinical diagnosis of facial dyskinesia for three severity grades: mild/moderate/severe | Prospective: cohorts assembled from a prevalence study on facial dyskinesia. N = 408 females divided by psychiatric diagnosis: functional disorder (N = 249) and organic brain syndrome (N = 159) | 15 yr | Sex (all females); age at cohort inception and psychiatric diagnosis enter as covariates in Cox proportional hazards model by study group (functional disorders and organic brain syndrome) | Moderate and severe TD are associated with shorter survival time in functional but not in organic disorders |
| Youssef and Waddington (1987)[13] | Psychiatric hospital (Ireland) | Based on the AIMS without further specifications | Prospective: cohorts assembled from prevalence studies on TD. N = 101 patients with Feighner criteria for schizophrenia | 32 mo | None by design or statistical analysis. TD patients were significantly older than controls | The mortality difference between TD cases and controls approaches but does not attain statistical significance; no formal statistical test provided |
| Yagi and associates (1989)[12] | Six mental institutions (Japan) | Based on research criteria: at least one AIMS item score ≥ 2 in patients exposed to neuroleptics in the absence of other condition prone to produce abnormal involuntary movements | Prospective: 61 schizophrenic patients with TD diagnosis and 70 concurrent schizophrenic patients without TD diagnosis | 10 yr | None by design or statistical analysis. Nonetheless, TD patients and controls were not significantly different on age, sex, and physical complications at the start of follow-up | The mortality experience is significantly higher in the TD group ($p < 0.05$) |
| Inada and associates (1992)[14] | Two psychiatric hospitals (Japan) | Based on research criteria as above. Measurements done in two periods (1 year apart) | Prospective: 45 matched pairs (TD/control patients) with diagnosis of schizophrenia at study inception | 50 mo | Age, sex; similar distribution on total years of exposure and average daily neuroleptic dosage at study inception | The mortality in the TD group tends to be higher than in controls but does not attain statistical significance ($p = 0.079$) |

[a]TD, tardive dyskinesia; AIMS, Abnormal Involuntary Movement Scale.

TABLE 2. Tardive dyskinesia and all-cause mortality: effect estimates for reviewed studies and summary of combined effects

| Reference | No. deaths/Total | | Estimated OR[a] (95% CI) | *p* Value[b] |
|---|---|---|---|---|
| | TD Patients | Control Patients | | |
| Mehta and associates (1978)[8] | 19/35 | 12/35 | 2.28 (0.88–5.91) | 0.15 |
| Kucharski and associates (1979)[9] | 4/11 | 12/21 | 0.43 (0.10–1.84) | 0.46 |
| Yasa and associates (1984)[10] | 10/18 | 8/18 | 1.56 (0.43–5.69) | 0.74 |
| McClelland and associates (1986)[11] | | | | |
| Functional disorders[c] | NA | NA | 1.44 (1.08–1.92) | 0.01 |
| Organic disorders[c] | NA | NA | 1.19 (0.88–1.61) | 0.27 |
| Youseff and Waddington (1987)[13] | 7/44 | 5/57 | 1.97 (0.61–6.35) | 0.36 |
| Yagi and associates (1989)[12] | 22/61 | 14/70 | 2.26 (1.04–4.90) | 0.05 |
| Inada and associates (1992)[14] | 7/45 | 2/45 | 3.96 (0.77–20.2) | 0.16 |
| Combined OR | | | | |
| Fixed-effects model | | | 1.40 (1.16–1.69) | <0.0005 |
| Random-effects model | | | 1.43 (1.14–1.81) | 0.002 |

[a]Odds ratio (OR) and 95% confidence interval (CI) estimates are based on the data extracted from the reviewed studies.

[b]*p* Values for individual studies report a two-sided Fisher exact test except for the study by McClelland and associates,[11] which reports *p* values associated with regression coefficients.

[c]Mean weighted estimates based on the individual Cox regression coefficients and their standard errors. NA, not available.

estimated. However, the within-designs OR estimates changed somewhat. Prospective uncontrolled studies gave a higher estimate than their controlled counterparts, whereas retrospective designs gave a nonsignificant estimate with wider confidence intervals. From data reported in Table 3, the only concern applies to the heterogeneity statistic calculated with the two retrospective controlled designs included in the overview. As can be seen in Figure 1, these studies were estimating effects in opposite directions.

### *Sensitivity analysis*

Because the combined OR estimate was strongly influenced by the most weighted data sets (Fig. 1), the analyses were performed without the data from the study of McClelland and colleagues.[11] Also, because the

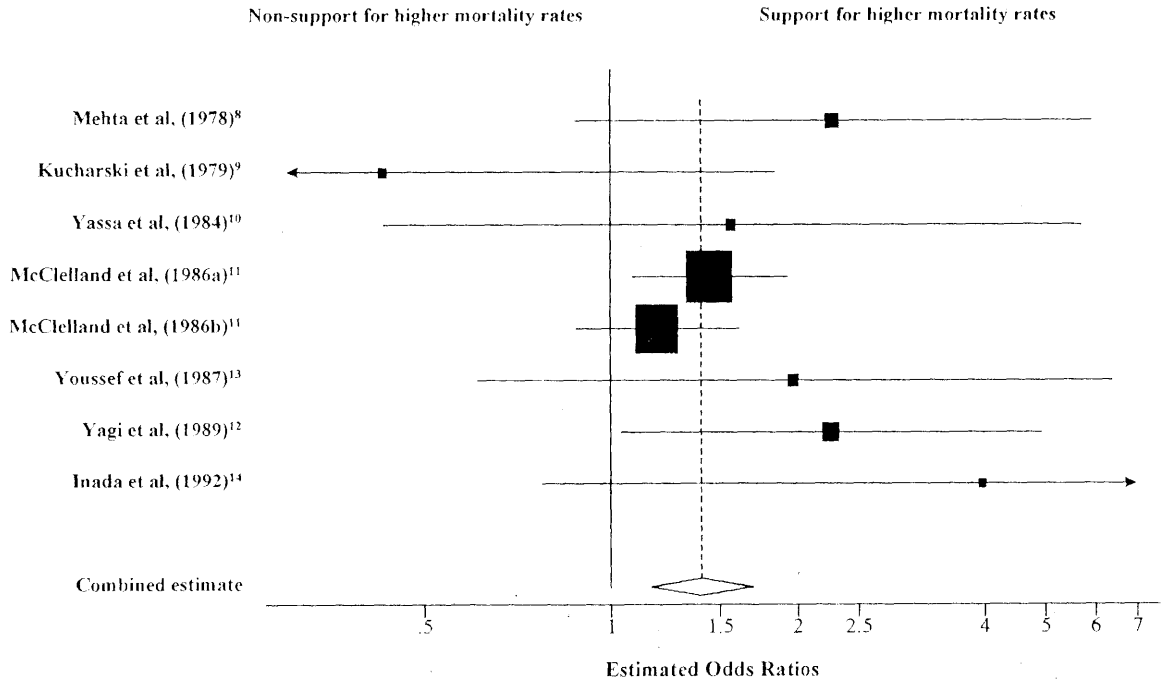


FIG. 1. TD and mortality: individual and combined effect estimates (fixed-effects model). Data from McClelland and associates (1986a) display the estimate for the functional disorders sample, and data from McClelland and associates (1986b) display the estimate for the organic disorders sample.

prospective controlled studies should be considered the strongest possible observational designs because they most closely resemble experimental trials. In those studies, contrary to retrospective designs, the selection and information biases are minimized because the exposure factor is assessed before the outcome, and the confounding bias is usually controlled either by design or statistical analysis. By restricting the overview to prospective controlled designs,[8, 11, 14] the results strongly support a direct relationship between TD exposure and all-cause mortality.

In summary, this meta-analysis, by combining data from seven independent studies, endorses former considerations on TD as a risk factor that acts to shorten the life span of psychiatric patients.[8, 11, 12] However, TD might also be categorized as a weak risk factor because of the cumulated evidence of this meta-analysis (all data sets and fixed-effects model; OR = 1.4, 95% CI = 1.2–1.7).

Although some treatments have shown some efficacy on reverting TD stages,[25, 26] the consensus is that none of the tested treatments have so far shown unambiguous efficacy.[27, 28] Thus, the result of this meta-analysis might raise concern about a previously diminished[9, 10] long-term deleterious effect on health associated with the development of TD in psychiatric patients. A note of caution applies because none of the authors of the reviewed studies were able to find an association between TD and any specific cause of mortality.[8, 10, 12–14] Also, patients who develop TD might have an organic liability that would, by itself, shorten their life expectancy.[27] If this were the case, TD would be considered a surrogate measure for that liability. Finally, from the publication dates of the reviewed studies, this meta-analysis likely focused on cases that developed TD before the clinical introduction of new neuroleptics. Thus, it tends to present TD as a long-term side effect of classic neuroleptic medications. Only as time goes by will we be in a position to accumulate new evidence regarding TD exposure, related either to the use of classic or new neuroleptics, and all-cause mortality.

## Acknowledgment

We thank José de León, MD, and Gohei Yagi, MD, for their help in retrieving a few elusive articles.

## References

1. Chatterjee A, Chakos M, Koreen A, Geisler S, Sheitman B, Woerner M, Kane JM, Alvir J, Lieberman JA. Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. Am J Psychiatry 1995; 152:1724–9.
2. Morgenstern H, Glazer WM, Niedzwiecki D, Nourjah P. The impact of neuroleptic medication on tardive dyskinesia: a meta-analysis of published studies. Am J Public Health 1987;77:717–24.
3. 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;50:723–33.
4. Chakos MH, Alvir JMJ, Woerner MG, Koreen A, Geisler S, Mayerhoff D, Sobel S, Kane JM, Borenstein M, Lieberman JA. Incidence and correlates of tardive dyskinesia in first episode of schizophrenia. Arch Gen Psychiatry 1996;53:313–9.
5. Glazer WM, Morgenstern H, Doucette JT. Predicting the long-term risk of tardive dyskinesia in outpatients maintained on neuroleptic medications. J Clin Psychiatry 1993;54:133–9.
6. Browne S, Roe M, Lane A, Gervin M, Morris M, Kinsella A, Larkin C, O'Callaghan E. Quality of life in schizophrenia: relationship to sociodemographic factors, symptomatology and tardive dyskinesia. Acta Psychiatr Scand 1996;94:118–24.
7. Casey DE, Rabins P. Tardive dyskinesia as a life-threatening illness. Am J Psychiatry 1978;135:486–8.
8. Mehta D, Mallya A, Volavka J. Mortality of patients with tardive dyskinesia. Am J Psychiatry 1978;135:371–2.
9. Kucharski LT, Smith JW, Dunn DD. Mortality and tardive dyskinesia [letter]. Am J Psychiatry 1979;136:1228.
10. Yassa R, Mohelsky H, Dimitry R, Schwartz G. Mortality rate in tardive dyskinesia. Am J Psychiatry 1984;141:1018–9.
11. McClelland HA, Dutta D, Metcalfe A, Kerr TA. Mortality and facial dyskinesia. Br J Psychiatry 1986;148:310–6.
12. Yagi G, Takamiya M, Kanba S, Kamijima K. Mortality rate of schizophrenic patients with tardive dyskinesia during 10 years: a controlled study. Keio J Med 1989;38:70–2.
13. Youssef HA, Waddington JL. Morbidity and mortality in tardive dyskinesia: associations in chronic schizophrenia. Acta Psychiatr Scand 1987;75:74–7.
14. Inada T, Koshiishi M, Ohnishi K, Yagi G. The life expectancy of schizophrenic patients with tardive dyskinesia. Hum Psychopharmacol Clin Exp 1992; 7:249–54.
15. Takamiya M, Yagi G, Tanoue A, Kamisada M, Kanba S, Kamizima K, Koga Y, Suzuki T, Kaizawa S, Saito F. Mortality rate in schizophrenia with tardive dyskinesia [in Japanese]. Seishin Shinkeigaku Zasshi 1988;90:559–69.
16. Breslow EN, Day NE. Statistical methods in cancer research, vol I: the analysis of case-control studies. Lyon: International Agency for Research on Cancer, 1980.
17. Petitti DB. Meta-analysis, decision analysis and cost-effectiveness analysis: methods for quantitative synthesis in medicine. New York: Oxford University Press, 1994.
18. Hedges LV. Fixed effects models. In: Cooper H, Hedges LV, eds. The handbook of research synthesis. New York: Russell Sage Foundation, 1994:285–99.
19. StataCorp. Stata statistical software, release 5.0. College Station, TX: Stata Corporation, 1997.
20. Sharp S, Sterne J. New syntax and output for the meta-analysis command. In: Newton HJ, ed. Stata technical bulletin. College Station, TX: Stata Corporation, 1998:6–8.
21. Guy W. ECDEU assessment manual for psychopharmacology. Publication ADM 76–338. Washington, DC: US Department of Health, Education and Welfare, 1976:534–7.
22. Begg CB. Publication bias. In: Cooper H, Hedges LV, eds. The handbook of research synthesis. New York: Russell Sage Foundation, 1994:399–409.
23. Shapiro S. Is meta-analysis a valid approach to the evaluation of small effects in observational studies? J Clin Epidemiol 1997;50:223–9.
24. Anello C, Fleiss JL. Exploratory or analytic meta-analysis: should we distinguish between them? J Clin Epidemiol 1995;48:109–16.
25. Adler LA, Edson R, Lavori P, Peselow E, Duncan E, Rosenthal M, Rotrosen J. Long-term treatment effects of vitamin E for tardive dyskinesia. Biol Psychiatry 1998;43:868–72.
26. Cowen MA, Green M, Bertollo DN, Abbott K. A treatment for tardive dyskinesia and some other extrapyramidal symptoms. J Clin Psychopharmacol 1997;17:190–3.
27. Ebadi M, Srinivasan SK. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. Pharmacol Rev 1995;47:575–604.
28. Egan MF, Apud J, Wyatt RJ. Treatment of tardive dyskinesia. Schizophr Bull 1997;23:583–609.