Historical Comments on Tardive Dyskinesia: A Neurologist's Perspective

George W. Paulson, M.D.

This article was undertaken to review the history of professional awareness of tardive dyskinesia (TD) and to address reasons for the delay in such recognition. The literature was reviewed, and selections are included to highlight some of the major issues. Personal recollections are deliberately emphasized since they may reflect the phenomenon of personal discovery familiar to others and the now widespread professional awareness of TD. TD is indeed well recognized by psychiatrists and neurologists, and most general practitioners are also aware that the syndrome exists. Physicians were once unfamiliar with the concept of a drug reaction that was so long delayed as is possible with TD, nor did they know that a drug side effect could present in this manner. The historical delay in initial recognition of TD, and the reason for such delay, remain of interest. The lack of a perfect therapy and the uncertainty regarding the precise pathophysiologic basis of TD remain as challenges. Most psychiatrists, and many neurologists, probably have vivid memories of specific patients with TD. This author, a neurologist, was blessed to work with George Crane and other investigators in the early days of TD and was witness to some of the original uncertainty regarding what seemed to be a new phenomenon. TD has reshaped our concepts of disease and our awareness that diseases can originate from deleterious late effects of beneficial agents.

(J Clin Psychiatry 2005;66:260–264)

Received April 21, 2004; accepted July 20, 2004. From the Department of Neurology, The Ohio State University, Columbus.

No financial assistance was received for this article.

Dr. Paulson reports no financial affiliations or other relationships relevant to the subject matter of this article.

Corresponding author and reprints: George W. Paulson, M.D., Medical Heritage Center, 376 West 10th Ave., Columbus, Ohio 43210-1240 (e-mail: paulson.2@osu.edu).

Few iatrogenic disorders have a more instructive history or more extensive literature than tardive dyskinesia (TD).[1–4] Delay and Deniker,[5] early leaders in the development of phenothiazine therapy, foresaw most of the major issues, but widespread recognition of TD was late in arriving. After recognition occurred, the phenomenon of TD alerted physicians and the public to iatrogenic diseases and to their medicolegal impact. TD also enhanced clinical awareness of a potential negative and delayed impact of useful drugs on the central nervous system. Some other disorders including Meige syndrome or the chorea of Huntington's disease are superficially similar to TD, but TD is now accepted as a separate and unique entity.

This article discusses the evolution of concepts regarding TD, partially from a personal viewpoint, but does not review the dozens of enthusiastically reported therapeutic approaches to TD, most of which actually turned out to be fruitless. TD, and later the amazing success of levodopa, were the most fascinating pharmacologic events in my professional life, and personal memories are freely included in this article.

WHAT IS TARDIVE DYSKINESIA, AND WHO DISCOVERED IT?

Called at various times *terminal extrapyramidal insufficiency syndrome*, *complex dyskinesia*, *persistent dyskinesia*, or even *neuroleptic withdrawal syndrome*, the now-accepted label of *TD* was coined by Faurbye et al.[6] *EPS*, for any of several extrapyramidal syndromes, was soon also employed.

One of the first features of TD ever described, a feature that is still one of the most obvious, is the oral-buccal movement.[7–9] In its most severe form, the writhing tongue and moving lips were almost impossible for the clinician to imitate and absolutely impossible for a normal individual to continue incessantly. Sigwald et al. reported, "the lips participate in this dyskinesia in the form of stereotypical suction motions, pursing, rolling, and incessant chomping in synergy with rhythmic contractions of the jaw."[10(p755)]

It was soon apparent that more than just the mouth was affected. Hunter et al.[11] noted spasms of the glottis and jerky movements of the fingers and toes, as well as arching of the back and abduction of the arms. Soon a host of

clever, not always kind, descriptive terms appeared. *Bonbon* became the label for the tongue in the cheek, *rabbit mouth* for lips pursing, *fly catcher movement* for the tongue darting in and out, and *piano-* or *guitar-playing* for movements of the digits, and a truncal lean was labeled the *pride of pregnancy gait.*

The TD syndrome had been well described by the late 1950s, and if there were only 2 dozen articles published in the first decade of awareness, in the decade of the 1990s, over 100 dozen articles were published. Schönecker described the syndrome in 1957[12] and may have been the first to recognize its widespread significance, although Kulenkampff and Tarnow had already emphasized the oral component in 1956.[13] In 1967, George E. Crane, M.D., and I[14] reported "involuntary movements," but we were not sure what to call them. Crane, who more than any single person alerted Americans about TD, reported in 1968[15] that since 1959 a total of 21 papers had been published by 18 authors. American physicians may have first learned of the issue from an American Medical Association editorial in 1965.[16]

WHY WAS ACCEPTANCE OF TARDIVE DYSKINESIA DELAYED?

Years passed before there was wide acceptance of the possibility that TD was common and that major neuroleptic drugs, at first only the phenothiazines, were causal. Immediately following Crane's early review, Kline[17] wrote the article "On the Rarity of 'Irreversible' Oral Dyskinesia Following Phenothiazines." At a major workshop in the fall of 1968, Kline, a prominent psychiatrist and the director of research at Rockland State Hospital in Orangeburg, N.Y., an institution now named for him, reiterated his opinion that TD was uncommon.[18] He felt the primary issue was whether or not the movements really continued after medications were discontinued.

Another concerned and prominent psychiatrist of the day, and one who later wrote very effectively about TD,[19] was Jonathan Cole, M.D. Immediately after the first National Institutes of Health–sponsored TD workshop that I attended along with neurologist Roger Duvoisin, M.D., in St. Louis. Mo., in 1967, Dr. Cole prepared a press release to reassure the public. It was stated to the 3 neurologists present that fewer than 100 patients had ever been reported with TD. Chairing the workshop was the third neurologist, Milton Shy, M.D., preeminent clinician scientist of the day. After we were shown a dozen patients, one who had Huntington's disease, Shy reviewed movement disorders for the participants. He suggested that what we were seeing in the patients was simply a variant of a tic. After the formal meeting, Duvoisin and I went around the wards and agreed, at least with one another, that we were seeing a new entity—new to us, not new to the Europeans.

Crane suggested in an article entitled "Clinical Psychopharmacology in its 20th Year,"[20] which was almost exclusively about TD, several explanations why there was a somewhat slow acceptance of the importance of TD. First, it was hard to prove in a population group receiving multiple medications, a group with a high prevalence of spontaneous "stereotypies" as well as organic diseases of the nervous system, that any particular drug was directly linked to TD. It was harder to accept that a drug side effect might continue, indeed might first appear, after the drug was discontinued. Toxins usually didn't work that way. Lastly, Crane intriguingly suggested that an iatrogenic disorder is hard for the iatros, the "Healer," to accept.

I suggest that Crane's style and manner with fellow psychiatrists also delayed widespread recognition. Many of his colleagues considered him difficult, even a zealot, on the issue. I twice saw him walk, even though not officially invited, through the unkempt wards of 2 different state hospitals while he recorded the number of patients with TD. He felt free both to talk to and to examine patients without formal permission of any sort. I had first met him on the wards of Dorothea Dix Hospital in Raleigh, N.C., when nurses called to ask me about a stranger who had appeared unannounced to check patients. It was, of course, a different era, and Crane cared a great deal about TD. Few physicians have cared so much about anything as Crane did about TD.

WHO IS AFFECTED BY TARDIVE DYSKINESIA, AND HOW WAS THE DIAGNOSIS MADE?

At first, and perhaps even now, the prevalence or number of affected patients at a specific unit was unclear, as was the incidence, meaning the number of new cases during a set period. Even if all early observers could have agreed about what precise movements represented TD, and could correctly identify all patients, there was variability among institutions in the average age of patients, dosages of medicine used, and length of stay. Most observers of TD soon suggested there was a prevalence of TD up to or above 25% in both psychiatric outpatients and the chronically institutionalized.[21–23] An early article insisted there was not a comparable problem in countries that had not yet gained access to the phenothiazines.[24]

TD was, and is, diagnosed by observation, not by laboratory testing.[25–27] Individuals with mental retardation, patients with chronic but untreated schizophrenia,[28] the edentulous, and otherwise healthy elderly individuals all may develop repetitive involuntary oral movements. Nevertheless, the rocking, finger movements, and writhing tongue movements seen in TD never really looked like the predictable repetitive motions that some psychotic patients performed ritualistically for decades.

Altrochi[29] reported patients with prominent mouthing movements that were totally independent of any medication at all. Several anticonvulsants, as well as metoclopramide,[30,31] were linked to dystonia and chorea, and many medications including lithium and valproate could cause tremor, but these movement disorders, with the possible exception of those due to metoclopramide, tended to subside when medication was discontinued. Clearly neurologists knew that movement disorders could occur during or after infections of the brain, anoxia, vascular insults, trauma, etc., but for the neurologist, none of these was likely to be confused with TD. Some clinicians[32] linked akathisia, an internal feeling of restlessness, with the movements noted with TD, and akathisia and TD usually did exist together. The motor restlessness of restless legs syndrome rarely affects the hands or oral area and was probably never confused with TD.

The acute dystonic reactions secondary to phenothiazines can be alarming to a young intern, as I well remember,[33] but were soon recognized as distinct from TD. The distinctions among the 3 movement disorders related to phenothiazines—parkinsonism, TD, and acute dystonic reactions—was apparent by the early 1970s. The phenomenon of tardive dystonia[34–36] was slower to be generally recognized.

Risk factors were mentioned in even the earliest reports. Medications were the first risk factors reported and now include even the "atypical" neuroleptics.[37] Age, organic brain disease, and prior electroconvulsive therapy or lobotomy were also mentioned.[38,39] The dystonic phenomena, both acute and chronic, seemed more common in the young, which is perhaps no surprise since the same is true when dystonia occurs in Wilson's or in Huntington's disease. There was uncertainty, and there still is, about whether the oral features of TD are more prominent in one or another group of psychiatric patients.[40] Can TD occur in nonpsychotic patients? There is no question about this: It can.[41] Several of the early investigators suggested that women were at greater risk than men, but articles that reported a female vulnerability rarely controlled for dosage or body weight.[42] The aged are at greater risk, perhaps 5-fold greater,[43] but even the young can be affected.[44] Even after 4 decades of speculation, whether or not anticholinergics increase or decrease risk still remains uncertain.[45,46] Clearly, after almost 50 years of reports, the risk factor of greatest relevance is prolonged exposure to major neuroleptics.

WHAT IS THE BASIS FOR TARDIVE DYSKINESIA, AND WHAT IS THE THERAPY?

Eloquent reviews, such as that by Tanner,[47] suggested more than 1 pathophysiological basis for TD. Denervation hypersensitivity, blockage of receptors by the drugs followed by intense responsiveness when the phenothiazines were withdrawn, was first popularized by Klawans and coworkers.[48] The enhanced responsiveness may reflect enlargement and up-regulation or other changes in dopamine-2 receptor sites on striatal neurons, which then become more responsive after neuroleptic blockade is terminated. There was a largely fruitless effort to identify a pathologic abnormality[49] or to prepare practical animal models.[50] It was found that TD could appear early, even while the patient continued taking medicine, but movements tended to become more apparent after months on therapy and could become even more apparent when medication was discontinued. Resumption of neuroleptic therapy could actually dampen the TD.

Even the early articles mentioned speech dysfunction, mouth trauma, and respiratory distress.[51–53] I remember inpatients on the back wards of state institutions with toes moving incessantly up and down. Their toes could be traumatized as they actually worked through the top of the patients' shoes. Falling, despite the mild hypotonia often associated with TD, was not reported as a complication, perhaps because most patients could suppress the movements in order to perform voluntary acts, swallow, or talk. Perhaps it was their psychosis (or was it their fatalism?) that made patients unlikely to complain, but many observers felt patients were less bothered by the movements than were those who witnessed them.

Just as there was delay in awareness of TD, there was similar uncertainty about prognosis. If one uses the commonly suggested definition of at least 6 months of medication, characteristic movements, and persistence 3 months after therapy is discontinued, then clearly there were patients for whom TD was at the very least "persistent," even if it was incorrect to call TD "permanent."[54] Most chronically psychotic patients are now in nursing homes, shelters, or on the street, and many are not predictable visitors to clinics, so follow-up is incomplete. The recent review of prevalence and incidence of TD by Kane[55] still confirms differences in the effects of conventional versus atypical antipsychotic drugs. It seems probable, however, from over 50 articles in the past 3 decades, that up to 50% of patients do slowly improve if they are taking no neuroleptics at all.[56,57]

Therapy for TD has always been discouraging. At least 30 medicines were recommended at one time or another, but the postulated cure usually failed when a double-blind study was performed. Such failure was true for deanol, baclofen, levodopa, benzodiazepines, and anticonvulsants, as well as for several vitamins and "organic" supplements. Most recently, with at least 1 double-blind study, tocopherol has been recommended.[58] The "hair of the dog that bit them," atypical neuroleptics or even older neuroleptics in small doses, may reduce the movements.[59,60] Even thalamotomy[61] has been suggested, and, for selected muscle groups with intense spasm, injection with botulinum toxin may be useful.[62]

CONCLUSION

Legal issues over TD surfaced early and hit hard for the physicians who were sued.[63,64] Today, the Internet offers ready access to lawyers and physicians who purport to specialize in TD cases. It was not, of course, the physicians who caused TD. It was the terrible psychiatric diseases that required therapy. Partially through experience with TD, physicians became more aware of the need for caution, informed consent, and appropriate but not excessive dosages. TD represents an amazing historical phenomenon, and one that may yet teach us fundamentals in brain function, just as it has in therapeutic caution.

Drug names: baclofen (Lioresal, Kemstro, and others), botulinum toxin (Botox), lithium (Lithobid, Eskalith, and others), metoclopramide (Reglan and others).

REFERENCES

1. Jeste DV, Wyatt RJ. Understanding and Treating Tardive Dyskinesia. New York, NY: Guilford Press; 1982
2. Wolf ME, Mosnaim AD. Tardive Dyskinesia: Biological Mechanisms and Clinical Aspects. Washington, DC: American Psychiatric Press; 1988
3. Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association. Washington, DC: American Psychiatric Association; 1992
4. Wolf MA, Yassa R, Llorca PM. Complications extrapyramidales induites par les neuroleptiques: perspectives historiques. Encephale 1993;19:657–661
5. Delay J, Deniker P. Drug-induced extrapyramidal syndromes. In: Vinken PJ, Bruyn G, eds. Handbook of Clinical Neurology, vol. 6: Basal Ganglia. Amsterdam: North Holland; 1968:248–266
6. Faurbye A, Rasch PJ, Petersen PB, et al. Neurological symptoms in pharmacotherapy of psychosis. Acta Psychiatr Scand 1964;40:10–27
7. Dynes JB. Oral dyskinesias: occurrence and treatment. Dis Nerv Syst 1970;31:854–859
8. Evans JH. Persistent oral dyskinesia in treatment with phenothiazine derivatives. Lancet 1965;1:458–460
9. Druckman R, Seelinger D, Thulin B. Chronic involuntary movements induced by phenothiazines. J Nerv Ment Dis 1962;135:69–76
10. Sigwald J, Bouttier D, Raymondeaud C, et al. 4 Cases of facio-bucco-linguo-masticatory dyskinesis of prolonged development following treatment with neuroleptics [in French]. Rev Neurol 1959;100: 751–755
11. Hunter R, Earl CJ, Thornicroft S. An apparently irreversible syndrome of abnormal movements following phenothiazine medication. Proc R Soc Med 1964;57:758–762
12. Schönecker M. Ein eigentumliches Syndrom in oralen Bereich bei Megaphenapplikation. Nervenarzt. 1957;28:35–41
13. Kulenkampff VC, Tarnow G. Ein eigentumliches Syndrom im oralen Bereich bei Megaphenapplikation. Nervenarzt 1956;26:178–180
14. Crane GE, Paulson G. Involuntary movements in a sample of chronic mental patients and their relation to the treatment with neuroleptics. Int J Neuropsychiatry 1967;3:286–291
15. Crane GE. Tardive dyskinesia in patients treated with major neuroleptics: a review of the literature. Am J Psychiatry 1968;124 (Suppl):40–48
16. Talbott JH. Irreversible side effects of phenothiazines. [editorial]. JAMA 1965;191:333–334
17. Kline NS. On the rarity of "irreversible" oral dyskinesia following phenothiazines. Am J Psychiatry 1968;124(Suppl):48–54
18. National Institute of Mental Health. Psychotropic drugs and dysfunctions of the basal ganglia. Oct 31–Nov 2, 1968; Workshop Series of Pharmacology Section, NIMH #3. Public health publication 1938:26
19. Gardos G, Cole JO, Tarsy D. Withdrawal syndromes associated with antipsychotic drugs. Am J Psychiatry 1978;135:1321–1324
20. Crane GE. Clinical psychopharmacology in its 20th year. Science 1973;181:124–128
21. Asnis GM, Leopold MA, Duvoisin RC, et al. A survey of tardive dyskinesia in psychiatric outpatients. Am J Psychiatry 1977;134:1367–1370
22. Crane G, Smith RC. The prevalence of tardive dyskinesia. In: Fann WE, Smith RC, Davis JM, et al, eds. Tardive Dyskinesia. New York, NY: Medical and Scientific Books; 1980:269–280
23. Jeste DV, Wyatt RJ. Changing epidemiology of tardive dyskinesia: an overview. Am J Psychiatry 1981;138:297–309
24. Gardos G, Samu I, Kallos M, et al. Absence of severe tardive dyskinesia in Hungarian outpatients. Psychopharmacology (Berl) 1980;71:29–34
25. Goetz CG. Diagnosis of tardive dyskinesia. Clin Neuropharmacol 1983; 6:101–107
26. Paulson GW. Tardive dyskinesia. Annu Rev Med 1975;26:75–81
27. Gershanik OS. Drug-induced dyskinesias. In: Jankovic J, Tolsa E, eds. Parkinson's Disease and Movement Disorders. 3rd ed. Baltimore, Md: Williams & Wilkins; 1998:579–599
28. Fenton WS. Prevalence of spontaneous dyskinesia in schizophrenics. J Clin Psychiatry 2000;61(suppl 4):10–14
29. Altrochi PH. Spontaneous oral-facial dyskinesia. Arch Neurol 1972;26: 506–512
30. Bateman DN, Rawlins MD, Simpson JM. Extrapyramidal reactions with metoclopramide. BMJ 1985;291:930–932
31. Miller LG, Jankovic J. Metoclopramide-induced movement disorders: clinical findings with a review of the literature. Arch Intern Med 1989; 149:2486–2492
32. Burke RE, Kang UJ, Fahn S. Tardive akathisia: motor phenomena and treatment. Neurology 1987;37(suppl):124–125
33. Christian CD, Paulson GW. Severe motility disturbance after small doses of prochlorperazine. N Engl J Med 1958;259:828–830
34. Kiriakakis V, Bhatia KP, Quinn NP, et al. The natural history of tardive dystonia. Brain 1998;121:2053–2066
35. Burke RE, Fahn S, Jankovic J, et al. Tardive dystonia: late onset and persistent dystonia caused by anti-psychotic drugs. Neurology 1982; 32:1335–1346
36. von Harten PN, Kahn RS. Tardive dystonia. Schizophr Bull 1999; 25:741–748
37. Ghaemi SN, Ko JY. Quetiapine-related tardive dyskinesia [letter]. Am J Psychiatry 2001;158:1737
38. Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. Arch Gen Psychiatry 1982;39:473–481
39. Edwards H. The significance of brain damage in persistent oral dyskinesia. Br J Psychiatry 1970;116:271–275
40. Nasrallah HA, Churchill RM, Handan-Allen GA. Higher frequency of neuroleptic induced dystonia in mania than in schizophrenia. Am J Psychiatry 1988;145:1455–1456
41. Klawans HL, Bergen D, Bruger GW, et al. Neuroleptic-induced tardive dyskinesias in nonpsychotic patients. Arch Neurol 1974;30:338–339
42. van Os, Walsh E, van Horn E, et al. Tardive dyskinesia in psychosis: are women more at risk? Acta Psychiatr Scand 1999;99:288–293
43. Jeste DV. Tardive dyskinesia in older patients. J Clin Psychiatry 2000; 61(suppl 4):27–32
44. Paulson GW, Rizvi CA, Crane GE. Tardive dyskinesia as a possible sequel of long term therapy with phenothiazines. Clin Pediatr (Phila) 1975;14:953–955
45. Borison RL, Diamond BI. Anticholinergics promote neuroleptic-induced TD. Adv Biochem Psychopharmacol 1980;17:359–362
46. Jellinck T, Gardos G, Cole J. Adverse effects of anticholinergic drug withdrawal. Am J Psychiatry 1981;138:1567–1571
47. Tanner CM. Drug induced movement disorders. In: Vinken PJ, Bruyn G, Klawans H, eds. Handbook of Clinical Neurology, vol 49: Extrapyramidal Disorders. Amsterdam, the Netherlands: Elsevier; 1986:185–204
48. Klawans HL, Tanner CM, Goetz CG. Epidemiology and pathophysiology of tardive dyskinesia. Adv Neurol 1988;49:185–197
49. Hunter R, Blackwood W, Smith MC, et al. Neuropathological findings in three cases of persistent dyskinesia following phenothiazine medication. J Neurol Sci 1968;7:263–273
50. Casey DE. Tardive dyskinesia: pathophysiology and animal models. J Clin Psychiatry 2000;61(suppl 4):5–9
51. Gerratt BR, Goetz CG, Fisher HB. Speech abnormalities in tardive dyskinesia. Arch Neurol 1984;41:273–276
52. Casey DE, Rabins P. Tardive dyskinesias as a life-threatening illness. Am J Psychiatry 1978;135:486–488
53. Klawans H. Respiratory dyskinesias: extrapyramidal dysfunction and dyspnea. Ann Intern Med 1978;88:327–331

54. Paulson GW. “Permanent” or complex dyskinesia in the aged. Geriatrics 1968;28:105–110
55. Kane JM. Tardive dyskinesia rates with atypical antipsychotics in adults: prevalence and incidence. J Clin Psychiatry 2004;65(suppl 9):16–20
56. Gardos G, Casey DE, Cole JO, et al. Ten-year outcome of tardive dyskinesia. Am J Psychiatry 1994;151:836–841
57. Fernandez HH, Krupp B, Friedman JH. The course of tardive dyskinesia and parkinsonism in psychiatric inpatients: 14 year follow-up. Neurology 2001;56:805–807
58. Lohr JB, Caligiuri MP. A double-blind placebo-controlled study of vitamin E treatment of tardive dyskinesia. J Clin Psychiatry 1996; 57:167–173
59. Ondo WG, Hanna PA, Jankovic J. Tetrabenazine treatment for tardive dyskinesia: assessment by randomized videotape protocol. Am J Psychiatry 1999;156:1279–1281
60. McGrath JJ, Soares KV. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia. Cochrane Database Sys Rev 2000;2:CD000459
61. Hillier CE, Wiles CM, Simpson BA. Thalamotomy for severe antipsychotic induced tardive dyskinesia and dystonia. J Neurol Neurosurg Psychiatry 1999;66:250–251
62. Rapaport A, Sadeh M, Stein D, et al. Botulinum toxin for the treatment of oro-facial-lingual-masticatory tardive dyskinesia. Mov Disord 2000; 15:352–355
63. Slovenko R. Update on legal issues associated with tardive dyskinesia. J Clin Psychiatry 2000;61(suppl 4):45–57
64. Wettstein RM. Tardive dyskinesia and malpractice. Behav Sci Law 1983;1:85–107