

# A Preventive Measure for Tardive Dyskinesia

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This paper is concerned ultimately with the presentation of a safe, effective and simple preventive measure for tardive dyskinesia (TD), a disease completely unknown to us during our years of early training in the 1950's, but one which seems now to be increasing in prevalence and severity before our eyes. Each month brings more journals with more reports concerning TD: two major articles in successive months this summer in the American Journal of Psychiatry; a major article in the summer issue of the Journal of the American Academy of Child Psychiatry, and so on. As seems to be the case so often with "new" diseases or with iatrogenic diseases, the articles read like detective stories: "The answers are here, Doctor, in front of you: but exactly where?" These are good papers, and like all good papers, they frequently admit to the unknown, sometimes contradict each other, but always show a desperate concern with trying to unravel the mystery that is TD. Two themes run through the history of

medicine and psychiatry: the theme of iatrogenic illness, together with the theme of more or less accidental therapeutic discoveries. Sometimes the two intertwine. The findings we present here toward a preventive for TD were unanticipated, fortuitous, almost unscientific and anecdotal, yet they point the way toward a safe and effective preventive for this puzzling disease.

There is almost universal agreement that TD is a movement disorder, associated somehow with long-term use of antipsychotic or neuroleptic medications. "Tardive" means of late onset; "dyskinesia" means abnormal movement. It is considered an extrapyramidal disorder yet distinct and, in fact, opposite from other extrapyramidal disorders such as pseudoparkinsonism.

Early descriptions of the disorder now called TD were concerned with face and mouth movements to the point where clumsy terms like "lingual-facial-buccal dyskinesias", or "orofacial dyskinesias", or "buc-co-lingual-masticatory dyskinesias" were used. These seem all to have given way to the term TD which the 1975 American Psychiatric Association Glossary defined as "untoward effect, appearing after long term use of antipsychotic drugs with muscle involvement about the face, neck and trunk, lead-

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ing to spasms, tics, eye signs, and speech disturbances." Even there, in 1975, the basic description was of face and mouth movements, with no mention of limb movements; yet there is general agreement now that any striated muscle can be involved in TD. One other term is becoming popular: "withdrawal emergent syndrome", describing a condition very much like TD but inherently reversible. "Withdrawal emergent syndrome" (WES) seems to be used as a term for a mild and reversible form of TD or perhaps a more benign pediatric form not, strictly speaking, identical with TD itself. Its usage seems not to have been solidified yet. It may even be best for the moment to think of TD as a group of disorders, rather than one disorder, or at least to deal with it as two disorders, one reversible and the other irreversible. TD then is one of four major extrapyramidal side effects associated with the use of neuroleptics or major tranquilizers; the other three are dystonias (or muscle spasms), akathisia (restlessness; the "inability to sit still"), and pseudoparkinsonism (tremors, rigidity, akinesias). These three unlike TD, are usually reversible with discontinuance of medication; they make their appearance early in treatment with neuroleptics while TD by definition appears late.

There is no consensus as to many aspects of TD: not as to its incidence or prevalence, nor to its cause (except insofar as its being associated somehow with long term use of neuroleptics, and even here one finds disagreements), nor to its neurophysiology, and certainly not as to its treatment.

There does seem to be a consensus that a poorly defined "at risk" population exists: that, for example, TD may be more common among the elderly (but, as an aside, is this because the population is elderly, or because the elderly have been on psychotropics for longer periods of time?) The "at risk" population may or may not include patients with organic brain syndromes and, depending on whose statistics one cites, the population may be mostly female. Confounding all this is the fact that some authors and senior psychiatrists maintain that a disease resembling TD, with a prevalence as high as 20 percent, has always ex-

isted in chronic psychiatric populations long before neuroleptics were dreamed of. Popular examination questions about "schnauz-krampf" certainly antedated major tranquilizers.

Additional research has centered on whether TD is associated with long term use of anticholinergics; on whether certain neuroleptics as opposed to others are more notorious in producing TD; on whether it occurs more frequently with certain psychiatric diagnoses as opposed to others; on whether drug holidays or intermittent treatments are of any value prophylactically; and on whether its incidence is higher among patients who should probably never have been on neuroleptics (that is, the non-psychotic). There is disagreement on all these points.

The true incidence of TD (that is, the number of new cases in a population identified over a period of time) is simply unknown, while the prevalences (the percentages of afflicted patients in a more or less controlled patient population) range from less than one percent to almost 60 percent in various reports. One wonders exactly what this extraordinary range represents. Is it due to differences in patient populations? Differences in defining the disease, in agreeing on its parameters, in the examination process itself? In using or not using some unknown prophylactic measure? Compare historically and as only one example the retrospective finding that using more oxygen in premature babies in more advanced premature nurseries led to retrolental fibroplasia. Then, too, and almost unique in medicine, the very disease-causing agent we are discussing — the neuroleptic itself—can mask and improve the clinical picture when given in larger dosages.

Since the changes of TD frequently remain after neuroleptics are discontinued, some neuropathologists have looked for evidence of structural changes; there is simply no agreement here. Researchers seem more concerned with the role of neurotransmitters and receptors and the biochemical evidence that many mental and neurological disorders result from mix-ups in these infinite combinations of receptors and chemicals. To oversimplify perhaps: when schizo-

phrenia is active, too much dopamine is produced and accepted at certain receptor sites in areas of the nervous system concerned with thoughts and feelings. Neuroleptics like chlorpromazine block this acceptance, but in a patient destined to get TD—and of course not all do—dopamine receptors in certain other areas of the nervous system, for reasons not entirely clear, become hypersensitized to whatever dopamine is available following their chronic blockade. There may be a sheer increase in the number of dopamine receptors as well. This is the "Chronic Blockade" Hypothesis. To recapitulate, two things happen when a patient is about to develop TD: dopamine receptors in certain areas of the nervous system now become exquisitely sensitive to what little amount of dopamine is available (which now explains why a patient with TD looks like a patient with Parkinsonism overtreated with l-Dopa); and secondly, perhaps the total number of these dopamine receptors, probably in areas involved in motor movements only, increase in number. This explains why putting a patient back on neuroleptics (that is, the very substance which caused the TD to begin with) relieves the symptoms of TD temporarily.

### Conventional Treatment

Current methods for treating TD are inadequate and sometimes contradictory. If the pathophysiology is thought to result from hypersensitivity of receptors to dopamine, then perhaps substances which reduce the amount of dopamine in the brain (such as reserpine or tetrabenazine) should work; in fact, they do, but at a great expense in side effects and in unpredictability.

Other neurotransmitters, such as choline and its precursors (lecithin, deanol) have been used to equalize other neurotransmitter imbalances thought to be present in TD. Apomorphine in small dosage has been used, as well as benzodiazepines and sodium valproate.

Clonazepam, ECT, lithium, even l-Dopa itself (in a sort of paradigm of making something better by first making it worse) have all been used. Friedhoff, with l-Dopa, and Kunin, with manganese, have suggested a sort of

prophylaxis using these substances together with neuroleptics and the use of lithium has been suggested prophylactically as well. With one more exception—the one we will present later—these represent the only instances of pharmacologic prophylaxis of TD. Other discussions of prophylaxis center on discontinuing the neuroleptic once TD is identified; on encouraging drug holidays (although there is now evidence that this may increase the prevalence of TD); and on eliminating the use of neuroleptics in possible "at risk" patients such as the elderly, the organically impaired, the female. The only measure that seems to work predictably is increasing the dosage of neuroleptics in the patient, a measure proclaimed self-defeating since it seems to "hide" the TD while escalating its pathophysiology, yet no studies seem to exist to confirm this impression.

### Our Observation

We became aware during the summer of 1978 that while reports concerning TD were appearing with alarming frequency and an almost infectious concern, we ourselves were seeing only patients who were already diagnosed elsewhere as TD, or patients whose TD symptoms were present on admission to our facilities (a busy private mental health center; a busy hospital practice). If we were not diagnosing cases, or "missing" cases, this would soon reveal itself because of our liberal use of cross-consultation among ourselves and our equally liberal use of neurological consultations, particularly among our hospitalized patients, and because of reports by staff, by relatives, by patients. Yet we were not exactly unfamiliar with this disorder; we and our staff were seeing enough cases among our new referrals, and at clinical conferences, and among patients at governmental hospitals with which we were affiliated. We saw the entire spectrum, from mild and cosmetic, to devastating.

A little explanation of the history of our Center is in order now. The North Nassau Mental Health Center is a busy center which has been active for over 20 years. It is a clinic licensed by the New York State Department of Mental Health. During the past 15

years, we have been heavily involved in using orthomolecular treatment methods elucidated in Hawkins and Pauling (1973).

Our results were as successful and pleasing to us as they were provocative and controversial to others. Our methods included using orthomolecular principles (only niacin and niacinamide at first), together with traditional psychiatric treatments including neuroleptics, ECT when indicated, various "talking" therapies when indicated, and a large dose of what there was no name for at the time but which we now recognize in retrospect was faith and a lot of preventive holistic health. An inevitable pragmatic pharmacopeia of orthomolecular preparations (now used at many centers across the U.S. and in fact the world) evolved. Our preparations whose formulation was arrived at empirically over the first years of our existence, contained:

Ascorbic Acid	333mg
Either Niacinamide (Formula 1) or Niacin (Formula 2)	333mg
Pyridoxine HCl	66mg
d-AlphaTocopheryl Acetate	66.I.U.

The dosages prescribed ranged from four to twelve capsules a day given with meals, in divided dosages. Dosages usually tended to be at the higher end of the scale after having been increased gradually. Side reactions were almost always those attributable to niacin or to niacinamide (peripheral flush; mild gastrointestinal upsets), and were handled by reducing dosages temporarily. This preparation was easily the most popularly prescribed item among our staff. We found to our astonishment that among our patient population (10,000 outpatients during a ten-year period; 1,000 inpatients at our hospitals during a ten-year period) not one case of tardive dyskinesia developed in any patient (who did not have TD to begin with) who was placed on this formulation as well as any neuroleptic in any dosage at all. Patients who did not receive neuroleptics, regardless of what else was done, were of course not included in these statistics.

There is more than enough precedent for postulating a biochemical mechanism for preventing tardive dyskinesia with one or more vitamins. Pyridoxine, for example,

aside from being important in blood and central nervous system metabolism, has several other functions in the body: the decarboxylation of various substances; the transamination of amino acids; the conversion of tryptophan to niacin; the decarboxylation of dopa to dopamine by acting as the source of a co-factor, pyridoxyl-5-P04.

It is easy to surmise pyridoxine's being involved somehow in the physiology of movement and movement disorders. There were simply no other common denominators other than vitamins to explain our good fortune but what we cannot answer now is which of the constituents, or which combination, is responsible for this phenomenon. Secondly, and remembering that TD is in many respects similar to the movement disorder induced by excessive l-Dopa, Yahr reported reversal of this movement disorder with massive dosages of oral pyridoxine. Thirdly, DeVeugh-Ceiss and Manion have published a study showing that "high doses of pyridoxine may reduce the frequency and severity of involuntary movements in tardive dyskinesia" which has already been diagnosed.

To our knowledge, then, this is the first study in which any vitamin or combination of vitamins is offered as the prophylaxis for tardive dyskinesia. We are not biochemists but rather biochemically oriented psychiatrists, yet we are in the process of submitting our findings to biochemical analysis and to further statistical analysis, under the very likely assumption that not all four constituents of our formulas No. 1 and No. 2 are necessary to prevent TD. Our impression is that pyridoxine alone seems not to be sufficient as a preventive although we have reason to believe it decreases the incidence and severity of TD when used alone. One can easily envision pathways by which one or all of the other three constituents may facilitate the anti-TD effects of pyridoxine.

### Summary

Tardive dyskinesia as a disease entity is reviewed briefly, and its current management and unsatisfactory treatment is discussed. When one reviews the literature one finds that the use of preventives against TD, when

neuroleptics are indicated, is almost nil. We herewith submit evidence that indicates the combined use of any neuroleptic given together with a megavitamin preparation well known in orthomolecular circles, has failed to yield evidence of a single case of TD.

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