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The Problem of Tardive Akathisia

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Akathisia is a disorder characterized by restlessness and dysphoria. Neuroleptic-induced akathisia is one of the acute extrapyramidal reactions caused by neuroleptic drugs, and tardive akathisia (TDAK) is a tardive dyskinesia (TD) variant caused by long-term neuroleptic treatment. Since TDAK is a movement disorder with a psychological dimension, it merits consideration as one of the behavioral variants of TD. TDAK is considered in light of an ongoing, prospective study in mentally retarded people. It is discussed in terms of the "cognitive" functions of the basal ganglia, and the known consequences of other diseases of the basal ganglia that almost invariably cause behavioral and cognitive deterioration.

Akathisia is a subjective state of motor restlessness and dysphoria. The word was coined by Haskovec (1902, 1903) to refer to patients whose problems were "hysterical" in origin. Later, Bing (1923) described akathisia in patients with postencephalitic parkinsonism. Since then, akathisia has been considered a disease of the basal ganglia (Bing, 1939).

Soon after the introduction of neuroleptic drugs, clinicians noted patients who had symptoms of restlessness and dysphoria (Ayd, 1961; Kruse, 1960; Steck, 1954). The term "Neuroleptic-induced akathisia" (NIA) joined "Pseudo-parkinsonism" and Dystonia in the trio of "acute extra-pyramidal reactions" caused by neuroleptic drugs.

Early reports of NIA also included descriptions of patients whose symptoms arose only after several years of neuroleptic treatment, and which co-occurred with symptoms of tardive dyskinesia (TD) (Ayd, 1961; Demars, 1966; Faurbye, Rasch, & Petersen, 1964; Uhrbrand & Faurbye, 1960). In 1977, Simpson suggested that late-onset NIA was persistent, even after neuroleptic withdrawal, and that it was virtually untreatable. In 1983, Munetz and Cornes introduced the term "tardive akathisia" (TDAK): "an akathisia-like syndrome [characterized by] late onset, treatment resistance and potential irreversibility despite discontinuance of neuroleptics" (p. 334). The overt symptoms of TDAK were indistinguishable from those of NIA, and the direct examination of the patient would

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yield the same findings. The symptoms of TDAK patients, of course, tended to increase when the neuroleptic dose was lowered, while the symptoms of NIA patients tended to improve.

TDAK was described in a series of clinical reports (Brandon, McLelland, & Protheroe, 1971; Chouinard, Annable, & Ross-Chouinard, 1982; Kennedy, Hershon, & McGuire, 1971; Mukherjee, Rosen, Cardenas, Varia, & Olarte, 1982; Wojcik, Gelenberg, LaBrie, & Mieske, 1980). and it was operationally defined in a systematic study by Barnes and Braude (1985). The prevalence of TDAK was reported to be 18% in patients referred for evaluation at a TD clinic (Davis & Cummings, 1988) and 6 to 14% in mentally retarded patients treated with neuroleptics (Ganesh, Rao & Cowie, 1989; Gualtieri, 1990).

TDAK is, therefore, a relatively common problem as well as a severe problem, causing distress to the patient and demanding a great deal of attention by physicians and direct care personnel. But since akathisia is a state of restless, dysphoric hyperactivity, it may also be the occasion of secondary behavior problems, a "setting event" for the occurrence of difficult behaviors like aggression (Keckich, 1978) or self-destruction (Drake & Ehrlich, 1985).

TDAK may typically arise during the course of a clinical attempt to lower neuroleptic doses to "minimally effective" levels, as mandated by regulatory agencies, for example. The emergence of what are referred to as "target behaviors" (e.g., disorganization, agitation, aggression, hyperactivity, self-injurious behavior) in the circumstances of a neuroleptic withdrawal program might represent the recurrence of a preneuroleptic psychiatric condition or alternatively the manifestation of TDAK. The diagnostic and therapeutic dilemma is daunting.

Since neuroleptic drugs have been prescribed quite heavily in the population of mentally retarded adults in the United States (Lipman, 1970; Sprague & Baxley, 1978), there has been, in recent years, a strong movement to reduce unnecessary or excessive neuroleptic use. In many clinical facilities, however, the reduction of neuroleptic prescriptions has led to the unmasking of neuroleptic side effects like TD and TDAK (Gualtieri, 1990). The author and his colleagues at the Metropolitan Developmental Center in Belle Chasse, Louisiana have been conducting a longitudinal study of TDAK and its behavioral concomitants. The Center is a large residential facility, with a population of 356. No fewer than 180 residents had been treated, long-term, with neuroleptic drugs. The first phase of the study was designed to establish the reliability of the assessment instruments and to validate the diagnosis of TDAK with independent raters (C. T. Gualtieri, N. Leslie, & N. Sanders, 1991). TDAK was diagnosed in 25 patients, 14% of the population at risk. Since many of the residents at the facility had not had neuroleptic reductions, the true rate of TDAK is probably higher.

The focus of research in progress with this group of 25 TDAK patients has been to assess the effects of treatment on the course of TDAK. As of this writing, and 3 years after the study began, 10 patients (40%) have been withdrawn completely from neuroleptics, and maintained neuroleptic-free for at least 2 years. Fifteen patients (60%) have remained on neuroleptics, despite the occurrence of TDAK. The reason for continued treatment, in every case, was the emergence of target behaviors that could not be controlled behaviorally or by alternative pharmacologic interventions.

It has not been possible to determine, at this time, whether any specific clinical element separates the two groups, beyond the fact that one was successfully withdrawn from neuroleptics and the other was not. They did not differ in age, sex, race, or IQ. The various etiologies of mental handicap were represented more or less equally in the two groups.

The severity of TDAK did not determine the success of neuroleptic withdrawal. The scores each group made on the Movement and Behavior Scale, a TDAK examination instrument, were not statistically different. Even the target behaviors displayed during neuroleptic reduction by the two groups were similar: self-injurious behavior, aggression, hyperactivity, stereotypy, agitation, tantrums, destructiveness. However, their severity and response to neuroleptic suppression was different, and that was what guided the clinical decision to continue treatment. The larger group required maintenance treatment, and successive attempts to withdraw neuroleptics, occurring at yearly intervals, have been unsuccessful. There has been no movement from one group to the other for any of the patients over the past 2 years.

These data describe a formidable problem. Retarded people have been treated long-term with neuroleptics for behavior problems that would not require such drugs by today's standards. Their families and clinicians agree the drugs should be withdrawn. But as the dose is gradually lowered, the patient becomes akathisic. That, in turn, evokes new behavior problems or aggravates preexisting problems; so the dose is raised again, and "treatment" must continue, for an indeterminate period. It is a catch-22: the dilemma of neuroleptic confinement.

The implications for the public health of mentally retarded people are well understood. Regulatory agencies insist on careful monitoring of neuroleptic therapy in retarded people, as well as regular attempts to lower doses or to withdraw the medications entirely. Professional groups recommend careful forethought before neuroleptics are prescribed to retarded individuals (American Psychiatric Association [APA], 1992). These laudable steps will prevent cases of TD and TDAK in the future. Of course, they will do little to alleviate the misery of people who are presently afflicted.

The problem of TDAK may also be considered in terms of the long-

sought "behavioral analog of TD" (Gualtieri & Barnhill, 1988; Gualtieri & Guimond, 1981). Stahl (1985), for example, has suggested that TDAK is both a movement disorder and a "mental disorder" because it has both "objective and subjective" components. In other words, TDAK is a movement disorder, a variant of TD that also has a psychological dimension.

One may expand this idea with the premise that TDAK, like TD, is a disease of the basal ganglia. That is a truism from classical neurology: akathisia and the hyperkinetic movement disorders are classic symptoms of basal ganglia disease. Postmortem studies (Christensen, Miller, & Faurbye, 1970; Hunter, Blackwood, Smith, & Cummings, 1968) and magnetic resonance imaging studies (Bartzokis, Garber, Marder, & Olendorf, 1990; Mion, Andreasen, Arndt, Swayze, & Cohen, 1991) have demonstrated basal ganglia lesions in TD patients, especially in the caudate nucleus.

Parkinson's disease (PD), Huntington's disease (HD), and Wilson's disease (WD) are progressive diseases of the basal ganglia, and they all have similarities to TD. Akathisia, for example, is a symptom of PD and chorea-athetoid dyskinesia is a sign of HD and WD. Although persistent TDAK and TD appear to be static, not progressive encephalopathies, it is appropriate to consider whether the similarities between TD and the major diseases of the basal ganglia go deeper than the surface manifestations of akathisia and dyskinesia.

The question is especially relevant to the putative cognitive and behavioral analogs of TD. PD, for example, is associated with depression and dementia (Mayeux & Stern, 1983; Mayeux, Stern, Rosen, & Leventhal, 1981; Taylor, Saint-Cyr, Lang, & Kenny, 1986). HD and WD are associated with affective instability, psychosis, and dementia (Brandt, Strauss, Larus, Jensen, Folstein, & Folstein, 1984; Dening & Berios, 1989; Folstein, Leigh, Parhad, & Folstein, 1986; Sax, O'Donnell, Butters, Menzer, Montgomery, & Kayne, 1983; Starosta-Rubinstein, Young, Kluin, Hill, Aisen, Gabrielsen, & Brewer, 1987). If behavioral instability and intellectual impairment are inevitably a part of PD, HD, and WD, should they not also occur in TD?

Patients with PD, HD, and WD also have neuropathological changes in cortical structures, so it is hardly possible to attribute all of the cognitive and behavioral elements of those conditions to lesions in the basal ganglia. On the other hand, intellectual impairment has been noted in PD patients with lesions in the subcortical nuclei but not in the cortex (Chui, Mortimer, Slager, Zarrow, Bondareff, & Webster, 1986) and also in patients with PD following MPTP exposure, who had neither cortical lesions nor motor impairment (Stern, Tetrud, Martin, Kutner, & Langston, 1990). In WD, the severity of neuropsychological impairment is correlated with abnormalities in the basal ganglia but not in cortex or cerebel-

lum (Medalia, Isaacs-Glaberman, & Scheinberg, 1988). We also know that circumscribed lesions in the basal ganglia are sometimes associated with significant psychiatric conditions (Rapoport & Wise, 1988; Trautner, Cummings, Read, & Benson, 1988) or neuropsychological deficits (Bowen, 1975; Buchwald, Hull, Levine, & Villablanca, 1975; Hassler, 1978; Teuber & Proctor, 1964).

The basal ganglia may be "the dark basement of the brain" but they are not dumb brutes. The basal ganglia do participate in, and may even regulate, some intellectual activities, particularly those involving complex or sequential motor activities (Mayeux & Stern, 1983). The corpus striatum subserves a number of frontal lobe functions in the juvenile primate (Divac, 1968). The frontal lobes are richly connected with areas in the neostriatum (Villablanca & Olmstead, 1982). Neostriatal lesions mimic the effects of frontal lesions (Rosvold, Mishkin, & Szwarcbart, 1958; Rosvold & Szwarcbart, 1964) and lesions in either the frontal lobes or the neostriatum disturb and slow down neural activities throughout the frontal–striatal circuit (Villablanca & Olmstead, 1982). Even more compelling, the mosaics of deficit caused by lesions of the frontal lobes are reflected by similar deficits caused by lesions in striatal areas to which the frontal cortex projects (Delgado, 1979; Iversen, 1979; Oberg & Divac, 1979).

One is entitled to surmise, therefore, that affective instability and intellectual impairment may be the consequence of neuropathology at the level of the basal ganglia. Since TD is the result of neurotoxicity in the basal ganglia, some patients with TD may be expected to have behavioral and cognitive deficits, too. TDAK is one manifestation of that effect. There are probably others. It is only fair to point out that this hypothesis is not (yet) widely accepted (APA, 1992). Furthermore, it is difficult to envision a research protocol that might settle the issue. Neuroleptics are, after all, prescribed to people who are behaviorally unstable or intellectually impaired to begin with, and many of them have conditions associated with cognitive or behavioral deterioration. When neuropathic findings or neuropsychological deficits are identified in TD patients, it has been possible for researchers to attribute these problems to the patient's psychiatric condition, or to a premorbid state that rendered the development of severe TD more likely. I think that is a mistaken attribution, but there are many psychiatrists who seem to hold to it.

The question of cognitive or behavioral variants of TD may not be amenable to resolution, in terms of the requirements of controlled clinical research. In terms of clinical treatment and the public health, however, TDAK is a fact, not a question. It is one more serious side effect of neuroleptic treatment, like TD and the Neuroleptic Malignant Syndrome. Taken together, they define neuroleptic treatment as a necessary evil, a

treatment that should be administered with care and caution, and reserved for patients who have no other recourse.

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