Symptomatic Treatment of Tardive Dyskinesia: A Word of Caution

by L. Thomas Kucharski and Ellen M. Unterwald

At Issue

Abstract

The search for a treatment of tardive dyskinesia (TD) has focused largely on cholinergic and GABAergic agents that are believed to attenuate striatal imbalances and bring about symptomatic control of dyskinetic movements. While numerous reports of the partial effectiveness of acute treatment with cholinergic or GABAergic agents have appeared, the effects of chronic administration of these substances are unclear. Results of chronic administration of cholinergic or GABAergic agents to animals are presented, and it is argued that these substances have the potential of eventually worsening TD. Alternative approaches aimed at modifying the theorized pathophysiology of TD, as opposed to symptom control methods, are presented.

In recent years numerous reports of the partial effectiveness of various pharmacological agents in the relief of the symptoms of tardive dyskinesia have appeared in the psychiatric literature. For excellent reviews the reader is referred to recent Schizophrenia Bulletin articles by Jeste and Wyatt (1979) and Berger and Rexroth (1980). The proposed mechanism of the effectiveness of these agents is believed to be the restoration of a dopamine-acetylcholine balance in the striatum with treatments centered around three neurochemical manipulations: (1) diminished dopamine activity via dopamine depletors, blockers, or synthesis inhibitors; (2) facilitation of acetylcholine via cholinergic agents such as lecithin; and (3) indirect attenuation of dopamine activity via γ-aminobutyric acid (GABA)-mimetic drugs that stimulate inhibitory feedback mechanisms. While it is generally believed that the dopamine blockers, depletors, and synthesis inhibitors carry the potential of increased dopamine supersensitivity by continuing or potentiating the pharmacological denervation of dopamine receptors and their subsequent hypersensitization, treatment approaches involving acetylcholine or GABA facilitation are seldom accompanied by warnings of their exacerbating potential. However, data from the animal laboratory and a logical extension of the rationale of these approaches lead one to the conclusion that GABA and/or acetylcholine facilitation given chronically may eventually worsen tardive dyskinesia.

If GABA-mimetic agents exert their therapeutic benefits by stimulation of inhibitory neurons, thereby indirectly reducing dopamine activity, theoretically this indirect "denervation" may also lead to an exacerbation of the dopamine supersensitivity and a worsening of tardive dyskinesia. There is now laboratory evidence that GABA-mimetics induce catalepsy in rats and that they potentiate neuroleptic-induced catalepsy (Balsara, Jadhav, and Chandorkar 1980). Similarly, muscimol, a GABA receptor agonist, has been shown to potentiate haloperidol-induced dystonia in monkeys (Casey, Gerlach, and Christensson).
1980). These findings suggest that treatment with GABA-mimetics results in hypodopaminergic striatal functioning. If so, chronic treatment would be expected to potentiate the supersensitivity induced by pharmacological denervation.

In a recent report, Ferkany, Strong, and Enna (1980) demonstrated that chronic elevation of brain GABA via GABA-T inhibitors increased $^3$H-spiroperidol and decreased $^3$H-muscimol binding in mouse corpus striatum. Stereotypic responses to apomorphine were also enhanced in GABA-T treated animals, suggesting that elevation of brain GABA alone is capable of inducing dopamine hypersensitivity. Another recent report has demonstrated that benzodiazepines potentiate stereotypic responses to dopamine agonists (Arnt, Christensen, and Scheel-Kruger 1979). In addition, Freed, Gillin, and Wyatt (1980) have demonstrated that chronic haloperidol treatment reduces the sensitivity of GABA-neurons. This suggests that GABA subsensitivity may play a role in the pathophysiology of tardive dyskinesia. The effects of subsequent GABA-mimetics on this already subsensitive inhibitory input are not known.

Taken together, these data suggest that caution be used in the extension of short-term clinical trials of GABA-mimetic drugs in the treatment of tardive dyskinesia because they may prove to be only temporary suppressors with an eventual breakthrough of symptoms of even greater severity—a situation that is analogous to treatment with antidopaminergics.

The use of cholinomimetics in tardive dyskinesia also requires some caution. It has been shown that chronic haloperidol treatment, in addition to producing dopamine hypersensitivity and GABA-subsensitivity, also decreases the sensitivity of cholinergic neurons (Gianutsos and Lal 1976). Again, the effects of cholinergic facilitation on already subsensitive cholinergic neurons are not known, and the risk of further potentiation of the striatal imbalances between dopamine, acetylcholine, and GABA cannot be determined at this time. Two recent reports (Schallert et al. 1980; Smith et al. 1980) demonstrated reduced $^3$H-quinuclidinyl benzilate binding following chronic acetylcholinesterase inhibition in rats. This suggests that chronic administration of cholinomimetics results in acetylcholine subsensitivity. If analogous effects occur in humans, then chronic cholinergic facilitation and the subsequent acetylcholine subsensitivity would lead to even greater acetylcholine/dopamine imbalances in the striatum and a worsening of TD.

It is important to view extrapyramidal function as a dynamic process with pharmacological agents having both acute and chronic effects. Acutely, antagonists attenuate neurotransmission while chronic antagonism may lead to compensatory increases in receptor sensitivity. Agonists in most cases initially increase neurotransmission. However, chronic agonist treatment may lead to compensatory decreases in postsynaptic activity. The phenomenon of tardive dyskinesia is a sad reminder of the importance of taking a long-term view of such dynamic changes. To continue to view only the acute manifestations of pharmacological manipulations to treat tardive dyskinesia may hold future unpleasant surprises.

To date, only one treatment approach to tardive dyskinesia has taken a dynamic reversal approach as opposed to the static symptom control methods discussed above. This approach, receptor sensitivity modification (Friedhoff and Alpert 1978), attempts to readjust downward the sensitivity of dopamine receptors by increasing the amount of dopamine available to the receptor via L-dopa. Initially, a worsening of tardive symptoms is observed, but after repeated L-dopa administration with a subsequent withdrawal, a decrease in abnormal movements is seen. Decreased receptor binding and diminished behavioral responses to dopamine agonists are observed with similar treatment of rodents. While the practicality of such an approach, considering the potential exacerbation of schizophrenic symptoms is somewhat limited, receptor sensitivity modification attempts to take advantage of the dynamic nature of receptor mechanisms. It is our impression that more research in this area is desperately needed. Broadening this perspective to include not only the readjustment of dopamine sensitivity downward but also the "resensitizing" of both the acetylcholine and GABA components would seem to be a fruitful area of research in the treatment of tardive dyskinesia. The use of dopaminergic agonists that have postsynaptic effects with less likelihood of exacerbating schizophrenic symptoms may be more practical than L-dopa. Recently, amantadine, when given concurrently with haloperidol, has been shown to prevent dopamine supersensitivity as measured by both behavioral re-

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responses to apomorphine and by receptor binding assays (Allen and Flemenbaum 1979; Allen, Lane, and Brauchi 1980). It is believed that the dopamine agonist action of amantadine is able to overcome the striatal neuroleptic blockade and, therefore, prevent the denervation of dopamine receptors. While several authors have demonstrated that amantadine, when given acutely, failed to improve dyskinetic symptoms (Crane 1971; Janowsky et al. 1972), none used a treatment approach consistent with a receptor sensitivity modification paradigm.

The research findings presented above come largely from neurochemical and behavioral studies using various animal models. There are numerous discrepancies between the animal models of tardive dyskinesia and the human condition (see Gerlach 1979). Nonetheless, animal research has led to many important findings and will guide the search for a safe and effective treatment—a search that will require the concerted efforts of both clinical and laboratory researchers. Until effects of chronic administration of GABA-mimetics and cholinergics on the dynamic interplay of striatal neurotransmission are known, caution in their use appears advisable.

**References**


**The Authors**

L. Thomas Kucharski, Ph.D., is Postdoctoral Fellow in Bio-behavioral Sciences, and Ellen M. Unterwald, B.S., R.Ph., is a graduate student, Division of Biomedical Sciences, Boston University, Boston, MA.