

# Tardive Dyskinesia: Pathophysiology and Animal Models

Daniel E. Casey, M.D.

Tardive dyskinesia stimulated extensive research into the mechanisms of antipsychotic drug action. A wide range of homologous, analogous, and correlational animal models have been developed to explore how typical neuroleptic drugs do and atypical antipsychotic agents do not seem to cause tardive dyskinesia. The leading hypotheses of the underlying pathophysiology of tardive dyskinesia include dopamine receptor hypersensitivity, GABA insufficiency, and/or structural abnormalities. All these hypotheses have data both for and against them. The roles of psychosis and aging must also be considered in any explanation of tardive dyskinesia. The challenge still remains of how to accurately attribute the relative contributions of each of these factors to the pathogenesis and pathophysiology of tardive dyskinesia. Fortunately, the atypical antipsychotic agents appear to greatly decrease the liability of developing tardive dyskinesia, but how this occurs remains an open and fascinating line of inquiry.

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Tardive dyskinesia stimulated substantial research into the basic mechanisms of the efficacy and adverse effects of traditional neuroleptics. Many preclinical models have been developed to identify the underlying pathophysiologic processes of tardive dyskinesia, but none has yet produced a parsimonious explanation.<sup>1-3</sup> The search for the cause of tardive dyskinesia had the additional benefit of reminding the field that spontaneously occurring abnormal movements that resemble tardive dyskinesia must also be accounted for in any explanation of this disorder.<sup>4</sup> One of the many challenges in developing models of tardive dyskinesia has been that both the preclinical and clinical knowledge about this disorder evolved along similar time frames. Fortunately, the risk of tardive dyskinesia with the atypical antipsychotic agents appears to be much less, although it is not clear what underlying mechanisms mediate this lowered liability.<sup>1</sup> The goals of this article are to review the purported pathophysiologic mechanisms underlying the etiology of

tardive dyskinesia and discuss some of the animal models that have been developed to better understand this complex disorder.

## MODELS OF TARDIVE DYSKINESIA

Three general types of animal models have contributed to our knowledge about tardive dyskinesia. These can be described as homologous, analogous, and correlational.<sup>5</sup> The homologous model requires that all the critical factors of tardive dyskinesia be highly similar to the clinical syndrome. This includes the etiology, biological basis, symptoms, response to treatment, course, and outcome, as well as unique features such as individual vulnerability. This model is best represented by long-term neuroleptic drug treatment studies in nonhuman primates.<sup>5,6</sup> The analogous model requires that some of the critical features be similar between the preclinical and clinical syndromes, but other features may not be similar. An example of this model is the vacuous chewing movements (VCMs) in rodents treated for brief to extended periods of time.<sup>7-10</sup> The correlational model requires that few or no factors between the preclinical and clinical observations be similar, but the results of the preclinical model are highly predictive of the clinical scenario. Potential examples of this model include the possible correlation between the future likelihood of specific antipsychotic drugs to cause tardive dyskinesia and (1) acute extrapyramidal syndromes (EPS) induced by neuroleptic drug treatment or (2) responses to dopamine agonists following brief neuroleptic treatment in rodents.<sup>1,5</sup>

The strength of the nonhuman primate homologous model is that it fits all the critical criteria for tardive dyskinesia in patients, particularly the factor of individual

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*From the Mental Illness Research, Education and Clinical Center, Veterans Affairs Medical Center, Portland; the Oregon Health Sciences University, Portland; and the Oregon Regional Primate Research Center, Beaverton.*

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*Reprint requests to: Daniel E. Casey, M.D., Mental Health Division (P-7-MHDC), VA Medical Center, 3710 SW U.S. Veterans Hospital Rd., Portland, OR 97201 (e-mail: daniel.casey@med.va.gov).*

vulnerability in which some monkeys develop tardive dyskinesia and some do not after chronic neuroleptic treatment. The limitation of this model is that it is very inefficient and expensive because large numbers of monkeys need to be treated for several years to develop a sufficiently large subgroup of animals with tardive dyskinesia symptoms. The rodent models of VCM represent the analogous model because of certain limitations. For example, the results appear to be dependent upon which type of rodents is tested, with the Sprague Dawley strain being the most reliable at producing symptoms.<sup>11</sup> This model has the advantages of being relatively efficient and inexpensive, although it may take up to 6 months to fully assess the onset and potential irreversibility of VCMs. The clear advantage of the correlational model is the efficiency and relatively lower cost of conducting acute studies that have high predictive power for chronic treatment outcomes. One limitation, on the other hand, is that this type of model usually does not inform the field about the critical underlying mechanisms of the disorder of interest.

Several different domains of central nervous system function have been assessed to explore the cause of tardive dyskinesia. Biochemical models have attempted to identify changes in specific receptor subtypes and/or interactions between receptor subtypes. Also, changes in neurotransmitter and metabolite levels have been assessed. Another approach has focused on attempting to identify structural brain abnormalities that may correlate with tardive dyskinesia. Finally, changes in motor function and behavior that are associated with long-term neuroleptic treatment in animals have been studied to provide additional insight into the understanding of this disorder.

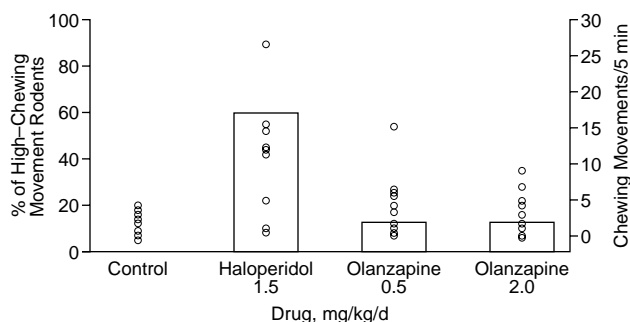
## PATHOPHYSIOLOGY

Several different pathophysiologic hypotheses have been proposed to explain tardive dyskinesia. The dominant hypothesis focuses on the concept of dopamine receptor hypersensitivity. Subsequently, a proposal for gamma-aminobutyric acid (GABA) insufficiency received attention, although data to support it have been limited. An alternate approach has been to hypothesize that tardive dyskinesia is due to structural abnormalities that may be related to cellular neurotoxicity and degeneration. Each of these hypotheses has data for and against it.

### Dopamine Receptor Hypersensitivity

The dopamine receptor hypersensitivity hypothesis has dominated the conceptual underpinnings of tardive dyskinesia research since the early 1970s. It proposes that the nigrostriatal dopamine receptor system develops increased sensitivity to dopamine as a consequence of chronic dopamine receptor blockade induced by traditional neuroleptic drugs.<sup>12,13</sup> Data regarding this hypothesis can be interpreted as providing either limited support for or ample evi-

Figure 1. Chewing Movements in Antipsychotic-Treated and Control Rodents<sup>a</sup>



<sup>a</sup>Adapted from Gao et al.,<sup>10</sup> with permission. The percentage of animals in each treatment group with high levels of purposeless chewing movements (> 8 chewing movements/5 min) is shown in the open columns and keyed on the left vertical axis. The open circles represent the individual levels of chewing movements for each individual rat in each treatment group and are keyed on the right vertical axis. In the haloperidol-treated animals, both the percentage of and individual levels of chewing movements were higher than in the control group. Neither measure was different from the control in any of the other treatment groups.

dence against it.<sup>1</sup> Much of what has been widely accepted as support for the dopamine hypersensitivity hypothesis comes from rodent models. Rodents show increased behavioral responses to dopamine agonists following dopamine antagonist treatment of a single dose, a few days, several weeks, and 1 year.<sup>1</sup> These changes occur in nearly all animals and are reversible within days to weeks of discontinuing traditional neuroleptics. Neurochemical changes of increased numbers of dopamine D<sub>2</sub> receptors in neuroleptic-treated animals correlate with behavioral changes in most but not all studies.<sup>1,14</sup> None of these observations is compatible with the essential clinical aspects of tardive dyskinesia: late onset, individual vulnerability, symptoms without agonist provocation, and a potentially irreversible course.

The VCM model shows that spontaneous VCMs increase with chronic neuroleptic treatment, as is reflected in the clinic. Typical neuroleptic drugs produce substantially more VCMs than the atypical antipsychotics.<sup>8-10</sup> However, a limitation of this model with the typical neuroleptics is that some compounds (such as chlorpromazine and thioridazine) produce fewer VCMs than other compounds (such as haloperidol). In the clinic, the risk of developing tardive dyskinesia across this range of typical neuroleptics is not substantially different. However, the distinction between typical and atypical antipsychotics in the VCM model does represent the differential effects seen in the clinic. It has been noted that clozapine, as well as olanzapine, produces far fewer VCMs than haloperidol when given chronically to rodents<sup>9,10</sup> (Figure 1). These findings are consistent with those from the clinic, where tardive dyskinesia liability for both clozapine<sup>15-17</sup> and olanzapine is low.<sup>18</sup> Reversibility of

VCMs is somewhat unclear; one study noted prompt resolution when discontinuing neuroleptics or giving anticholinergics,<sup>7</sup> but others have observed persistence of these movements for greater than 2 months.<sup>8,9,14</sup>

The model of tardive dyskinesia in nonhuman primates partially supports the dopamine receptor hypersensitivity hypothesis. Dopamine turnover was significantly decreased in the caudate and substantia nigra in monkeys with tardive dyskinesia for as long as 2 months after neuroleptics were discontinued in one study.<sup>19</sup> Although no receptor quantification was conducted in this study, monkeys did fit the clinical picture of tardive dyskinesia symptoms that occurred in the clinic late in the course of neuroleptic treatment.

It is difficult to reconcile all the clinical data with the dopamine receptor hypersensitivity hypothesis. There are virtually no direct data in humans supporting this hypothesis. Postmortem studies have been unable to find differences in D<sub>1</sub> or D<sub>2</sub> receptors in patients.<sup>20</sup> Analyzing cerebral spinal fluid in a number of studies in the 1970s and 1980s also was unable to identify consistent differences in dopamine turnover or metabolites in patients with and without tardive dyskinesia.<sup>1</sup>

Yet, clinical data suggest that dopamine antagonism has an important role associated with the pathophysiology of tardive dyskinesia. All the typical neuroleptics that block D<sub>2</sub> receptors have the capacity to cause tardive dyskinesia. Similarly, these compounds can suppress tardive dyskinesia in patients who already have tardive dyskinesia symptoms. In contrast, the atypical antipsychotic drugs, which have modest dopamine receptor antagonism, appear to cause much less tardive dyskinesia.<sup>17,18,21</sup> Therefore, the most efficient explanation of the data regarding the dopamine receptor hypersensitivity hypothesis is that dopamine may play a secondary or modulatory role. If the primary pathophysiology lies external to the dopamine system, but this pathophysiology is indirectly influenced by dopaminergic mechanisms, the clinical pharmacologic impact of perturbations on the dopamine system could explain the absence of direct evidence supporting dopamine receptor hypersensitivity.<sup>1</sup>

### GABA Insufficiency

GABA insufficiency in the anatomical loop controlling motor function also has received considerable attention as a possible explanation of tardive dyskinesia.<sup>22</sup> As in the dopamine receptor hypersensitivity hypothesis, the data for GABA insufficiency are also conflicting. In rodent models, behavioral and biochemical results both support and do not support altered GABA function associated with acute and chronic neuroleptic treatment.<sup>1,22</sup> Investigations in nonhuman primates indicate that tardive dyskinesia may be associated with decreased glutamic acid decarboxylase, the GABA-synthesizing enzyme, in the substantia nigra, medial globus pallidus, and subthalamic nuclei in dyskinetic

monkeys compared with similarly neuroleptic-treated non-tardive dyskinetic monkeys.<sup>19</sup>

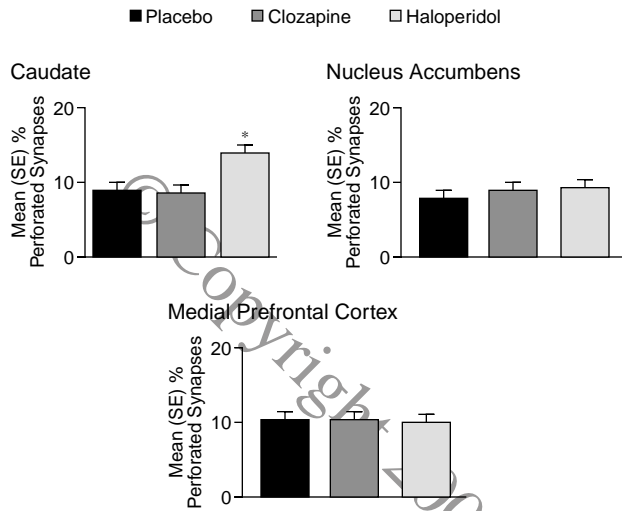
Data from the clinic are partially supportive of a role of GABA in tardive dyskinesia. Clinical investigations of patients with tardive dyskinesia found a trend toward decreased glutamic acid decarboxylase levels in the medial globus pallidus, and a separate study noted decreased cerebral spinal fluid levels of GABA in tardive dyskinetic patients.<sup>1</sup> However, treatment trials with GABA-enhancing drugs have not produced clinically significant or sustained improvement in tardive dyskinesia.<sup>1</sup>

### Structural Abnormalities

A separate line of investigation has pursued the possibility that tardive dyskinesia may be represented by structural abnormalities that could be due to neurotoxicity followed by cellular changes. One hypothesis suggested that free-radical formation from catecholamine metabolism in the brain caused cellular injury.<sup>23</sup> Vitamin E, a free-radical scavenger, would be a potentially useful treatment approach. Clinical trials have produced highly conflicting results, with benefit in some studies but not in others.<sup>2,24</sup> Studies in rodents have also found conflicting evidence regarding cell loss and tardive dyskinesia. Some studies looking at the potential of neuronal loss with chronic neuroleptic treatment in rodents have shown cell loss that is associated with higher drug doses and longer treatment periods. However, other studies have not attributed cell loss only to drug treatment, but have noted a complex interaction of aging and drug effects on brain cytoarchitecture.<sup>1,25</sup> Neuroimaging also has been used to study tardive dyskinesia. Several studies compared the ventricular brain ratio of patients with tardive dyskinesia with those of patients without tardive dyskinesia, but did not find consistent differences. This lack of differences is likely due to the wide range of ventricular brain ratios in normal subjects and patients with schizophrenia, as well as varying measurement techniques.<sup>1,26</sup> Positron emission tomography has not shown consistent differences across studies between patients with and without tardive dyskinesia.

More recently, studies have shown that patients taking typical neuroleptic drugs have a larger caudate region of the basal ganglia compared with the size shown by imaging assessments prior to starting these drugs.<sup>27</sup> In contrast, patients taking clozapine, an atypical antipsychotic, did not show these increases.<sup>28</sup> This line of inquiry parallels studies in rodents that found alterations in the number of perforated postsynaptic densities in the basal ganglia that were associated with neuroleptic treatment. The postsynaptic density is a measure of how synapses connect to each other. These short-term studies found that the number of postsynaptic densities increased by 50% in the caudate with the typical neuroleptic haloperidol, but not with the atypical antipsychotic clozapine.<sup>29</sup> This effect was regionally selective, as there were no effects in the medial pre-

**Figure 2. Mean (SE) Percentage of Perforated Synapses Within the Caudate Nucleus, Nucleus Accumbens, and Medial Prefrontal Cortex Following 14-Day Treatment With Saline, Clozapine (35 mg/kg/day), or Haloperidol (0.5 mg/kg/day)<sup>a</sup>**



<sup>a</sup>Adapted from Meshul et al.,<sup>29</sup> with permission.

\*Significantly different versus saline or clozapine ( $p < .05$ ), using the Peritz F test.

frontal cortex and nucleus accumbens with clozapine, haloperidol, or placebo (Figure 2). Thus, these effects were limited to the caudate region of the brain, which modulates motor function, suggesting that structural abnormalities may occur in this brain region with typical neuroleptic treatment.<sup>29</sup> It is not yet known whether alteration in the number of postsynaptic densities in the caudate is correlated with EPS or tardive dyskinesia, or both, but awareness of this alteration could be useful in testing for motor side effects with future drugs in development.

### Other Neurochemical Hypotheses

It is well recognized that neuroleptic drugs also antagonize many other receptor subtypes besides dopamine. Therefore, it is possible that some other neurotransmitter system plays a key role in the pathophysiology of tardive dyskinesia. One line of investigation assessed the possibility of noradrenergic overactivity with the suggestion that  $\beta$ -hydroxylase activity was greater in patients with tardive dyskinesia.<sup>1</sup> However, noradrenergic agents have not been successful treatment strategies for tardive dyskinesia.<sup>1</sup>

The recent resurgence of interest in serotonin receptor subtypes has also been applied to tardive dyskinesia. To date, there have been no consistent findings of alterations in serotonin parameters, nor have there been effective selective serotonin treatment approaches for tardive dyskinesia.

Metabolic issues may play a contributory role in tardive dyskinesia, but these concepts need to be developed much further. Meals that alter the phenylalanine–large

amino acid ratio temporarily decrease tardive dyskinetic symptoms.<sup>30</sup> Another interesting observation is that patients with type 2 diabetes mellitus have a nearly doubling of increase in risk for developing tardive dyskinesia.<sup>31</sup> It is not clear whether altered glucose or insulin mechanisms are associated with this altered risk for developing tardive dyskinesia.

### SPONTANEOUS DYSKINESIAS

As clinical research evolved in the tardive dyskinesia field, it became apparent that it was necessary to consider the possibility that the primary pathophysiologic mechanisms underlying psychosis may also contribute to the etiology of tardive dyskinesia–like movement disorders. Thus, factors such as psychotic disease and increasing age may play contributing roles in tardive dyskinesia. Both Kraepelin<sup>32</sup> and Bleuler<sup>33</sup> described abnormal movements of the orofacial and limb regions that are quite similar to the abnormal movements described as tardive dyskinesia. However, because neuroleptic drugs were not available at the beginning of the 20th century, these abnormal movements described by Kraepelin and Bleuler must be considered as spontaneously occurring dyskinesias. In one intriguing study, the type and severity of dyskinesias were similar in neuroleptic-treated and -untreated patients, but the prevalence was significantly higher in the neuroleptic-treated group when age was controlled for.<sup>20</sup> More recently, studies in neuroleptic-naïve patients further support the conclusion that psychosis may play a significant role in contributing to the prevalence and severity of abnormal movements in neuroleptic-treated patients.<sup>34</sup>

Age also plays an important role in the expression of dyskinesias. Spontaneously occurring orofacial dyskinesias occur more often in aging rodents and nonhuman primates and in elderly patients with neuromedical conditions.<sup>1,4</sup> Thus, the underlying syndromes of psychosis, particularly schizophrenia, advancing age, and some yet unknown component of traditional neuroleptic drug action may combine to convert a covert vulnerability to dyskinesias to overt symptomatology in the clinical representation of tardive dyskinesia. The challenge still remains to attribute accurately the relative contribution of each of these factors to the pathogenesis and pathophysiology of tardive dyskinesia.

### SUMMARY

Extensive research has explored the pathophysiology of tardive dyskinesia. Animal models and clinical investigations have developed along parallel paths to produce a rich research base for understanding neuroleptic drug action. However, no direct evidence of any specific pathophysiologic process has been identified. Dopamine and surely other neurotransmitter systems play a critical role in tardive

dyskinesia, but that role remains to be elucidated. The new atypical antipsychotic drugs appear to have greatly reduced or nearly eliminated the liability of tardive dyskinesia when these drugs are used within the recommended therapeutic dose range. Exactly how these atypical antipsychotic drugs have greatly decreased the tardive dyskinesia liability remains an open and fascinating line of inquiry.

*Drug names:* chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), thioridazine (Mellaril and others).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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