

New Nomenclature for Drug-Induced Movement Disorders Including Tardive Dyskinesia

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Psychotropic agents are increasingly being prescribed by different specialty clinicians for a variety of psychiatric illnesses, making it necessary to improve understanding of the etiology, diagnosis, and management of drug-induced movement disorders (D-IMD) across medical specialties. Early descriptions of movement disorders were based on identifiable disease states such as parkinsonism, dystonia deformans, and Huntington's chorea, which introduced complicated and often overlapping nomenclature. This has hindered communication about, description of, and diagnosis of these drug-induced disorders. Research criteria for tardive dyskinesia, a specific, purposeless, involuntary, hyperkinetic, potentially persistent D-IMD, have varied, with relatively few data-driven conclusions available to support clinical decision-making. The differences in research criteria among published reports on rates of tardive dyskinesia with atypical antipsychotics make it difficult to find meaningful comparisons and conclusions between atypicals. A novel system for classifying D-IMD according to whether they are reversible or persistent, hypokinetic or hyperkinetic, and dystonic or nondystonic is proposed. This new classification system will provide clinicians and researchers across specialties a more precise language, which will hopefully improve the diagnosis of and research criteria for D-IMD.

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Psychotherapeutic agents are increasingly being prescribed for a variety of psychiatric illnesses. As the use of these medications grows, so do the number and specialties of clinicians prescribing these agents. As of 2001, approximately 20% of prescriptions for antipsychotic medications in the United States were written by primary care physicians.¹ Because of this increase in the use of psychotherapeutic medications by physicians who are not psychiatrists, it is imperative to address disparate levels of understanding across specialties with regard to the etiology, diagnosis, and management of drug-induced movement disorders (D-IMD). Early reports of these clinical phenomena were based on identifiable idiopathic disease states such as parkinsonism, dystonia deformans, and Huntington's chorea. However, this early work introduced complicated and often overlapping descriptions of D-IMD, which has affected the optimal communication

about, description of, and diagnosis of these disorders. For example, because the terminology for D-IMD includes "parkinsonism," patients are often afraid that antipsychotics will cause them to develop Parkinson's disease.

Research on D-IMD has thus far focused on their role as adverse effects of antipsychotic agents; however, movement disorders are being reported in association with the use of other types of psychotherapeutic agents. Well-validated research instruments have significantly advanced our understanding of antipsychotic agents and movement disorders by employing disease-state classifications, but the use of these instruments across research designs and psychiatric diagnoses deserves reevaluation.

The novel classification system for D-IMD that my colleagues and I have proposed² will provide clinicians and researchers across specialties a more precise language, which will hopefully improve the identification of and research criteria for both reversible and persistent D-IMD.

OVERVIEW OF MOVEMENT DISORDERS

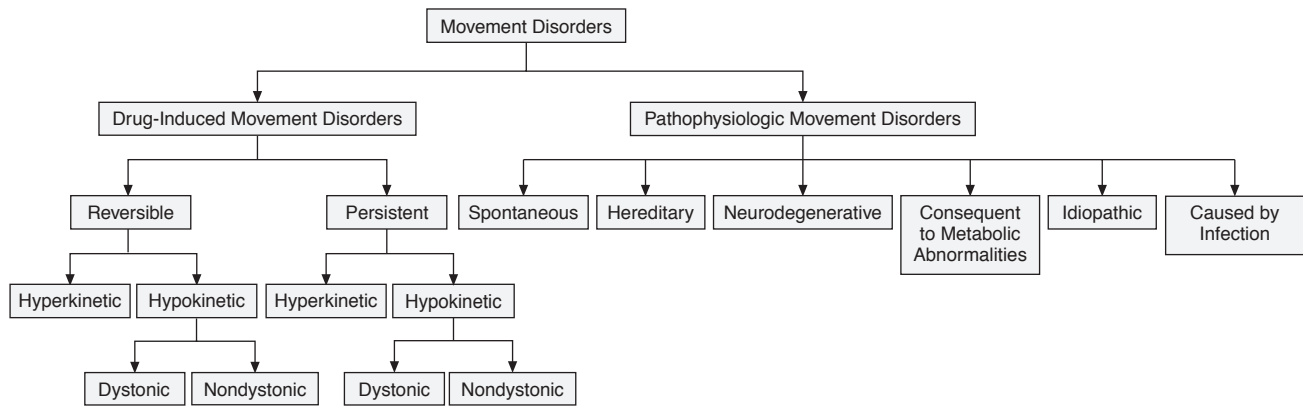
Movement disorders are neurologic motor disturbances characterized by abnormally increased motor activity or impaired back posture or by abnormally decreased motor function, mobility, or posture. They may be either pathophysiologic or drug-induced (Figure 1). Pathophysiologic movement disorders can be neurodegenerative, hereditary, spontaneous, caused by infection, consequent to metabolic

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Figure 1. Types of Movement Disorders



abnormalities, or idiopathic. Drug-induced movement disorders are generally either reversible or persistent, hypokinetic or hyperkinetic, and dystonic or nondystonic.

Drug-induced movement disorders were first described in the 1950s shortly after the introduction of antipsychotic agents. They have more recently been described with other central nervous system drugs (L-dopa, central anticholinergics, antihistaminics, and dopamine agonists) and with other psychotropic agents including selective serotonin reuptake inhibitors, antiepileptics, lithium, and mood stabilizers.

Although D-IMD have been the focus of many research reports since the introduction of antipsychotic agents, the estimated rates of these disorders have been inconsistent. It is generally accepted that atypical antipsychotics are associated with a lower risk for D-IMD than conventional antipsychotic agents. However, D-IMD, especially the persistent forms such as tardive dyskinesia, remain as a serious concern in the management of patients taking these agents.

CONFOUNDING TERMINOLOGY AND TARDIVE DYSKINESIA

[Tardive dyskinesia](#) (click for video) is a useful example to illustrate confounds encountered in the assessment of D-IMD. Research criteria for tardive dyskinesia—a hyperkinetic, repetitive, purposeless, persistent drug-induced movement disorder—have varied, with relatively few data-driven conclusions available to support clinical decision-making. An examination of the many aspects of defining and evaluating tardive dyskinesia will illuminate the challenges researchers face in studying D-IMD.

Of published reports on the risk of tardive dyskinesia with atypical antipsychotics, several have had a number of variables and limitations. The disparity in research criteria among published reports on rates of tardive dyskinesia in

patients taking atypical antipsychotics makes the identification of meaningful comparisons and conclusions difficult. Although many studies use the research criteria defined by Schooler and Kane³ in 1982, significant differences among studies exist. These differences include prospective versus retrospective assessment of tardive dyskinesia, available baseline information (including ability to confirm the presence of baseline tardive dyskinesia, history and duration of antipsychotic drug use, and polypharmacy), definitions for baseline and emergent tardive dyskinesia, consideration of withdrawal dyskinesia and persistent dyskinesia, consideration of dystonic dyskinesias and mixed D-IMD, dystonia, factors leading to remission, factors related to masking dyskinesias, rating scales used, duration of study period, and other patient characteristics and risk factors (including age, sex, and diagnosis).

To illustrate the problems encountered when comparing studies with different research criteria, it is helpful to look at several recent studies evaluating tardive dyskinesia in patients treated with atypical antipsychotics (Table 1). There is disagreement in the literature about how to define tardive dyskinesia at baseline. Some studies⁴⁻⁹ used the Abnormal Involuntary Movement Scale (AIMS),¹⁰ but while Tollefson et al.⁴ defined baseline tardive dyskinesia as a score ≥ 3 on 1 item or ≥ 2 on 2 items, Beasley et al.⁷ used a total score ≥ 3 and at least 1 item score ≥ 2 . However, instead of the AIMS, Jeste et al.¹¹ and my colleagues and I¹² used the Extrapyrarnidal Symptom Rating Scale (ESRS).¹³ The Simpson-Angus Scale¹⁴ and Barnes Akathisia Rating Scale¹⁵ are also commonly used to assess other types of D-IMD. In addition, the duration of these studies varied from 9 months⁵ to 2.6 years,^{4,7} as did the mean patient age, from 42 years¹² to 82.5 years¹¹ (or age was unavailable for comparison^{4,7,9}).

The overall prevalence or incidence of tardive dyskinesia in patients treated with antipsychotic medications is

Table 1. Reports Using Research Criteria for Tardive Dyskinesia in Patients Receiving Atypical Antipsychotics

Study	Treatment Arms	Patient Population	Duration	Criteria	Scale	TD Rate
Jeste et al ⁵	Risperidone, haloperidol	Mixed psychotic disorders; mean age 66 y	9 mo	Insufficient information (based on Schooler and Kane)	AIMS	Cumulative risperidone to haloperidol approximately 1:8
Jeste et al ¹¹	Risperidone	Dementia; mean age 82.5 y	1 y	Baseline dyskinesia = score ≥ 3 on 1 item or ≥ 2 on 2 items of ERSR (E51–E57) Emergent TD = increase ≥ 3 on 1 item or increase ≥ 2 on 2 items of the ERSR (E51–E57), absent at baseline Persistent TD = emergent TD at ≥ 2 consecutive visits	ESRS increase in score over baseline	Cumulative 2.6%
Tollefson et al ⁴	Olanzapine, haloperidol	Schizophrenia, schizoaffective; mean age not available	Up to 2.6 y	Baseline TD = score ≥ 3 on 1 item or a score ≥ 2 on 2 items of the AIMS (items 1–7) Emergent TD = score > 3 on 1 item, or > 2 on 2 items of the AIMS (items 1–7), absent at baseline	AIMS absolute score	Any time point: 7.1% for olanzapine, 16.2% for haloperidol Last assessment: 2.3% for olanzapine, 7.6% for haloperidol Last 2 assessments: 1% for olanzapine, 4.6% for haloperidol
Beasley et al ⁷	Olanzapine, haloperidol	Schizophrenia, schizoaffective; mean age not available	Up to 2.6 y	Baseline TD = total AIMS score ≥ 3 and at least 1 item score ≥ 2 (AIMS items 1–7) Emergent TD = score ≥ 3 on item, or ≥ 2 on 2 items of the AIMS (items 1–7) at 2 consecutive assessments, absent at baseline	AIMS absolute score	1-year risk: 0.52% for olanzapine, 7.45% for haloperidol
Jeste et al ⁶	Quetiapine	Mixed psychotic disorders; mean age 76.7 y	52 wk	Insufficient information, based on Schooler and Kane (only poster abstract available)	AIMS	Cumulative 2.7%
Glazer et al ⁹	Quetiapine	Schizophrenia, schizoaffective disorder; mean age not available	Not available	Insufficient information, based on Glazer-Morgenstern and Schooler and Kane (only poster abstract available)	AIMS	Incidence lower than that found with conventional antipsychotics
Chouinard et al ¹²	Long-acting risperidone	Schizophrenia, schizoaffective disorder; mean age 42.1 y	50 wk	Jeste et al ¹¹ criteria followed by expert case assessment. Case assessments consider each dyskinesia score at baseline, change, time to change, and persistence of change to identify withdrawal dyskinesia, reversible dyskinesia and emergent persistent TD	ESRS	Cumulative 0.68%

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, ERSR = Extrapyramidal Symptom Rating Scale, TD = tardive dyskinesia.

difficult to determine, in part because of differences in study design. In studies^{4,7} with olanzapine and haloperidol, Tollefson et al.⁴ gave the prevalence of tardive dyskinesia as the percentage of patients who met the criteria for tardive dyskinesia at any visit after baseline (7.1% for olanzapine and 16.2% for haloperidol), while Beasley et al.⁷ determined the 1-year risk of development of tardive dyskinesia (0.52% for olanzapine and 7.45% for haloperidol).

The rating scales used in the studies mentioned above, the AIMS and the ESRS, are 2 of the most common instruments used to rate the severity of tardive dyskinesia. They use different criteria and scoring systems to measure tardive dyskinesia, and although each is considered to be reliable and valid, there were no published reports cross-validating the 2 rating scales until my colleagues and I carried out a study¹⁶ of their correlation. We analyzed data from 2 studies that assessed patients for baseline tardive dyskinesia using both the AIMS and the ESRS. Data were available for 230 patients. Tardive dyskinesia was defined as 2 scores of 2 or 1 score of 3 on the AIMS and 2 scores of 2 or 3 or 1 score of 4 on the ESRS. We found that most AIMS and ESRS dyskinesia ratings were low; 67% of patients had total scores of zero on the AIMS, and 71% of patients had total scores of zero on the ESRS. The 2 rating scales agreed on the severity of abnormal movements in 220 (95.7%) of the 230 patients. Four patients had tardive dyskinesia according to the ESRS but not the AIMS, and 6 had tardive dyskinesia according to the AIMS but not the ESRS. The ESRS Clinical Global Impressions of Severity of Dyskinesia (ESRS CGI-SD) was the single best predictor of tardive dyskinesia as found by the AIMS; a score of 4 or greater on the ESRS CGI-SD was associated with a 95% or greater probability of AIMS-defined tardive dyskinesia.

TARDIVE DYSKINESIA IN THE LITERATURE

The problems with defining tardive dyskinesia are evident in both clinical and research studies. They were present in the first reports of this disorder and still exist in the present day.

Studies With Classical Antipsychotics

Early reports¹⁷⁻²¹ of tardive dyskinesia were not free from the confusion of terminology that has occurred in more recent studies. The causes and effects of tardive dyskinesia were very much in debate in the 1970s and 1980s, with little standard terminology on which to base findings.²²⁻²⁵

In 1979, my colleagues and I¹⁷ published the results of a 1975 study of 261 patients in an outpatient clinic for schizophrenia. Using the National Institute of Mental Health psychopharmacology service center collaborative study diagnostic criteria for tardive dyskinesia and the

ESRS, we found a 31% incidence of tardive dyskinesia in patients at the clinic. We also evaluated patients according to the Schooler and Kane research diagnostic criteria and found a 22% incidence of tardive dyskinesia, a 9% difference. This variability of findings between rating scales complicates comparisons of incidence and prevalence rates across studies.

In 1988, we¹⁸ published a 5-year follow-up study of patients included in the 1975 study.¹⁷ In 1980, the time of the follow-up, 45% of patients in the clinic met the Schooler and Kane criteria for tardive dyskinesia using the ESRS. The researchers were careful to differentiate tardive dyskinesia from other neurologic disorders with similar movements, such as Huntington's chorea and Sydenham's chorea, and from stereotypies and mannerisms often seen in patients with schizophrenia.¹⁸ One hundred sixty-nine patients were examined in both 1975 and 1980. In 1975, 131 of these patients did not meet the Schooler and Kane criteria for tardive dyskinesia. When these patients were reassessed in 1980, the researchers found tardive dyskinesia in 46 of the patients who did not have it in 1975, for a 5-year cumulative incidence of 35% and a mean annual incidence of 8.4%. However, 9 patients who had tardive dyskinesia in 1975 were not found to have it in 1980. Corrected for remissions, the mean annual incidence was 2.9%.¹⁸ This incidence and the fact that patients both developed and remitted from tardive dyskinesia over time are similar to results found by other studies^{26,27} conducted around the same time.

Studies With Newer Antipsychotics

The problems with defining terminology and characteristics of tardive dyskinesia are still present in recent studies with atypical antipsychotics. My colleagues and I²⁸ analyzed the relationship between patient demographics, Positive and Negative Syndrome Scale (PANSS) scores, and extrapyramidal symptoms (EPS) in baseline data from 3 multicenter studies (Ris USA-121,²⁹ Ris Int-57,³⁰ and Ris Int-61³¹) that included their first patient on October 21, 1999, and their last patient on December 1, 2000. We found that 970 (47.4%) of the 2048 patients whose data were included had 1 EPS. Tardive dyskinesia was present in 209 (10.2%) of the patients. Patients with EPS were significantly older than patients without EPS ($p < .0001$). Race was significantly associated with the presence of EPS ($p < .004$), but sex was not. Baseline PANSS total scores were higher in patients with EPS ($p < .0001$). Overall, the incidence of EPS was related to patient demographics, such as age and race, and severity of psychotic symptoms.

In another study, my colleagues and I³² analyzed baseline data on EPS and suicidality from an international, multicenter trial.³³ Suicide in patients with schizophrenia has been associated with akathisia and tardive dyskinesia related to treatment with conventional antipsychotics.

Data from 958 patients were included in this study of EPS, from March 19, 1998 (first patient), to February 14, 1999 (last patient). Using the ESRS to measure EPS, we found that patients taking an atypical antipsychotic alone or an atypical antipsychotic and a conventional antipsychotic together tended to have fewer EPS than patients taking a conventional antipsychotic alone. Patients who had made 1 or more suicide attempts were more likely to have EPS. EPS were present in 551 (57.5%) of the patients and tardive dyskinesia was present in 115 (12%) patients. Tardive dyskinesia was more common with increasing age and a higher score on the Lindenmayer depression PANSS scale. An especially high correlation was found between a high score on the ESRS and a high score on the Lindenmayer depression PANSS scale in patients taking only conventional antipsychotics ($p < .0003$). In patients taking an atypical antipsychotic alone or a combination of an atypical and a conventional antipsychotic, suicidality was not significantly associated with tardive dyskinesia.

Atypical antipsychotics are associated with a lower risk of tardive dyskinesia compared with conventional antipsychotics. My colleagues and I¹² evaluated the rate of tardive dyskinesia in patients treated with the first long-acting formulation of an atypical antipsychotic. We analyzed data from an open-label trial in which patients were treated with long-acting risperidone every 2 weeks for up to 50 weeks. Data on tardive dyskinesia, measured by the ESRS and using Jeste et al.¹¹ criteria, were available for 696 patients. At baseline, 587 patients did not have dyskinesias. Of these, 12 met the criteria for tardive dyskinesia at endpoint. Tardive dyskinesia was evident in 7 patients at week 8 or week 12; this was classified as withdrawal dyskinesia. The dyskinesia resolved in 3 of these patients by endpoint and remained in 4. One patient developed tardive dyskinesia during the study that resolved by endpoint; this was classified as a reversible dyskinesia. Four patients developed tardive dyskinesia during the study that did not resolve by endpoint, which gives an annual incidence rate of 0.7% versus the 29% reported with classical antipsychotics.^{18,26-27} These patients were classified as having persistent emergent tardive dyskinesia. Of the 109 patients who had dyskinesias at baseline, 26.6% no longer met the criteria for tardive dyskinesia at endpoint. ESRS total dyskinesia scores in this group improved significantly during the course of the study ($p < .001$).

As can be seen from this study, there are many aspects to the abnormal movements currently grouped together under the term *tardive dyskinesia*. Because of the varying circumstances under which dyskinesias appear and remit, and the varying lengths of time they are present in patients, it is necessary to consider the many variables related to dyskinesias when diagnosing abnormal movements in patients or when setting up guidelines for a study in order to properly evaluate D-IMD.

CONSIDERATIONS IN PROPOSING TERMINOLOGY FOR TARDIVE DYSKINESIA

Given the confounds in measuring the drug-induced movement disorder tardive dyskinesia, many factors must be considered when proposing criteria for its study. These include the presence of tardive dyskinesia at baseline; the definition of baseline characteristics; the defined criteria of tardive dyskinesia; the evaluation of withdrawal, precursor, reversible, and remitted dyskinesias by experts; and the duration of the study.

First, researchers must determine whether tardive dyskinesia is present at baseline. They must consider the possibility of concomitant hypokinetic and dystonic D-IMD, which have masking effects on tardive dyskinesia, as well as the presence of other hyperkinetic D-IMD that might evolve into tardive dyskinesia over time and make the diagnosis difficult, especially for mixed form and dystonic components of the movement disorders.

Researchers should next consider how to define and measure baseline characteristics. Patients with differing severities of baseline dyskinesias or none at all should be given separate assessments. The antipsychotic drug regimen that the patient is on at intake should be recorded, including the types of antipsychotics taken by the patient (atypical or conventional, polytherapy or monotherapy, depot or nondepot) and dosage schedule. The presence of any anticholinergics or antiepileptics at intake, including anti-parkinsonian central anticholinergics, antihistaminics, and valproic acid should be noted and total cumulative effect considered. Demographic information such as age and sex should be considered, along with the patient's diagnosis and any history of brain injury or damage.

Another consideration is the definition of tardive dyskinesia. Researchers must decide which rating scales and score cutoffs to use for inclusion criteria. When calculating the prevalence or incidence of tardive dyskinesia in a particular population, researchers have to consider whether to calculate total cumulative rates of tardive dyskinesia or rates by duration of exposure. It must be decided whether to chart absolute scores or calculate the change-from-baseline scores when measuring changes in the severity of tardive dyskinesia. Researchers must also determine how to distinguish tardive dyskinesia from other movement disorders, i.e., whether the change in tardive dyskinesia severity or prevalence in a given population is due to the masking effects of a concomitant hypokinetic D-IMD that might have appeared, to precursor effects of a hyperkinetic D-IMD, or to a mixed form with dystonia or other D-IMD. Lastly, the criteria for true remission from tardive dyskinesia must be determined.

Other study design aspects must also be determined carefully, especially how subjects are evaluated, for what, and by whom. For example, withdrawal dyskinesias must be evaluated by experts who take into account prior depot

Table 2. Proposed Classification of Drug-Induced Movement Disorders^a (click links to see video illustrations)

	Hyperkinetic	Hypokinetic
Reversible	Acute akathisia Tremor (high frequency or rapid) Athetosis Withdrawal dyskinesia Chorea ballismus Myoclonus Myorhythmias Acute gait abnormalities Acute dyskinesia Early onset dyskinesia Acute choreoathetoid dyskinesia (off/on effects of L-dopa)	Hypertonia (muscle rigidity) Akinesia Bradykinesia Acute dystonia, including: General Segmental or focal Blepharospasm Spasmodic torticollis Oculogyric crisis Laryngeal/ respiratory dystonia Oromandibular dystonia Deformans dystonia
Persistent	Buccolingual dyskinesia Choreoathetoid dyskinesia Tardive chorea Tardive akathisia Tardive tics Tardive myoclonus Tardive/parkinsonian tremor (pill rolling) Dystonic dyskinesia	Nonacute dystonia Dyskinetic dystonia

^aBased on Chouinard et al.²

versus oral antipsychotic regimen. Precursor, reversible, remitted, dystonic, or akathic dyskinesias should also be reviewed by experts who will assess dose effect (suppression, remission, and precursor) and rater effect, taking into account other medications. It could be helpful to have experts with different backgrounds look at the rating of tardive dyskinesia over time, or to have some raters blinded to the prior medication and some not blinded in order to assess the pattern of abnormal movements in the patients.

Of course, the best-designed study of tardive dyskinesia can be successful only if the follow-up period is long enough. The minimum length of time that is adequate for evaluating incidence of tardive dyskinesia is 1 year. That time period should be sufficient for assessing emerging tardive dyskinesia, identifying possible masking of pre-existing and precursor dyskinetic movements, and evaluating true remission and reversibility.

PROPOSED NOMENCLATURE FOR DRUG-INDUCED MOVEMENT DISORDERS

In our proposed classification system,² D-IMD would be categorized according to the answers to 4 questions. First, is the disorder reversible or persistent? Second, is it hyperkinetic or hypokinetic? Third, is the disorder dystonic or not? And fourth, is it mixed or not? This system is based on 6 categories of D-IMD: reversible hyperkinetic, reversible hypokinetic (dystonic or nondystonic), reversible mixed form, persistent hyperkinetic, persistent hypokinetic (dystonic or nondystonic), and persistent mixed form. The proposed components of each of these

categories are listed in Table 2. This classification system will guide clinicians by providing a precise and consistent language for better identification and diagnosis.

CONCLUSION

The increasing use of psychotropic medications by multiple medical specialists necessitates a better understanding of their adverse event profiles. The lack of a simple and clear classification system for D-IMD probably contributes to underdiagnosis and mismanagement of these disorders.

Tardive dyskinesia, in particular, is a disturbing movement disorder associated with psychotropic agents that has received much attention in the literature. However, inspection of published reports reveals considerable variability and confounds that complicate the assessment of tardive dyskinesia. We have suggested some key issues specific to tardive dyskinesia that could be considered in developing useful research criteria to better assess the risk and to aid in early identification of this disorder.

My colleagues and I have suggested a simple classification system to help guide clinicians and lead to an overall better understanding of movement disorders.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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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