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Review Article

# Tardive dyskinesia: Epidemiology

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A B S T R A C T

The term tardive syndrome (TS) encompasses a few different phenomenologic conditions, some of which occur in isolation and others in association with each other. This, along with the unusual confound for a drug side effect, in which increased use of the drug improves the problem, and the need for most patients to continue taking the offending drug, makes understanding the epidemiology difficult and unreliable. While the change from the "first generation" to the "second generation" of antipsychotic drugs is generally believed to have reduced the incidence of TS, prospective research studies have not supported that contention. Published reports have found point prevalences of 13% with second generation antipsychotics and 32% with first, yet others have found no differences. One study found increasing rates of TS with a 68% prevalence by 25 years, while another found a decreased prevalence over time, due presumably to masking effects of the antipsychotic drugs. Regardless of the possible differences, it is clear that TS remains a significant and common problem associated with almost all antipsychotic drugs. There have also been scattered reports of TS caused by drugs not known to inhibit dopamine receptors. These are reviewed and were found to be often of dubious reliability.

## 1. Introduction

Despite the recognition that tardive dyskinesia (TD) may be a side effect of antipsychotic drugs (APDs) – or neuroleptics – for over 50 years, its epidemiology is not well defined. There are many reasons for this. The nature of the studied population, whether drug naïve or not when entering the study, the psychiatric diagnosis, gender and age of the patients, the duration of the studies, and the length of time the subjects were on the neuroleptic medication all may be important risk factors. Almost all studies are also affected by the unusual confound that the drugs that cause TD can also mask it [1]. This results in the counterintuitive situation in which a cohort of patients treated with a neuroleptic for many years will reveal their previously masked TD when taken off the drug, which is pharmacologically equivalent to being placed on placebo. This might lead to the deduction that placebo is associated with a high incidence of TD. This phenomenon was likely seen in a large meta-analysis in which clozapine, a drug that has no extrapyramidal side effects other than neuroleptic malignant syndrome [2] was linked to a relatively high incidence of TD when patients taking typical neuroleptics were switched to clozapine [3]. A long-term observational or "naturalistic" study looked at 55 patients in a state psychiatric hospital who had been evaluated by the same author 14 years earlier found that, counterintuitively, TD scores had improved despite continued use of first generation antipsychotics [4]. Notably, parkinsonism had increased, suggesting that their TD was masked either by increased dosing or the increased sensitivity to dopamine receptor blockade that occur with aging.

A second confound is the fact that many patients taking neuroleptics, especially those with psychotic disorders that are chronic and incurable, need to continue to take their drugs, despite experiencing TD as a side effect. Typically, patients cannot be taken off their drugs for extended durations. Ethical considerations thus mandate that for most trials, patients remain on their baseline APDs and either have a placebo or an experimental drug added, in a double-blind manner, after a hiatus of 1–2 weeks with either the baseline drug or no APD for the abstinent period. Since TD is often masked by parkinsonism, it must be kept in mind that the parkinsonian side effects of neuroleptics may last many weeks or even months after the offending drug is discontinued. Some dopamine antagonists have been shown to cause persistent, non-progressive parkinsonism for 10 years off the offending agent [5].

Another factor that probably plays a minor role is the spectrum of tardive dyskinesia syndromes [6]. While the most common is the oral-buccal-lingual form of choreic-athetoid movements of the lip, tongue and jaw, these dyskinesias can involve any part of the body and mimic Huntington's disease [7]. In addition, tardive dystonia, unlike the tardive choreo-athetoid syndromes, in our experience, tends not to be

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masked by the offending agent. Tardive akathisia, in our experience, similar to the choreo-athetoid syndrome, can be masked by increasing doses of neuroleptic medication, but is not assessed with the Abnormal Involuntary Movement Scale (AIMS), and is often overlooked as a tardive phenomenon by treating physicians. The other tardive syndromes, such as tardive myoclonus, tics, and tremor, are rare. Since TD is among a group of phenomenologically heterogeneous conditions, which makes categorization more nonspecific and recognition more difficult, it is proposed that these heterogeneous entities be referred to as tardive syndromes (TS). However, since this chapter deals with epidemiology, we have used terminology identical to the articles we are referencing.

A stunning observation in support of the difficulty understanding the epidemiology of TD is the CATIE study (see below), in which a panel of experts designed and executed a study to support the widely held belief that second-generation antipsychotics are associated with less TD than first-generation drugs. Their results, however, demonstrated no significant difference, leading to a flurry of papers attempting to understand what went wrong, rather than believing that there were, in fact, no major differences. The jury is still out.

Although spontaneous dyskinesia has been observed in institutionalized elderly patients, such movement disorders are most commonly a delayed complication of medication exposure. Dopamine receptor blocking drugs (DRBDs), including antipsychotic drugs (APDs) and metoclopramide and prochlorperazine, anti-emetic agents, are the major culprits. Tardive dyskinesia (TD) is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V) as a medication-induced movement disorder, caused by DRBDs, that starts after a few months of medication use (or less in an older patient) and persists at least 1 month after medication change or discontinuation. TD is encountered fairly commonly in a psychiatric or movement disorders practice, but its reported incidence and prevalence vary greatly. Many factors contribute to these large discrepancies, including study population, clinical setting, definition of TD, and other methodological differences. Case in point: a large, multi-site study found TD prevalence to be 13% in patients at a voluntary psychiatric hospital and 36% in patients at a state psychiatric facility [8]. Furthermore, longitudinal, randomized controlled trials (RCTs) are the gold-standard for evaluating the incidence and prevalence of TD among users of typical, or first-generation, APDs and atypical, or second-generation, APDs. However, patients with treatment-refractory psychiatric symptoms are often excluded from RCTs and some subjects are unable, or unwilling, to provide consent to participate due to the severity of their symptoms. Additionally, many psychiatric patients are life-long consumers of APDs and since the medications may be switched from one class to another, the ability to identify a "causative" agent is impossible, as the long-term effects of several different APDs are likely to be contributory. By definition, the symptoms of TD present after "a few" months, sometimes only after the patient is no longer taking the offending drug. Lastly, TD symptoms are not only caused by APDs but are also masked by the same APDs, thus reducing the true magnitude of the problem. With these caveats in mind, the following discussion is meant to provide a general picture of the incidence and prevalence of this common problem.

## 2. Incidence and prevalence

Reports of TD in psychiatric patients date as far back as the 1950s, soon after the APDs were first introduced [9]. These reports were initially received with skepticism, but an abundance of publications and worldwide experience have confirmed this association. In the age of the typical APDs, the risk of TD after APD exposure for 5 years was estimated to be 32%; 57% for 15 years, and 68% after 25 years [10].

It was hoped that the "atypical APDs," or second-generation APDs, would minimize this complication. Indeed, the early comparison studies did show a significantly lower risk of TD with atypical APDs. A review of the studies conducted in the early 2000s comparing the two classes found that the point prevalence of TD was 13.1% with atypical APDs and 32.4% with typical APDs [11]. However, later publications failed to confirm these findings. The incidence of TD was found to be no different over a 2.5-year study in patients treated with typical versus atypical APDs in an outpatient psychiatric cohort [3]. Furthermore, large, prospective studies based in the UK (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study, CUtLASS-1) [12] and the US (Clinical Antipsychotic Trials of Intervention Effectiveness, CATIE) [13] failed to show the anticipated decrease in TD with atypical APDs.

A recent meta-analysis of 41 studies published between 2000 and 2015 comparing typical and atypical APDs demonstrated an estimated weighted mean prevalence of 25.3% for all treatment groups [14]. However, prevalence varied greatly in the populations studied, ranging from 8.5% in some populations to 75.3% in others. Factors associated with higher prevalence included APD class (20% with atypical and 30% with typical APDs), longer duration of psychiatric illness, baseline parkinsonism, and prior typical APD usage. TD prevalence even varied by geographical region, ranging from 17.3% in Asia to 31.8% in Australia, Africa and the Middle East. Due to the lack of a uniform TD severity measure in these studies, this variable was not analyzed in this meta-analysis.

Studying the incidence of a disorder like TD is challenging and requires close, thorough, longitudinal follow up of patients. In 1977, Kane et al. [15] initiated the Hillside Study, a decade before the first atypical APD was introduced. In this study, 908 patients were enrolled and prospectively monitored for 20 years. They found the cumulative incidence of TD to be 5% at year 1, 27% at year 5, 43% at year 10, and 52% after 20 years of exposure [16]. This study suggested an annual incidence of 5% overall (including both transient and persistent TD), and about 3% for persistent (> 3 months) TD. Another longitudinal study of typical APDs [10] estimated the annual incidence of persistent TD at 5.3% with a spontaneous remission rate of 2.5% per year. These findings were remarkably similar to the Hillside study, even though the patients were about 10 years older and exposure to APDs was 14 times longer (7 months vs 8 years). In the elderly population, however, the estimated annual TD incidence is much higher: 26% after 1 year and about 60% after 3 years [17]. Pooling the data of studies published between 2004 and 2008, the annual incidence of TD with typical APDs was 7.7% and with atypical APDs was 2.9% [11].

Several risk factors for TD have been recognized. The strongest of these is older age. Patients over the age of 50 years are 3 to 5 times more likely to develop TD than younger patients, and patients over 65 are 5 to 6 times more likely [15]. Other risk factors, with variable certainty of association with TD, are presence of a mood disorder, longer duration of APD exposure, female gender, history of acute EPS (such as a dystonic reaction or akathisia), presence of dementia, African-American race, high APD doses and use of anti-cholinergic drugs.

## 3. Antipsychotic drugs

The earliest reports of TD prevalence in chronic APD users ranged from 24% to 56%, with an average prevalence of 20% among a variety of studies with variable methodologies [18]. A cross-sectional study estimated the TD prevalence at 33% in 180 patients, with the most common culprits being perphanazine (34.4%), fluphenazine decanoate (16.6%), thioridazine (15.6%), chlorpromazine (11.1%), trifluoperazine (8.3%), fluphenazine orally (6.7%), thiothixene (5.3%), and haloperidol (5.0%) [19]. Interestingly, neither the chlorpromazine-equivalent dose, nor the potency of the APD had any significant effect on prevalence of TD. The 5 predictive factors for TD were: age > 55, depot version of the APD, > 6 years of APD use, male gender, and prolonged hospitalizations (> 6 months).

Due to the magnitude of public health effects of TD, it was hoped that atypical APDs would be accompanied by a lower risk of EPS and TD. With increasing availability of atypical APDs in the 90s, early trials