Neuroleptic-Induced Movement Disorders: Deconstructing Extrapyramidal Symptoms

Richard M. Trosch, MD

The neurological risks and benefits of atypical neuroleptics have received considerable attention in the medical literature, but there have been few controlled studies examining these risks in elderly patients. Well-designed, long-term prospective studies are needed to identify the safest and most effective treatment regimens for elderly patients, but until these studies are complete, clinicians will need to rely on available studies in making clinical decisions. This article is not an exhaustive systematic review of this topic; rather it is an attempt to integrate recent studies and the author’s clinical experience to provide an approach to understanding the risks of movement disorders associated with the use of antipsychotic medications.

NEUROLOGICAL RISKS AND BENEFITS OF ATYPICAL NEUROLEPTICS

Within the field of geriatrics, neuroleptics (also called antipsychotics) are among the most commonly prescribed medications. In part, their popularity may be attributed to the growing list of difficult-to-manage psychiatric uses, on- and off-label, for which these agents have potential benefit. Also contributing to their increasing usage is the commonly held belief that atypical neuroleptics possess a lower risk of tardive dyskinesia (TD) and other movement disorders, but whether all atypical neuroleptics are indeed safer or less likely to induce movement disorders than typical neuroleptic agents is unclear. Studies examining this issue are conflicting, and assumptions concerning the risks of movement disorders associated with atypical neuroleptics remain speculative.1–5

When considering the risk of TD from the typical neuroleptic agents, there is no clear distinction of risk between the various agents.6 All typical neuroleptic agents are generally held to cause TD with the same proclivity. Of the atypical neuroleptics, clozapine and quetiapine have not been reported to induce TD or parkinsonism in patients not previously exposed to these neuroleptics, but case reports of new-onset TD have emerged in association with other atypical neuroleptics.7–10 The reporting of multiple cases of typical TD after a singular neuroleptic exposure is sufficient to suggest that a particular neuroleptic possesses a risk of causing TD, but isolated case reports do not instruct us on issues of relative risk or the incidence of TD from any particular agent. In most patients, TD begins after prolonged exposure to a neuroleptic agent, and reasonable estimates of TD risk are best derived from the completion of prospective, long-term trials designed to specifically examine this issue. In the case of the atypical agents, no studies meeting these criteria have been conducted. Arguably, short-term Phase II and III industry-sponsored clinical trials are primarily designed to measure efficacy of these agents in psychosis and present a poor substitute for prospective, long-term studies when assessing TD incidence. Inherent methodological flaws, including placebo-group contamination, short duration of study, the use of inexperienced movement disorder raters, and the lack of withdrawal-emergent assessments, further limit assessment of TD risk from clinical trials. Because of these limitations and the absence of prospective, long-term TD incidence studies, current assumptions regarding the risk of TD or neuroleptic-induced parkinsonism (NIP) from the atypical neuroleptics remain speculative.11

The common use of the term “extrapyramidal symptoms” (EPS) when referring to some or all of the variety of abnormal movements associated with neuroleptic use has further obscured understanding of risk of neuroleptic-induced movement disorders. In the author’s experience, this term has taken on different meanings for different clinicians and has been used nonspecifically, in the psychiatric literature and in the clinic, to denote all of the neuroleptic-induced movements, a single, specific type of reaction, or a combination of several types of movements. This lack of specificity impedes the understanding of the relative safety of the various neuroleptic agents by treating all neuroleptic-induced movements as equivalent, impeding any discrimination of risk between the available agents. To illustrate this point, consider a comparison of two agents, one associated with a 5% risk of acute dystonic reaction and another with a 5% risk of neuroleptic malignant syndrome. If no other adverse effects were noted, then both agents could be considered to have an EPS risk of 5%, but the actual risk would be 5% of a brief, transient, and typically benign reaction from the first agent versus a 5% risk of a fatal or potentially permanently disabling reaction from the second. The differences in risk between these two agents would be considerable, and the practice of lumping all neuroleptic-induced movements

From the Parkinson’s Disease and Movement Disorder Center, Southfield, Michigan; and Department of Neurology, Wayne State University School of Medicine, Southfield, Michigan.

Address correspondence to Richard M. Trosch, MD, 26400 West Twelve Mile Road, Southfield, MI 48202. E-mail: rtrosch@ameritech.net
together as EPS serves to obscure the relative risk of different agents. When considered individually, the various neuroleptic-induced adverse events, including TD, parkinsonism, acute dystonic reactions, and neuroleptic malignant syndrome, are significant. These adverse events vary not only in their severity, but also in their associated risk factors, time to onset, duration, clinical presentation, and persistence. For these reasons, the risk of neuroleptic-induced movement disorders are best assessed by considering the risk associated with each type of adverse event individually.

To deconstruct the nosological term EPS, the neuroleptic-induced movement disorders may instead be organized into clinically meaningful categories based on their shared clinical course and risk factors.

**A PARADIGM OF MEDICATION-RELATED MOVEMENT DISORDERS**

Each of the neuroleptic-induced movement disorders may be placed into one of four categories: limited reactions, idiosyncratic events, toxic effects, and tardive syndromes (Table 1). Each of these four categories shares a common cause of neuroleptic exposure but differs in its time to onset, persistence, severity, and risk factors. Additionally, the risk of causing different types of neuroleptic-induced movement disorders appears to differ between the available agents, with some agents possessing no reported risk of inducing some of the categories of reactions.

**CATEGORIES OF NEUROLEPTIC-RELATED MOVEMENT DISORDERS**

**Limited Reactions**

Limited reactions, consisting of the acute dystonic reactions (ADR) oculogyric crisis and acute laryngospasm, have been reported to follow exposure to each of the available typical and atypical neuroleptics but may also result from the use of numerous nonneuroleptic medications, including several illicit drugs and over-the-counter medications. Some investigators found lower risk of an ADR with atypical neuroleptic use than with use of typical agents.

The designation “limited” denotes a transient reaction, distinguishing this category from the tardive or persistent reactions, which may share similar phenomenological features of dystonia, chorea, or stereotypy, but the term “limited” does not describe their severity or imply that these reactions are mild or benign. ADR are typically intermittent or sustained, often painful, muscular spasms producing twisting or abnormal postures of the eyes, jaw, face, neck, limbs, or axial structures. Severe events may produce dysphagia, mandibular dislocation, or laryngeal obstruction and may constitute a neurological emergency. The limited reactions are the first neuroleptic-induced movements to appear, beginning within a few hours or days after exposure or dosage increase of an offending medication, with practically all events occurring within a week of new exposure. Limited reactions last from hours to weeks but are not persistent reactions. Although symptoms may be distressing and temporarily painful or disfiguring, the limited reactions generally respond well to treatment. Because of their transience, most are relatively benign compared with other neuroleptic-induced movements. Reported risk factors include male sex, young age, neuroleptic dose and potency, prior acute dystonic reactions, and cocaine abuse. Younger patients, particularly boys in their first 2 decades of life, are at greatest risk for this occurrence, with incidence peaking during the first 2 decades of life and decreasing after age 40. Elderly patients infrequently suffer ADR.

**Idiosyncratic Events**

The idiosyncratic events consist of neuroleptic malignant syndrome (NMS), a rare medication-induced reaction characterized by encephalopathy, rigidity, dystonia, fever, elevated creatine phosphokinase, autonomic lability, movement disorders, and a variety of transient or persistent neurological disorders. NMS affects patients of all ages, but younger adults are reported to have a higher prevalence. Onset of symptoms often occurs after a first exposure to a neuroleptic. Most cases occur within the first 7 to 9 days of neuroleptic treatment, but patients may also develop NMS after years of exposure. Case reports have indicated that all available neuroleptic agents, inclusive of all atypical agents, cause NMS. Because NMS incidence is low, affecting an estimated 1.0% of neuroleptic-exposed patients, data are insufficient to compare the relative risk of different neuroleptic agents. Neuroleptic dose has not been established as a risk factor for NMS, nor has NMS been reported as a feature of neuroleptic overdose. NMS may also rarely follow exposure to dopamine-depleting drugs and nonneuroleptic agents and in Parkinson’s disease (PD) after an abrupt withdrawal of dopaminergic agents. Signs of NMS appear within days or weeks of starting a neuroleptic or after an increase in dose, with symptoms rapidly evolving over 24 to 72 hours and persisting over a period of 1 to several weeks. Rates of mortality and morbidity from NMS remain high and may result from a variety of conditions, including pulmonary embolism, pneumonia, myoglobinuria with renal failure, and complication of autonomic lability. Persistent neurological residua may occur in some patients, with reports of persistent dementia, ataxia, peripheral neuropathy, parkinsonism, dyskinesia, and dystonia. With the exception of the potential for neurological and end-organ residual damage, NMS shares with the limited reactions a temporally discrete clinical course, followed by the eventual resolution of the acute syndrome.

**Toxic Effects**

NIP and acute akathisia are distinguished as dose-related phenomena, with their severity closely tied to the extent to which the postsynaptic striatal D2 receptors are blocked. Studies are mixed on whether the limited reactions, idiosyncratic reactions, or TD are dose related, and the importance of dose in the severity of these reactions remains controversial. Most clinicians are aware of this dose-related association; neuroleptic dose reduction and substitution with a lower-potency agent are strategies commonly used to diminish symptom severity. The importance of neuroleptic dose or potency for limited reactions, NMS, and the tardive syndromes is less clear. After neuroleptic discontinuation, most patients become free of akathisia or parkinsonism...
with a few weeks, but for some elderly patients parkinsonism may persist for several months or up to a year.\(^6\)\(^3\)

Clinically, NIP can be difficult to distinguish from the idiopathic form of the disease. Both conditions display the same cardinal features of rigidity, tremor, postural instability, akinesia/bradykinesia/hypokinesia, simian posture, and motor blocks. Patients are considered to have parkinsonism when two or more of these cardinal features are present.\(^6\)\(^4\),\(^6\)\(^5\) Although idiopathic PD (IPD) progresses slowly and, in many cases, it takes several years for symptoms to become debilitating, most cases of NIP occur within 20 days, and 90% occur within 72 days.\(^6\)\(^6\) Akinesia, an absence or poverty of movement, and bradykinesia, a slowness of movement, are the most common manifestations of NIP. In the author’s experience, limb rigidity is universally present in IPD but is frequently absent from NIP; this distinction may help differentiate NIP from IPD at the bedside.

Reported estimates of NIP incidence and prevalence rates vary widely.\(^6\)\(^6\) This may, in part, be attributed to the characteristics of the patient cohort or which particular neuroleptic agents were studied. For example, older patients are observed to have a higher risk of NIP, and greater risk is associated with higher-potency neuroleptic agents. Documented risk factors for NIP include advanced age, female sex, underlying IPD, and the use of high-potency D\(_2\) receptor antagonists.\(^6\)\(^6\) One study\(^6\)\(^7\) proposed that the rate at which a neuroleptic dissociates from the D\(_2\) receptor, identified as its dissociation constant, may predict the likelihood of that agent to cause NIP and TD. By this model, drugs producing only a transient receptor blockade (fast dissociation from the D\(_2\) receptor), which include the atypical neuroleptics clozapine and quetiapine, would permit a physiological stimulation of the striatal postsynaptic D\(_2\) receptor by endogenous dopamine. In turn, these agents would pose lower risk of inducing TD or NIP movements than agents producing a sustained D\(_2\) blockade or no risk at all.

For NIP, incidence data from most Phase II and III trials are difficult to interpret.\(^6\)\(^8\) Because of a lack of sufficient washout (usually lasting only 4 to 14 days) at the start of a trial, there is contamination of the placebo group from the patient’s prior neuroleptic use. Additionally, reliance on the Simpson-Angus scale (SAS), a measure of NIP, may under-report NIP incidence.\(^6\)\(^9\) Scored items on the SAS favor the presence of rigidity, a feature typically absent in NIP. Finally, many studies report only a total EPS incidence, without a separate reporting of NIP incidence.

### Table 1. Neurologic Paradigm of Medication-Related Movement Disorders

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<th>Limited reactions</th>
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<td>Acute dystonic reaction</td>
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<td>Idiosyncratic events</td>
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<td>Neuroleptic malignant syndrome</td>
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<td>Tardive syndromes</td>
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**Table 2. Recognized Tardive Syndromes**

| Stereotypy (classical orobuccal lingual dyskinesia) | Dystonia          | Akathisia          | Chorea             | Myoclonus          | Oculogyric deviations | Tic           | Tremor | Pain |

Excluding clozapine and quetiapine, the other atypical neuroleptics are reported to cause NIP in patients not previously exposed to these neuroleptics.\(^7\)\(^0\)–\(^7\)\(^2\) Their reported tendency to worsen the motor symptoms in IPD or Lewy Body dementia further supports their potential to cause NIP. Several studies examining risperidone or olanzapine use for psychosis in parkinsonism have demonstrated a consistent worsening of parkinsonian symptoms.\(^7\)\(^3\)–\(^7\)\(^6\) Accordingly, risperidone and olanzapine should be considered to be contraindicated in patients with parkinsonism or at risk for this condition. Conversely, clozapine and quetiapine have been reported to treat symptoms of psychosis in parkinsonism effectively without worsening motor symptoms.\(^7\)\(^6\)–\(^7\)\(^8\)

**Tardive Syndromes**

A group of investigators first used the term tardive dyskinesia (TD) in 1952 to describe the late onset of persistent orobuccal stereotypy occurring in three women within several months of neuroleptic exposure.\(^7\)\(^9\) The term tardive, or late, was used to draw a distinction between these cases and previously observed ADR. TD in the elderly typically presents as an orobuccal-facial-lingual stereotypy. Younger patients, in turn, are more likely to experience dystonic symptoms.\(^8\)\(^0\) The “tardive syndrome” actually refers to several different varieties of hyperkinetic involuntary movements present concurrently in a patient. This may include the tardive subsyndromes of dystonia, akathisia, chorea/athetosis, tremor, tic, myoclonus, or characteristic pain complaints (Table 2).\(^6\),\(^8\)\(^1\) Other investigators also described TD pain while reporting on 11 patients with chronic oral or genital pain after neuroleptic use.\(^8\)\(^2\) The incidence of TD pain is unknown, but because patients with schizophrenia or dementia commonly experience difficulties reporting their subjective complaints, it is likely that this TD subsyndrome is underreported.

TD may be defined as a movement disorder beginning within 3 months, after an exposure to a striatal dopamine receptor blocking agent, and persisting despite discontinuation of the offending agent.\(^8\)\(^3\) In another study, TD was divided into persistent (\(>3\) months) and chronic (\(>6\) months).\(^8\)\(^4\) It is now recognized that TD can rarely occur acutely after a brief exposure to a neuroleptic, although in most instances, TD begins after chronic exposure of several months or years. More importantly, in contrast to other neuroleptic-induced movements, TD is set apart by its persistence. Remissions of TD can occur but are uncommon, typically limited to younger patients or if the course of
neuroleptic exposure was brief. In the geriatric population, TD remissions are rare, and TD is typically a persistent disorder.

Many potential TD risk factors have been identified. Advancing age has been consistently found to correlate with TD severity and prevalence. Elderly patients are also more likely to develop TD early in their course of treatment and less likely to remit after neuroleptic discontinuation. The importance of sex as a TD risk factor may be related to age. Women are at greater TD risk in the geriatric age group, whereas an association between sex and TD is unclear in younger patients. Drug dose and potency have long been suspected as contributing to TD risk, and it is a common practice among physicians to limit the dose of drug used in the hopes of diminishing a patient’s risk of TD. Recent studies have supported this assumption, finding a correlation between dose and TD risk in geriatric patients. Several other reported TD risk factors remain controversial and include genetic factors, concurrent use of anticholinergic medications, diabetes mellitus, addictive disorder, prior electroconvulsive therapy, smoking, and alcohol use.

All typical neuroleptics have been reported to cause the tardive syndromes, and there are insufficient data to predict whether one agent is any worse or better than another in this regard. The reported incidence of TD with neuroleptics is highly dependent on the population studied and associated TD risk factors. A prospective observational study of neuroleptic-induced movements in recently diagnosed schizophrenic patients reported a 5% per year incidence of TD, increasing linearly over a period of 5 years of exposure to a typical neuroleptic medication. Another prospective study of an elderly population of patients not previously exposed to these neuroleptics who were beginning typical neuroleptic treatment found that TD rates were three to five times the rates in younger patients, beginning at 25% for the first year and 53% by Year 3, despite treatment with smaller drug doses. The course of TD, once established, is often progressive. A study of the natural history of tardive dyskinesia dystonia (TDd) in 107 neuroleptic-treated patients between 1972 and 1995 found that there was no safe period of neuroleptic exposure (the onset of TD was documented as early as after 4 days or as late as after 23 years of neuroleptic use); men were younger than women at onset of TDd; specific psychiatric or medical illnesses posed no additional risk; all typical neuroleptics were implicated in causing TDd; for most patients, TDd progressed over 1 to 2 years from a focal or segmental dystonia to a generalized state; discontinuation of dopamine-receptor agonist treatment quadrupled the odds of remission; and continued neuroleptic exposure after the onset of TDd symptoms diminished the likelihood of remission. The natural history of the other TD subsyndromes has not been adequately studied, but given the potential for symptomatic progression with continued neuroleptic exposure, once symptoms of any TD subsyndrome are recognized, measures to reduce or eliminate further neuroleptic exposure are appropriate.

Case reports of TD occurring in patients after a singular neuroleptic exposure have been reported in connection with risperidone, olanzapine, and ziprasidone use. Clozapine and quetiapine have been implicated in causing TD in patients with a previous exposure to (an)other neuroleptic agent(s) but not in previously neuroleptic-naïve patients. The contribution of clozapine or quetiapine to causing TD in these reports is difficult to establish because of the possibility of a late unmasking of a TD syndrome caused by a prior neuroleptic exposure. Aripiprazole has not been reported to cause TD either, although there is only limited clinical experience with this drug. Until the mechanisms responsible for causing TD and NIP are understood, it cannot be assumed that any neuroleptic is completely safe or devoid of potential for causing TD. Accumulated case reports, although not providing any insight into the risk of these conditions, suggest that the risk of TD from the various atypical neuroleptics is not equal, with greater safety associated with clozapine and quetiapine.

Unlike the typical neuroleptic drugs, no long-term prospective studies have been conducted to examine the incidence of TD caused by the atypical neuroleptic agents. One study compared the risk of an acute movement disorder after exposure to risperidone versus haloperidol in a prospective, short-term trial. Incidence rates of dyskinesia, parkinsonism, akathisia, and dystonia were found to be equivalent. Similarly, the Nithsdale survey, compared the prevalence rates of TD, NIP, and dystonia before and after the introduction of atypical neuroleptics and found a lack in anticipated reduction in the risk of these adverse events despite the introduction of atypical neuroleptics. Despite claims of improved safety, empirical evidence collected outside of Phase II and III pharmaceutical company–sponsored trials have not confirmed a lower risk of TD with the newer atypical agents as a class, and this widely held assumption remains controversial.

**SUMMARY**

The use of neuroleptics remains vital to the management of an expanding number of psychiatric conditions but has the potential to cause disabling and persistent movement disorders. Despite the common practice of lumping all of the neuroleptic-induced movement disorders under the rubric of EPS, an examination of the differences in the temporal course, risk factors, phenomenology, and persistence of these movements suggests that splitting these movements into the categories of limited reactions, idiosyncratic events, toxic events, and tardive syndromes adds precision to the understanding of these disparate disorders. The use of atypical neuroleptics, as suggested by Phase II and III clinical trials, may diminish the risk of neuroleptic-induced movements, but long-term prospective incidence studies have not been conducted with these drugs, and prevalence studies have failed to demonstrate a difference between the typical and atypical agents. TD and parkinsonism have not been reported with clozapine or quetiapine use in previously neuroleptic-naïve patients. These agents may represent a unique class of atypical agent, providing a lower risk of neurological adverse effects.

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