Brain-Disabling Treatments in Psychiatry

4 - Severe and Potentially Irreversible Neurological Syndromes (Tardive Dyskinesia and Neuroleptic Malignant Syndrome) Caused by Neuroleptics

Drugs, Electroshock, and the Psychopharmaceutical Complex


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Chapter 4

Severe and Potentially Irreversible Neurological Syndromes (Tardive Dyskinesia and Neuroleptic Malignant Syndrome) Caused by Neuroleptics

This chapter focuses on two well-known neurological disorders caused by the neuroleptics - tardive dyskinesia (TD) and neuroleptic malignant syndrome (NMS) - with emphasis on their frequency and their destructive impact on the physical and emotional life of the individual. It also discusses neuroleptic withdrawal syndrome. The next chapter will explore irreversible damage to the brain that primarily affects mental functioning, including tardive psychosis and tardive dementia. However, as products of neuroleptic neurotoxicity, all these drug-induced abnormalities are clinically and neurologically interrelated. Chapter 5 will examine the neurotoxic effects of these medications that cause or contribute to these adverse drug effects.

The so-called clinical effect of neuroleptics, their chemical lobotomizing impact, is primarily caused by the blockade of dopaminergic nerves, especially the $D_2$ receptors, in the ventral striatum, with their connections to the limbic system and frontal lobes (chapters 1 and 2). However, blockade of the same $D_2$ receptors in the dorsal striatum is the probable cause of extrapyramidal reactions, including TD (Ethier et al., 2004 [41]; Seeman, 1995 [91]). Hence, as described in chapter 1, the so-called therapeutic effect is inextricably entwined with some of the worst adverse effects.

4.1 Tardive Dyskinesia (TD)

4.1.1 Clinical Manifestations of TD

TD often begins with uncontrolled movements of the face, including the eyes (blinking or blepharospasm), tongue, lips, mouth, and cheeks, but it can start with almost any group of muscles. The most common early sign is a quivering or curling of the tongue. Tongue protrusions and chewing movements are also common and can become serious enough to harm teeth and impair chewing and swallowing. The hands and feet, arms and legs, neck, back, and torso can be involved.

The movements displayed are highly variable and include rapid jerking movements (chorea) or slower twisting movements (athetosis), tics, spasms, and tremors. The person’s gait can be badly impaired. More subtle functions can be affected and are easily overlooked: respiration (involving the diaphragm), swallowing (involving the pharyngeal and esophageal musculature as well as the tongue), the gag reflex, and speech (Yassa et al., 1985 [107]).

The movements usually disappear during sleep, although I have seen exceptions. They sometimes
can be partially suppressed by willpower, frequently are made worse by anxiety or tiredness, and can vary from time to time (see subsequent discussions).

Many cases of TD appear to be relatively mild, often limited to movements of the tongue, mouth, jaw, face, or eyelids. Nonetheless, they are frequently disfiguring and often embarrassing. Patients have been known to commit suicide (Yassa et al., 1985 [107]).

The abnormal movements can sometimes become totally disabling. Turner (1971) [99] described patients who cannot eat and must have their teeth removed to facilitate the entry of food into their mouths. He also described patients who cannot keep shoes on their feet because they wear them out while sitting with the constant foot-shuffling activity. I have evaluated a number of cases in which the TD was wholly disabling, including massive distortions of the position of the neck or body, rocking and swaying, shoulder shrugging, and rotary or thrusting movements of the pelvis as well as disturbances of respiration, such as periodic rapid breathing, irregular breathing, and grunting.

Ironically, the disease makes the patient look very crazy because of the seemingly bizarre facial and bodily movements. Tragically, this has often led to patients being treated more vigorously with neuroleptics, ultimately worsening their TD.

As in other neurological disorders, the patient may attempt to hide the disorder by adding voluntary movements to the involuntary ones to disguise them. For example, to cover up a tendency to move the arms continually, the patient may make grooming movements around the face and hair. This can make it seem as if the individual suffers from a psychological compulsion instead of a neurological disorder. Or the patient may clasp his or her arms together to control the movements, making it seem as if he or she is trying to psychologically hold onto himself.

4.1.2 TD Rates

As the following section will document, rates for TD among patients treated with antipsychotic drugs are astronomical. Otherwise healthy adults develop TD at the cumulative rate of 3% to 8% per year of exposure to neuroleptics. The elderly (over age 55) develop TD at a cumulative rate that can exceed 20% per year of drug exposure. Children are at high risk as well.

In 1980 the APA produced a detailed analysis of the iatrogenic disease in its Task Force Report: Tardive Dyskinesia. The task force made it clear that TD is a serious, usually irreversible, largely untreatable, and highly prevalent disease resulting from therapy with neuroleptics. The task force estimated the prevalence rate for TD in routine treatment (several months to 2 years) as at least 10% to 20% for more than minimal disease. For long-term exposure to neuroleptics, the rate was at least 40% for more than minimal disease.

Even after the publication of the 1980 task force report and a mountain of confirmatory evidence, some biologically oriented psychiatrists, such as Nancy Andreasen (1984) [110], in The Broken Brain: The Biological Revolution in Psychiatry, continued to misinform the public that TD is “infrequent” (p. 210) and occurs in “a few patients” (p. 211).

A more recent APA (1992) [3] task force report cited a rate of 5% per year, cumulative over the first several years of treatment. Jeste and Caligiuri (1993) [60] estimated the annual incidence rate among young adults at 4% to 5%. According to these two estimates, 12% to 15% of patients will develop TD within the first 3 years of exposure to antipsychotic drugs. In reality, the rates are probably even higher.

In a prospective project emanating from Yale, Glazer et al. (1993) [49] reported a long-term evaluation of 362 outpatient psychiatric patients who were free of TD at baseline and who were being maintained on neuroleptics. For patients who are starting neuroleptics, according to projections from their data, the risk of TD will be 31.8% after 5 years of exposure - a rate of slightly over 6% per
year. The risk is 49.4% after 10 years, 56.7% after 15 years, 64.7% after 20 years, and 68.4% after 25 years.

Chouinard et al. (1986)\textsuperscript{[24]} followed a group of 136 persons who had already been receiving neuroleptics but had not yet manifested TD. Over 5 years, 35% - a rate of 7% per year - developed the disorder.

The American Psychiatric Association is a conservative organization that tends to be self-protective of psychiatric treatments. Nonetheless, the two most recent editions of the APAs Diagnostic and Statistical Manual of Mental Disorders (1994 \textsuperscript{[4]}, 2000 \textsuperscript{[5]}) find a prevalence of 20% to 30% for TD in long-term patients (meaning a few years or more). The estimated rate for “younger individuals” is 3% to 5% per year.

Overall, in relatively young and healthy patients, the cumulative risk of contracting TD when exposed to neuroleptics ranges from 4% to 7% per year during the first several years of treatment. Approximately one third of the patients will develop this largely irreversible disorder within the first 5 years of treatment. This represents an astronomical risk for patients and should become part of the awareness of all mental health professionals, their patients, and their patients’ families. Furthermore, we shall find that TD brings with it the additional risk of irreversible cognitive dysfunction and dementia (chapter 5).

There is evidence that rates for TD increased in the 1990s. It may have been caused by the tendency to use drugs with seemingly more toxic effects on the extrapyramidal system such as Haldol and Prolixin (see, Jeste et al., 1981 \textsuperscript{[62]}). These drugs also come in long-acting intramuscular preparations that do not permit patients to independently lower their own dosages by taking fewer pills than prescribed. The development of long-acting forms of newer neuroleptics, such as Zyprexa, is likely to continue this trend.

It is unusual for TD to develop in less than 3-6 months of treatment. However, as Tepper and Haas (1979) \textsuperscript{[96]} and others (e.g., Hollister, 1976 \textsuperscript{[54]}) noted, TD can develop even in low-dose, short-term treatment. DeVeaugh-Geiss (1979) \textsuperscript{[37]} saw cases develop in a matter of weeks. I have evaluated several cases of TD that developed at around 3 months of treatment. One patient developed TD after 1 month of recent exposure, with a history of 2 months’ prior exposure several years earlier. I have also seen cases develop after a few doses of Compazine or Reglan for the control of nausea, for example, 3-5 doses given over a several month period. In the elderly, many cases may develop within a few weeks (see subsequent discussions).

\subsection*{4.1.3 Atypical Neuroleptics Cause TD in Adults}

All the neuroleptics (see the appendix) can cause TD, including the atypical neuroleptics such as clozapine (Weller et al., 1993 \textsuperscript{[102]}), olanzapine (Herran, 1999 \textsuperscript{[56]}), and risperidone (Addington et al., 1995 \textsuperscript{[1]}; Buzan, 1996 \textsuperscript{[22]}; Kumar et al., 2000 \textsuperscript{[71]}; Kwon, 2004 \textsuperscript{[72]}). Aripiprazole (Abilify) has been considered one of the safer atypicals, but there are already reports of tardive dyskinesia (Maytal et al., 2006 \textsuperscript{[70]}; Oommen et al., 2006 \textsuperscript{[84]}). Given that the atypicals, with the exception of clozapine, are all potent dopamine (D\textsubscript{2}) blockers (chapters 2 and 3), it is irrational to anticipate that they will produce a significantly lesser amount of TD when given at equivalent doses to the older neuroleptics.

As already noted, in the clinical antipsychotic trials of intervention effectiveness among adults exposed to older neuroleptics and several atypicals (Nasrallah, 2007 \textsuperscript{[81]}), no difference was found between the older antipsychotic drugs and the newer ones in regard to producing extrapyramidal effects, movement disorders, or akathisia.

One variant of TD called rabbit syndrome is characterized by fine, rapid, rhythmic movements
along the vertical axis of the mouth. A recent review found 11 cases associated with atypicals, mostly risperidone (Dell'Ossio et al., 2007\textsuperscript{36}). All of the FDA-approved atypical neuroleptic labels carry the same class warning as the older neuroleptics.

A key study in misleading the medical profession was published by the American Journal of Psychiatry in 1997, comparing TD rates on olanzapine and on haloperidol. It seemed lost on psychiatrists that the first two authors, Gary Tollefson and Charles Beasley, were longtime employees of Eli Lilly, the manufacturer of olanzapine, and well known for stepping into the fray in defense of the company’s products, going all the way back to early days of the Prozac controversies (Breggin et al., 1994a\textsuperscript{16}). The study purported to show that olanzapine had a lower rate of TD over a several-month period. But three factors were noteworthy. At the last visit, 2.3% of the olanzapine patients displayed treatment-emergent TD. But the average exposure time was less than a year. If the actual annual rate of TD on olanzapine were calculated, it would be approximately 3%, which is within the range of rates for classic neuroleptics (3% to 8%).

Furthermore, at the times they were being evaluated, the patients continued to take the olanzapine, which, like all neuroleptics, suppresses the appearance of TD symptoms while at the same time causing or worsening the underlying disorder (see subsequent section). Therefore, the only way to determine an accurate rate of TD is to withdraw the patients from the offending drug before the final evaluation. In this study, the actual rate of TD would have been much higher than 3% per year if the patients had been withdrawn from the olanzapine before the final TD evaluation.

Finally, the dose of olanzapine was relatively low compared to haloperidol, an old trick for making one drug look safer than another. The recommended starting dose of olanzapine is 5-10 mg with the aim of achieving 10 mg within several days. The recommended starting dose of haloperidol is 1-6 mg/day (Drug Facts and Comparisons, 2007\textsuperscript{38}). The patients were given up to 20 mg of either drug as if they were of comparable strength milligram for milligram.

The average physician does not have the time or inclination to analyze a study in the depth with which I have evaluated the Tollefson et al. report\textsuperscript{38}. Often physicians will not notice or grasp that the main authors are drug company employees flogging their product under the guise of publishing a scientific study. Physicians are not likely to know that these particular authors specialize in fixing potential promotional problems as they surface among professionals or with the public. As a result, this study convinced many physicians that Zyprexa is safer than it is.

As of May 2006, two of the more knowledgeable TD experts, Daniel Tarsy and Ross Baldessarini\textsuperscript{94}, concluded that the risk of TD with atypicals had not been clearly established to be less than that with the classic neuroleptics and that patients should be treated with atypicals with the usual caution concerning neuroleptic treatment.

### 4.1.4 Atypical Neuroleptics Cause TD in Children

In 1983, while writing the earliest edition of this book, I became one of the first to conclude and to emphasize that TD is a major risk in children. While too many psychiatrists have continued to minimize the risk to children, awareness has grown. In the 2003 edition of The American Psychiatric Publishing Textbook of Clinical Psychiatry, now in the era of the atypical antipsychotics, Cozza et al.\textsuperscript{29} explained,

“Tardive or withdrawal dyskinesias, some transient but others irreversible, seen in 8%-51% of antipsychotic-treated children and adolescents, mandate caution regarding casual use of these drugs. Tardive dyskinesia has been documented in children and adolescents after as brief a period of treatment as 5 months and may appear even during periods of constant medication dose. Cases of tardive dyskinesia have been reported in youths treated with risperidone, indicating that atypical antipsychotics may also cause this serious adverse reaction.” (p. 1422)\textsuperscript{29}
To further examine the risk of atypical neuroleptics causing TD in children, Wonodi and a team from the Maryland Psychiatric Research Center (2007)\textsuperscript{[105]} followed up 118 children who had been taking neuroleptics, mostly atypicals, for at least 6 months. As a sign of the irrational overprescription of these drugs, only 19\% of the children on antipsychotic drugs had ever displayed psychotic symptoms.

Eleven (9\%) of the children developed TD, compared to 0\% in a matched control group (p = .003). The TD rate was particularly high among African American children (15\%). Given the relatively short period of exposure, these rates are astronomically high and should discourage any attempts to give neuroleptics, atypical or not, to children.

4.1.5 History of TD

Within a few years after the development of the first neuroleptic, it became obvious that many patients were not recovering from their drug induced neurological disorders, even after termination of the drug treatment. Reports were made in the late 1950s, and Delay and Deniker (1968)\textsuperscript{[35]} date their awareness of irreversible neurological syndromes to 1959. By 1968, they were able to provide a vivid review of several varieties, including buccolingual, truncal, and variable choreic movements. In 1964, Faurbye et al. (1964)\textsuperscript{[43]} named the disorder tardive dyskinesia.

As if governed by one mind, psychiatry as a profession for two decades refused to give any official recognition to this potential tragedy. Then, nearly two decades after chlorpromazine initially flooded the state mental hospitals of North America, Crane (1973)\textsuperscript{[30]} made it a personal crusade to gain the profession’s recognition of the problem. In the same year, the American College of Neuropsychopharmacology / Food and Drug Administration Task Force (1973)\textsuperscript{[8]} described the syndrome in a special report. Following 1973, everyone in the profession should have been alerted to the dangers of neuroleptic-induced TD, but too many psychiatrists have continued to act as if the risk is too inconsequential to affect their treatment decisions.

In 1980, the American Psychiatric Association (APA, 1980b\textsuperscript{[7]}) published a task force report on TD. In 1985, the FDA took the unusual step of setting specifically worded requirements for a class warning in association with all neuroleptic labeling and advertising (“Neuroleptics,” 1985). The FDA’s decision to reexamine the labeling for neuroleptics was driven in large part by the 1983 publication of the first edition of this book, Psychiatric Drugs: Hazards to the Brain, and the national campaign I conducted to alert the nation and the profession to the dangers of TD, including a special Dan Rather report that highlighted my book and my concerns. In a wholly unprecedented move, in the same year, the APA sent out a warning letter about the dangers of TD to its entire membership (see chapter 13 for further discussion of the FDA’s role).

4.1.6 Masking the Symptoms of TD with Continued Neuroleptic Treatment

The symptoms of TD are paradoxically masked or suppressed by the drugs that cause them so that the disease symptoms do not fully appear until the patient has been removed from the treatment. For this reason, in addition to using the smallest possible dose for the shortest possible time, whenever possible, patients should periodically be removed from their neuroleptics, if only for a short period, to determine if they are developing TD. Permanent removal from the neuroleptics is a more difficult matter, often requiring many months of gradual withdrawal for the brain to adjust to the drug-free environment. The best approach to neuroleptics, in this author’s opinion, is never to use them (chapter 16).

Because the neuroleptics suppress TD symptoms, some physicians have advocated their use for the treatment of TD. Harold Klawans\textsuperscript{[67]} has discussed the danger of trying to control or treat TD
with the causative agent. He asserts (in the discussion following Goetz et al., 1980 [50]), “Treatment of tardive dyskinesia with neuroleptics themselves is clearly treatment with the presumed offending agent and should be avoided.” He calls it short-sighted to use the neuroleptics in the treatment of tardive dyskinesia and concludes that the therapy “serves to aggravate its pathogenesis." Unhappily, Klawans himself, in the same article, too readily recommends reserpine as a helpful agent in the treatment of TD, because it also has neuroleptic effects and can cause the disorder.

Despite my serious reservations, I have seen cases of TD that were so disabling that the only recourse was treatment with a neuroleptic. But two points must be borne in mind about these cases. First, in each instance, the case became so severe because physicians failed to detect the TD when it first appeared and continued neuroleptic treatment long after it should have been terminated. This has been true in nearly all the most disabling cases I have examined. Second, the individuals in question were overcome with suffering and rendered wholly unable to function by the TD. They and their families were warned about the danger of worsening the TD and then made informed decisions to continue the offending agent because the TD was making life unbearable for the patient. By contrast, most patients who develop severe cases of TD have not been warned about the risk.

The anticholinergic drugs typically used to ameliorate the symptoms of drug-induced parkinsonism also may aggravate the symptoms of TD (Yassa et al., 1992 [109]). They include benztropine (Cogentin), biperiden (Akineton), and trihexyphenidyl (Artane, Tremin). These agents are known to worsen similar symptoms in Huntington’s chorea (Hunter et al., 1968 [59]; Klawans, 1973 [67]). At present, the role of these drugs in the development or exacerbation of TD is controversial and undetermined, but caution is required in giving them to patients on neuroleptics. These agents are often used to treat acute extrapyramidal symptoms and may be mistakenly prescribed for TD.

4.1.7 Extrapyramidal Symptoms as Predictors of Future TD

The neuroleptics produce a variety of acute, temporary neurological disorders referred to as extrapyramidal symptoms (EPS) in the great majority of patients. As described in chapter 3, drug-induced parkinsonism is one of the most common, probably occurring to some degree in the vast majority of patients exposed to effective doses of neuroleptics; akathisia is also very common. Dystonia, often characterized by cramping of the muscles of the neck and shoulders, is less common but can be extremely painful and disabling.

These acute EPS reactions often resemble TD, and indeed, the dystonias and akathisia can become tardive (persistent) disorders. All of them, including parkinsonism, result from neuroleptic effects on the dopaminergic neurotransmitter system in the basal ganglia.

I have already noted that the atypical neuroleptics can cause EPS and that studies indicating lower rates have sometimes used lower equivalent doses. A Taiwanese research team tried to determine the comparative frequency of EPS by examining the rates at which patients taking one or more of 14 different neuroleptics were coprescribed anti-Parkinson drugs (Yang et al., 2007 [106]). They found a tendency for the anti-Parkinson drugs to be prescribed less frequently to patients taking atypicals, but there was considerable overlap. Quetiapine had the lowest coprescribing rate (27%), but risperidone had one of the highest (66.5%). Mellairil was lower (61%) than risperidone, and loxapine was the highest (96%). A confounding factor, however, is the tendency for doctors to prescribe anti-Parkinson drugs as a prophylaxis and to prescribe them more readily if they consider the drug likely to cause EPS.

The question naturally arises, Do acute EPS increase the risk of TD? If acute EPS do predict an increase in future TD, then the emergence of EPS indicates an increased need to terminate the medication. These questions have been debated over the years, but recent research gives the best informed answer to date. In 2006 a prospective follow-up study of 9,298 patients by the European
Schizophrenia Outpatient Health Outcomes (SOHO) Study found a statistically significant correlation between baseline EPS and later TD. According to Tenback et al. (2006)\(^9\), “about half of the patients who developed tardive dyskinesia had earlier extrapyramidal symptoms”. They concluded that “drug regimens. . . that increase extrapyramidal symptoms are likely to result in increased risk of tardive dyskinesia.”

4.1.8 The Elderly and Other Vulnerable Populations

Medication adverse effects in general are more likely to develop in the elderly (Nolan et al., 1988\(^8\)). People who are elderly and people suffering from dementia are at extreme risk for many different adverse effects when exposed to neuroleptics. A recent study of administrative data from a health care insurer in the United States examined 959 cases of patients at least 45 years old who had been diagnosed with dementia, who had made a claim for at least one prescription drug, and who had been enrolled for 3 years (Kolanowski et al., 2006\(^1\)). They found that 29% of this community-dwelling population had been dispensed antipsychotic treatment, with a disproportionate number being female. The atypicals were the most commonly prescribed. Even when controlled for polypharmacy, age, and sex, the group treated with neuroleptics, either classic or atypical, had an increased risk of adverse events, including delirium, depression, hip fracture, falls, and syncope. Combined with research showing increased rates of cardiovascular problems and death as well as the metabolic syndrome, neuroleptics should be contraindicate in the elderly.

The vulnerability of the elderly is nowhere more apparent than in regard to TD. The two most recent editions of the Diagnostic and Statistical Manual of Mental Disorders (APA, 1994\(^4\), 2000\(^5\)) provide a consensus statement that sums up the degree of risk in the elderly, noting “prevalence figures reported up to 50% and an incidence of 25%-30% after an average of 1 year’s cumulative exposure to neuroleptic medication”. This is so hard to believe that it is worth paraphrasing: More than one-quarter of the elderly will develop TD within the first year of exposure!

In addition to age, prior brain damage probably increases the risk of TD (Breggin, 1983\(^b\); Chouinard et al., 1979\(^2\); McKeith et al., 1992\(^1\)). Cohen and Cohen (1993)\(^2\) found a correlation between TD and prior organic brain disorder.

Yassa et al. (1988)\(^1\) found that 41% of elderly patients developed TD over a period of only 24 months and that none fully recovered. None of the non-drug-treated controls made up of elderly patients developed spontaneous dyskinesias during the 2 years. Yassa et al. (1988)\(^1\) found TD in 45% of an outpatient clinic population with a mean age of 60. Yassa et al. (1992)\(^1\) found that 35.4% of patients developed TD after a mean exposure of 20.7 months. Saltz et al. (1991)\(^1\) found that the incidence of TD was 31% following 43 weeks of cumulative neuroleptic treatment in the elderly. The incidence was higher among patients who had previous electroshock treatment. Patients with early signs of parkinsonism developed TD at a faster rate. Of great importance, in this older population, the mean cumulative time while taking neuroleptics was very brief, a mere 22.7 weeks. One patient developed TD at 2 weeks.

Jeste et al. (1993)\(^6\), in an ongoing prospective study, found that 26% of middle-aged and elderly patients developed TD after 12 months. Reviewing the literature on neuroleptic withdrawal, the authors found “that almost 60 percent of the patients withdrawn from neuroleptics did not relapse over a mean period of 6 months”. They concluded, “It seems feasible to discontinue neuroleptic medication from a select population of older schizophrenic patients, if it is done carefully with adequate monitoring and follow up”. They also experimented with brief 2-week placebo-substituted withdrawal in their own group of patients, both younger and older patients, and found it relatively benign: None relapsed or required resumption of neuroleptics. They concluded, “Given the heightened risk of TD in older patients, it seems that a trial of neuroleptic withdrawal is warranted in this population.”

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would add that the same is true for all ages: Take as many as possible off these drugs.

Jeste et al. (1993) emphasized, “The potential seriousness of neuroleptic-induced TD warrants obtaining competent, informed consent to treatment from patients or guardians.” They recommended that consent be periodically renewed and cited other sources to confirm their position.

Woerner et al. (1998) studied a group of neuroleptic-naive patients aged 55 and above, evaluated them at baseline before the start of neuroleptics, and followed up at 3-month intervals. Relatively low doses of conventional neuroleptics were used: “The rates of TD were 25%, 34%, and 53% after 1, 2, and 3 years of cumulative antipsychotic treatment.” Once again, the rates were astronomically high: “A greater risk of TD was associated with history of [electroconvulsive therapy] treatment, higher mean daily and cumulative antipsychotic doses, and presence of extrapyramidal signs early in treatment.”

Jeste et al. (1999) concluded, “The risk of tardive dyskinesia in older outpatients is high, even with relatively short treatment with low doses of conventional neuroleptics.”

Although there appear to be few, if any, studies of the rates of TD induced by atypical drugs in the elderly, they, too, will undoubtedly be high. In the meanwhile, the other risks associated with atypical drugs in the elderly—including cognitive impairment, neuroleptic malignant syndrome, EPS, stroke, sudden death, hypertension, diabetes, pancreatitis, obesity, and elevated cholesterol—provide ample reason never to give these drugs to older people. Again, in rational and ethical medicine, the neuroleptics would be contraindicated-forbidden-in the treatment of the elderly.

4.1.9 Relapse, Exacerbation, and Delayed Onset After Termination

TD typically waxes and wanes, both in the course of a day and in the course of weeks or months. Especially in the elderly, both partial remissions and relapses are common (Lacro et al., 1994)

As in many neurological disorders, the manifestations of TD can worsen during stress and can be somewhat calmed with sedation (Jeste et al., 1993). In my clinical experience, and as confirmed by the literature, anxiety, exhaustion, and other general stresses to the mind and body can temporarily exacerbate the symptoms, while relaxation, when possible, can temporarily reduce them.

With great effort, patients can sometimes suppress some of their symptoms for a short time. As mentioned earlier in the book, they can also integrate their movements into more natural-looking actions, such as grooming or smiling, to disguise them. One patient with whom I consulted would hide her involuntary facial grimaces by trying to smile. Unfortunately, the effect was to make her look even stranger to the casual observer. Neither the fact that TD waxes and wanes, sometimes in response to stress, nor the patient’s ability to partially suppress it with an exertion of will should mislead observers into believing that it is psychological or emotional in origin. Too often, the early signs of TD are overlooked, denied, or dismissed by physicians on these mistaken grounds.

I have, on occasion, seen cases that did not become apparent until several months or more after termination of treatment. Christensen et al. (1970) have documented that a significant percentage of TD cases may not show up at all until many months or even several years after discontinuation of the treatment. They believe that the symptoms are brought on by the interaction between the damage caused by the drugs and by the aging process. If this is true, then a tragic reality may develop as we observe the evolution of TD in aging populations.

4.1.10 Reversibility is Rare

In the vast majority of cases, TD is irreversible, and there is no effective treatment. One report indicated that among patients with persistent TD, followed for a period of 5 years, 82% showed no
overall significant change, 11% improved, and 7% became worse (Bergen et al., 1989 [11]).

Another study followed 49 outpatient TD cases for a mean of 40 weeks (range 1-59 months) after discontinuation of medication (Glazer et al., 1990 [49]). Many patients showed noticeable improvement in their movements within the first year after stopping neuroleptics, but only 2% showed complete and persistent recovery. The authors conclude, “A major finding of this study is that complete reversal of TD following neuroleptic discontinuation in chronically treated patients was rare.”

With the increasing number of children receiving neuroleptics, in the last few years, I have evaluated several dozen cases of TD in youngsters. Atypicals like Risperdal and Zyprexa commonly cause TD in children. However, the rate of recovery in my experience seems better than in regard to adults, and I have seen a few cases completely resolve. Nonetheless, TD remains a catastrophic disorder in children in terms of its frequency, its incapacitating and disfiguring effects, its associated cognitive deficits, and the sheer number of children afflicted.

4.1.11 Physician and Patient Denial of TD

Physicians understandably find it painful to face the damaging effects of their treatments. Too often, it is difficult for them to confront the damage done to patients by other physicians as well. In addition, physicians may consciously seek to protect themselves or their colleagues from criticism or malpractice lawsuits by failing to acknowledge or to record obvious symptoms of TD. I have seen many hospital and outpatient records in which obvious, severe cases of TD have gone either unrecognized or undocumented, some times by several physicians in succession. For example, the nurse’s notes may make clear that the patient is in constant motion, yet the doctor’s physical examination or progress notes will give no indication of the disorder. Even official discharge summaries may fail to record TD in patients who have been demonstrating the disorder throughout the period of hospital or clinic treatment. Even when the TD diagnosis has been made during the hospitalization and can be found buried inside the chart, the diagnosis may not be put in the discharge summary, even though it is critical for future physicians to be warned about the patient’s condition in order to avoid further exposure to neuroleptics. This denial of the obvious is mirrored within the profession itself, which has been very remiss in recognizing or emphasizing the seriousness of the problem (for an analysis of this history of denial, see Breggin, 1983b [17]; Brown et al., 1986 [18]; Cohen et al., 1990 [26]; Wolf et al., 1987 [104]).

Psychiatrists sometimes accuse patients of exaggerating their TD. In reality, most patients tend to deny the existence or severity of their TD. As discussed in detail in chapter 5, patient denial is caused in part by neuroleptic-induced lobotomy effects and in part by denial associated with TD brain damage. Patient nonrecognition of TD symptoms is a reflection of the spellbinding effects of the drug when being taken and the continued spellbinding effect of the biological disorder itself.

The mutual denial of TD by physician and patient is an aspect of iatrogenic helplessness and denial - the use of brain-disabling treatments in psychiatry to enforce the patient’s denial of both his or her original personal problems as well as the iatrogenic brain dysfunction and damage (chapter 1).

4.1.12 The Size of the Epidemic

It is difficult to determine the total number of TD cases. Van Putten (as cited in Lund, 1989 [74]) estimated 400,000 - 1,000,000 in the United States. My own earlier estimate is higher, ranging in the several millions (Breggin, 1983b [17]). It is no exaggeration to call TD a widespread epidemic and possibly the worst medically induced catastrophe in history.
4.2 Tardive Dystonia

There are at least two relatively common variants of TD: tardive dystonia and tardive akathisia. According to Burke et al. (1982) [21], tardive dystonia involves “sustained involuntary twisting movements, generally slow, which may affect the limbs, trunk, neck, or face” (p. 1335). The face and neck are by far the most frequently affected areas of the body. Severe deformities of the neck (torticollis) can cause extreme pain and disability. I have seen several cases affecting the orbital muscles of the eyes (blepharospasm) to the degree that the individual’s vision was impaired, requiring botulinum (Botox) injections to paralyze the muscles. I have also seen respiratory and abdominal muscles affected in a painful and debilitating manner.

Tardive dystonia can produce cramplike, painful spasms that temporarily prevent the individual from carrying out normal activities. Sometimes the spasms are so continuous that the individual is largely disabled. Damage to the joint and skeleton system, including fractures, can occur (Burke et al., 1988 [20]). The pain and muscle tension as well as the effort to compensate for the spasms can be exhausting and demoralizing.

The torsions (twisting movements, often involving the neck) can be worsened by activity such as attempts to write or walk. Sometimes they can be relieved by particular movements such as touching the chin to relieve torticollis or touching the brow to relieve blepharospasm.

As Burke and Kang (1988) [20] pointed out, tardive dystonia can be mistakenly dismissed as a manifestation of hysteria or some other psychological problem: “In this regard it is important to realize that dystonia, like many other neurological disorders, can be influenced transiently by suggestion, placebo, or sedation (e.g., during an ambobarbital interview) and such maneuvers cannot exclude a true dystonia.” Also, like many other neurological disorders, it can sometimes be partially controlled by extreme exertions of will.

Tardive dystonia can make an individual appear unsympathetic or bizarre, especially to the uninformed observer, who equates the facial grimaces or neck distortions with being crazy. As in all the drug-induced dyskinesias, the individual may try to cover up the disorder with additional movements that make the disorder seem voluntary and therefore not a product of mental illness. The result can be very confusing and even distressing to the observer. I have read several medical records in which nurses recorded their complaints about supposedly rude patients who seemingly stuck out their tongues or made faces at them. The patients had undiagnosed TD. The nurses’ errors in clinical judgment delayed recognition of the disorder and speedy termination of the causative drugs.

In a 1988 review of tardive dystonia, Burke and Kang [20] found 21 reports describing 131 patients (for reviews, see also Greenberg et al., 1985 [52]; Kane et al., 1992 [63]). As already emphasized, because all the atypical neuroleptics are potent dopamine blockers (except clozapine), it should have been assumed that all of them could cause TD and tardive dystonia. Case reports confirm that risperidone (Vercueil et al., 1999 [101]; Narendran et al., 2000 [80]) and olanzapine (Gunal et al., 2001 [55]; Dunayevich et al., 1999 [40]) can cause tardive dystonia.

Tardive dystonia is a particularly painful, disabling, and intractable disease often requiring injections of Botox or even surgical excision of muscle to relieve the spasms. In a review of 107 patients by Kirikakis et al. (1998) [66], only 14% had a remission over a mean of 5.2 years from onset and 2.6 years after discontinuation of neuroleptics (range 1 month to 9 years). According to Kirikakis et al. (1998) [66], “discontinuation of neuroleptics increased the chances of remission fourfold”. Patients with 10 years or less exposure to neuroleptics had a 5 times greater chance of remission. Therefore, as in regard to TD in general, it is imperative to limit long-term exposure to neuroleptics and to stop them at the earliest sign of tardive dystonia.

Kirikakis et al. (1988) confirmed my experience that neck pain can be a precursor to cervical dystonia. Some patients also experience “odd somatic sensations heralding their tardive dystonia”.

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The most common presentations were blepharospasm (with or without oromandibular dystonia) or torticollis. Less common initial symptoms included pharyngeal dystonia, causing dysphagia, and oromandibular dystonia, causing severe disturbance. Other patients experienced dystonia of the limbs or trunk. Five had “very bizarre” disturbances of gait. The dystonia often progressed stepwise, involving additional parts of the body. Thirty percent of the patients also had TD, 22% had akathisia, 27% had parkinsonism, and 9% had a prior acute dystonic reaction.

Kiriakakis et al. (1988) concluded, “Tardive dystonia can develop at any time between 4 days and 23 years after exposure to [neuroleptics] and there is no ‘safe’ period.” It can afflict anyone independently of their psychiatric diagnosis, and patients with schizophrenia have accounted for only half of reported TD cases. From assorted studies, they estimate the prevalence at 2.8% among neuroleptic-treated patients.

In my clinical and forensic practice, I have consulted with and evaluated many cases of tardive dystonia, mostly involving the face, neck, and shoulders, but sometimes the torso. I see a disproportionate number of dystonia cases, probably because they suffer from considerable pain and disability and are therefore more likely to seek a clinical consultation or to hire me as a medical expert in a malpractice or product liability case.

In my clinical experience, patients who develop permanent dystonias during neuroleptic therapy are sometimes misdiagnosed with idiopathic (of unknown origin) dystonia. The argument is made that neuroleptic induced dystonia is rare compared to dystonia of unknown origin in the general population. However, the reverse is true. Friedman et al. (1987) [47] found a prevalence rate of tardive dystonia of 1.5% among chronically hospitalized patients, but as they pointed out, the rate in the U.S. population as a whole is a mere 0.00003% (0.3 per 100,000). When a persistent dystonia appears in association with neuroleptic exposure, by 500,000 to 1, the odds are overwhelming in favor of a diagnosis of tardive dystonia, rather than idiopathic dystonia.

4.3 Tardive Akathisia

Tardive akathisia involves a feeling of inner tension or anxiety that drives the individual into restless activity, such as pacing (see chapter 3 for details), although on occasion, it can occur with little or no display of hyperactivity. The first report of tardive akathisia that I was able to locate in the literature was published by Walter Kruse in 1960 [70]. He described three cases of muscular restlessness that persisted at least 3 months after discontinuation of treatment with the classic neuroleptics fluphenazine and triflupromazine. The “akathisic syndrome …consisted of inability to sit still, pacing the floor all day, jerky movements of arms and shoulders”. Once again, Delay and Deniker (1968) [35] were also among the first clinicians to notice the disorder. In discussing “syndromes persisting after cessation of medication,” they mentioned “hyperkinetic” ones. As early as 1977, Simpson [92] more definitively made an association between TD and irreversible akathisia. Gualtieri and Sovner (1989) [54] reviewed the subject of tardive akathisia, cited studies with prevalence rates of 13% to 18% among neuroleptic-treated patients, and called it “a significant public health issue”.

The anguish associated with both acute and persistent akathisia should not be minimized. Consider Van Putten’s (1974) [100] description of a mild, temporary akathisia or hyperkinesia: “Patient feels ‘all nerved up,’ ‘squirmy inside,’ ‘upright,’ ‘nervous,’ ‘tense,’ ‘uncomfortable,’ ‘impatient.’ …Subjective feeling of ill-being may be accompanied by restless changes in posture.”

One reason that so little attention has been given to the mental disruption associated with the dyskinesias is the tendency to blame the mental component on preexisting emotional problems attributed to the patient. Indeed, it has been commonplace to blame the obvious motor disturbances on the so-called mental illness, often resulting in increased treatment, and a worsening of the symptoms, until neuroleptic-induced immobility sets in, masking the entire process.
It takes no great imagination to grasp the suffering of a patient condemned to even a relatively mild tardive akathisia for a lifetime. I have seen cases of this kind that were previously mistaken for severe anxiety or agitated depression. Chapter 3 reviewed research indicating that acute akathisia can drive a patient into psychosis and to violence and/or suicide. Considering the millions of patients subjected to this torment, the problem takes on epidemic proportions.

Tardive akathisia can be subtle. A woman in her mid-60s consulted me because of seemingly bizarre feelings that other doctors attributed to her depression and to delusions or hallucinations. She had a feeling of “electricity” going in periodic bursts throughout her body. Although she sat quietly in the office, she spoke of feeling fidgety and driven to move about.

Her hospital and clinic charts disclosed that 2 years earlier, she had been treated for approximately 6 months with neuroleptics. The sensation she was describing had first been noted while she was taking the medication. I concluded that she probably had tardive akathisia, a subtle case that did not force her to move about. However, because she did not show external signs of the disorder, other physicians were reluctant to make the diagnosis. The patient felt “driven to distraction” and even to suicide, but after my diagnosis, she felt somewhat relieved. At last, a physician was taking her seriously and talking honestly to her.

In 1993, Gualtieri [53] wrote,

“In terms of clinical treatment and the public health, however, TDAK [tardive akathisia] is a fact, not a question. It is one more serious side effect of neuroleptic treatment, like TD and the Neuroleptic Malignant Syndrome. Taken together, they define neuroleptic treatment as a necessary evil, a treatment that should be administered with care and caution, and reserved for patients who have no other recourse.”

I agree with Gualtieri about everything, except for the “necessity” of this evil. It is entirely possible and even preferable to treat children and adults without resort to these highly toxic agents (chapter 16).

4.4 Complications of Tardive Disorders

TD is a complex disorder with mental and emotional effects that are often overlooked by health care providers. In my professional capacity as a doctor of last resort for patients with iatrogenic disorders, and as a medical expert on behalf of injured patients, I often am confronted with the task of evaluating the overall damage to patients and their families by the various tardive disorders, including classic TD, tardive dystonia, and tardive akathisia.

4.4.1 Physical Exhaustion

Fatigue to the point of exhaustion almost always accompanies tardive disorders of any severity. Patients often become exhausted by the movements, by the effort to hide them, and by increased difficulty associated with carrying out daily activities. The primary impact on the brain itself may also produce fatigue. Although the disorders tend to disappear in sleep, they can make it difficult to fall asleep, adding to the exhaustion. Having to contend with the physical pain associated with tardive akathisia (inner torment) and with tardive dystonia (muscle spasms) can also wear a person down.

Because of the fatigue, as well as any motor disabilities, patients are often unable to continue working. Many give up recreational activities such as bike riding, walking, and swimming. As a result, they gain weight and feel sluggish.
4.4.2 Psychological Suffering

Because TD often makes the sufferers look odd or even bizarre, they experience shame and humiliation, typically leading to lowered self-esteem and social withdrawal. Even a seemingly mild dyskinesia that affects facial expression can be sufficiently humiliating to cause a person to want to stay at home and away from people. Similarly, a speech abnormality that makes a person “talk funny” can lead to the avoidance of communicating.

The experience of constant pain from dystonia or inner torture from akathisia can drive a person to suicidal despair. The physical disabilities associated with disorders can also become very depressing to patients.

In a clinical report from the Mayo Clinic by Rosenbaum (1979) [88], depression was found to be closely linked to TD. Rosenbaum stated, “Almost all patients in our series had depressive symptoms accompanying the onset of tardive dyskinesia,” and he cited other studies confirming his observation.

TD patients often feel very betrayed by the doctors who prescribed the medication or who failed to detect the disorder or to tell the patients about it. Too frequently, perhaps in a self-protective stance toward their colleagues, several psychiatrists or neurologists in a row will fail to inform the patient or family about the obvious iatrogenic disorder. This neglect of the truth can leave patients feeling that they cannot trust psychiatrists.

Chapter 5 will look at impairments to mental functioning that are almost always found in patients with drug-induced tardive disorders. Overall, even a slight or minimal degree of tardive disorder can end up seriously impairing an individual’s quality of life.

4.5 Neuroleptic Withdrawal Symptoms

Withdrawal frequently causes a worsening mental state, including tension and anxiety. Drugs that produce potent anticholinergic effects, such as Thorazine and Mellaril, can cause cholinergic rebound that mimics the flu, including emotional upset, insomnia, nausea and vomiting, diarrhea, anorexia and weight loss, and muscle aches.

Withdrawal symptoms often include a temporary worsening of dyskinetic effects, both painful and frightening. As documented in chapter 3, withdrawal from neuroleptics commonly produces a level of emotional suffering and disturbance more severe than anything the individual experienced prior to starting the medication. In adults, this frequently manifests as psychotic symptoms worse than anything experienced prior to starting on the medication. In children, it can result in very disturbed behavior.

The atypical or newer neuroleptics are not free of withdrawal symptoms. In one of my cases, a young woman became extremely fatigued, depressed, and suicidal when withdrawing from Zyprexa. I have seen severe dyskinetic symptoms during withdrawal from Zyprexa, Risperdal, and Abilify. While on the drug, she was zombielike. Withdrawal took careful supervision over several months. Clozapine may have an especially marked withdrawal syndrome characterized by a worsening psychosis, angry or abusive language, hyperactivity, agitation and restlessness, dyskinesia, confusion, and aggressive or suicidal behavior (“Clozapine,” 1994). Chapter 5 will discuss a variety of neuroleptic withdrawal symptoms, including tardive psychosis.

How to withdraw from psychiatric drugs is discussed in chapter 15.
4.5.1 Are Neuroleptics Addictive?

While classic addiction to these substances has not been demonstrated, the antipsychotic drugs can cause severe withdrawal symptoms, making it impossible for patients to stop taking them. For this reason, I long ago suggested viewing these drugs as addictive (Breggin, 1989a [12], 1989b [13]). I believe that my earlier observations need modification. It is more accurate to say that neuroleptics create dependence in the form of withdrawal reactions that prevent patients from stopping them, but they do not cause the compulsive drug-seeking behavior commonly associated with dependence and with the older term addiction. Instead, individuals often find neuroleptics unpleasant, painful, or debilitating but cannot endure the withdrawal process.

For clarification, it is necessary to discuss the terms dependence and addiction. For generations, the term addiction had been used to describe the effects of drugs, such as alcohol, stimulants, and benzodiazepines, that cause physiological tolerance, physical withdrawal symptoms, and, in the extreme, compulsive drug taking that results in harmful physical, psychological, social, and economic consequences. Addiction is a term that continues to be used in the professional community that treats addicts as well as in the lay community. However, by one vote, a DSM committee voted to replace the term addiction with the term dependence in the DSM-III (APA, 1980a [6]), in part to remove some of the stigma. The result has been enormous confusion (O'Brien et al., 2006 [83]).

Many people exposed for months or years to psychiatric drugs such as the SSRI antidepressants and the neuroleptics find that they cannot easily withdraw from them, but they do not, like the classic addict, compulsively pursue drug seeking. Similarly, people treated for pain often become dependent on the opiates without necessarily seeking ever-increasing doses. For clarity, I propose using the term dependence to describe primary drug effects, such as tolerance and withdrawal symptoms, while reserving the term addiction for cases that involve compulsive, escalating, drug-seeking behavior. In short, antidepressants, neuroleptics, and some mood stabilizers cause dependence without causing addiction; stimulants, benzodiazepine tranquilizers, and related sleeping medications can cause both dependence and addiction.

Because of the withdrawal symptoms, it is often necessary to reduce neuroleptic drugs at a very slow rate. Sometimes withdrawal seems to become impossible. I describe the principles of safely withdrawing from psychiatric drugs in chapter 15.

4.6 Other Adverse Reactions

The neuroleptics can produce a variety of other symptoms of central nervous system dysfunction, including abnormal electroencephalogram (EEG) findings, an increased frequency of seizures, respiratory depression, and disturbances of body temperature control (Davis, 1980 [34]; Davis et al. 1975 [33]). Endocrine disorders, especially in females, may also be of central nervous system origin (Davis, 1980). There is some evidence that autonomic dysfunction can become irreversible (tardive autonomic disorders).

4.7 Neuroleptic Malignant Syndrome

This devastating disorder was seemingly so bizarre, unexpected, and inexplicable that physicians for years literally refused to believe their eyes. Seven years after the introduction of the drugs into North America, Leo Hollister (1961) [58] reviewed their side effects in the New England Journal of Medicine. In two separate places, he referred to syndromes that probably were NMS. He described a “bizarre” dystonic syndrome that can be “confused with hysteria, tetanus, encephalitis or other
acute nervous-system disorders; a rare fatality may occur”. Later, he mentioned, “Other clinical syndromes attributed to central nervous-system effects of these drugs have resembled acute encephalitis, myasthenia gravis, bulbar palsy or pseudotabes”.

Although NMS was identified in an English-language publication by Delay and Deniker as early as 1968 [35], physicians continued to be reluctant to recognize the syndrome. Delay and Deniker declared that it was caused by the neuroleptics, specifically including haloperidol (Haldol) and fluphenazine (Prolixin), although we now know that any neuroleptic can cause NMS, including the newer ones such as Zyprexa and Risperdal. Clinicians have also found an increased danger with long-acting injectable neuroleptics, probably because patients are unable to secretly cut back on the amount they are taking.

Delay and Deniker (1968) [35] were already able to identify many of the components of NMS, including pallor, hyperthermia, a severe psychomotor syndrome with akinesia and stupor, or hypertonia with varying dyskinesias. They warn that at the first suspicion, “one must stop medication immediately and completely”. They were already aware of fatalities. That the syndrome was named and definitively identified in English in 1968 is most remarkable in light of the failure of drug companies to give it formal recognition until compelled to do so by the FDA almost 20 years later (see chapter 13 for further discussion).

NMS is characterized by “such symptoms as severe dyskinesia or akinesia, temperature elevation, tachycardia, blood pressure fluctuations, diaphoresis, dyspnea, dysphagia, and urinary incontinence” (Coons et al., 1982 [28]). The DSM-IV-TR establishes criteria of severe muscle rigidity and elevated temperature plus 2 more of 10 associated features, including sweating, swallowing problems, tremor, incontinence, changes in level of consciousness from confusion to coma, mutism, elevated heart rate, unstable blood pressure, elevated white count, or laboratory evidence of muscle injury (e.g., elevated serum level of creatine phosphokinase, or CPK).

In my clinical and forensic experience, rigidity is too narrow a criterion for establishing NMS. Instead, the clinician should look for any acute, severe increase in abnormal movements, including any one or several of the movements associated with TD and tardive dystonia. Consistent with my experience, after reviewing episodes of NMS in 20 patients, Rosebush and Stewart (1989) [87] found that most cases fit the following cluster of symptoms: delirium; a high fever with diaphoresis; unstable cardiovascular signs; an elevated respiratory rate; and an array of dyskinesias, including tremors, rigidity, dystonia, and chorea. Patients spoke little during the acute illness and later reported that they had found themselves unable to express their anxiety and feelings of doom.

Almost all patients were agitated shortly before developing NMS, suggesting to Rosebush and Stewart (1989) [87] that they were undergoing akathisia. White blood cell counts were elevated in all cases, dehydration was common, and lab tests showed a broad spectrum of enzymatic abnormalities, including indications of muscle breakdown such as an elevated CPK.

If unrecognized, as too often happens, NMS can be fatal in more than 20% of cases. The syndrome frequently leaves the surviving patient with permanent dyskinesias and dementia (see chapter 5).

Most cases develop within the first few weeks of treatment (even within 45 minutes), but some develop after months or years or after increased dosage (Gratz et al., 1992 [51]).

Estimates for rates of NMS vary widely, but studies indicate that they are very high. Pope et al. (1986) [85] surveyed 500 patients admitted during a 1-year period to a large psychiatric hospital and found a rate of 1.4%. The cumulative rate for patients would be much higher. The authors remarked, “Neuroleptic malignant syndrome may be more common than previously thought and may be underdiagnosed.”

Addonizio et al. (1986) [2] carried out a retrospective review of 82 charts of male inpatients and found an even higher prevalence of 2.4% for diagnosed NMS. Again, the cumulative rate over repeated
hospitalizations or years of treatment would be much higher. Although it is sometimes called “rare,” NMS should be described as common or frequent (1/100 is common by FDA standards).

The rates for NMS, as well as its potential severity and lethality, make it an extreme risk for patients receiving antipsychotic drugs. A risk of this size would probably result in most drugs in general medicine being removed from the market.

As a medical expert, I have reviewed cases in which several physicians at a time missed making the correct diagnosis in what seemed, from my retrospective analysis, like an obvious case of NMS. The failure to stop the neuroleptic and to institute proper treatment resulted in severe, permanent impairments, or death. The mistaken idea that NMS is rare may contribute to these errors in judgment. In several of my forensic cases, the tendency to attribute anything strange to the patient’s mental illness played an obvious role in physician failure to make the proper diagnosis.

There is little or nothing about acute NMS to distinguish it from an acute, severe episode of encephalitis, especially lethargic encephalitis (also called von Economo’s disease), except for the fact of recent exposure to neuroleptic therapy. I have previously compared neuroleptic toxicity and lethargic encephalitis in detail (Breggin, 1983b [17], 1993 [15]; see also chapter 5).

Although Rosebush and Stewart (1989) [87] provided insufficient data to draw exact parallels, their NMS patients also suffered chronic impairments similar to those reported in lethargic encephalitis patients. Of the 20 patients, 14 continued to have “extrapyramidal symptoms or mild abnormalities of vitals signs and muscle enzymes at the time of discharge” (p. 721), but we are not told how many of the 14 specifically had persistent extrapyramidal signs. In a striking parallel with lethargic encephalitis, three patients displayed persistent parkinsonism symptoms until they were lost to follow-up. One patient, who had mild cognitive impairment prior to NMS, developed a persistent worsening of her dementia.

The DSM-IV-TR indicated,

“The essential feature of Neuroleptic Malignant Syndrome is the development of severe muscle rigidity and elevated temperature in an individual using neuroleptic medication. This is accompanied by two (or more) of the following symptoms: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and laboratory evidence of muscle injury (e.g., elevated creatine phosphokinase [CPK]).”

In my clinical and forensic experience, the emphasis on muscle rigidity is much too narrow. NMS can be accompanied by any kind of severe extrapyramidal reaction. Especially early in NMS, patients can display any of the wide array of neuroleptic-induced abnormal movements, including choreoathetoid movements, dystonia, and akinesia. Some cases look very much like severe TD, and often, the patients are left with persistent symptoms of TD.

NMS has been reported with the atypical neuroleptics clozapine (Anderson et al., 1991 [9]; Dasgupta et al., 1991 [31]) and risperidone (Dave, 1995 [32]; Mahendra, 1995 [75]; Raitasuo et al., 1994 [86]; Singer et al., 1995 [93]).

In 2007 Zarrour and Bhanot [110] published the most extensive recent review and identified 88 reports of NMS associated with six atypical neuroleptics: olanzapine, clozapine, risperidone, ziprasidone, quetiapine, and aripiprazole. As a warning to those doctors who cavalierly resume neuroleptics once the NMS has gone into remission, 20 cases showed a “clear history” of prior NMS, indicating that a patient’s first case of NMS predisposes toward another when reexposed to neuroleptics. Olanzapine (Zyprexa) has been touted as being relatively free of the risk of NMS, but the authors located 36 cases.

1Mycoglobinuria should be added to this list.
Zarrouf and Bhanot (2007) \(^{110}\) confirmed that NMS often leads to irreversible brain damage in the form of various manifestations of tardive dyskinesia, ataxia and balance problems; abnormal movements of the trunk and limbs; speech abnormalities; and violent, unilateral outbursts of movement (hemiballismus). NMS also left patients suffering from multiple cognitive disabilities including difficulties comprehending commands, attention problems, and persistent amnesia. Postmortem studies revealed “cerebellar degeneration, reduction of the Purkinje and granule cells, and gliosis in the dentate nucleus” (p. 93).

Zarrouf and Bhanot correctly find that “no conclusive evidence indicates which antipsychotic might lower a patient’s risk of recurrent NMS” (p. 94). NMS is one more devastating risk associated with all neuroleptics, including the newer atypicals!

Research indicates that typical and atypical neuroleptic drugs increase the vulnerability of neurons to cell death and even kill brain cells and that the risk increases in patients already suffering from brain disorders such as Alzheimer’s (chapter 9). Consistent with this, Sechi et al. (2000) \(^{190}\) reported on a case of NMS following exposure of a patient with familial dementia with Lewy bodies to low doses of risperidone.

### 4.8 Biological Basis of Neuroleptic-Induced Neurological Syndromes

Drug-induced parkinsonism apparently develops in part, but not wholly, from blockade of dopamine receptors in the basal ganglia, specifically the striatal region or striatum (the caudate and putamen), producing motor retardation, rigidity, and other symptoms. Damage and degeneration in the pigmented neurons of the substantia nigra play a key role. These neurons terminate in the striatum, where, when functioning normally, they release dopamine to act on striatal dopamine receptors.

TD is a more delayed reaction, probably based in part on the development of reactive supersensitivity or hyperactivity in these same striatal dopamine receptors following continuous blockade (see APA, 1980b \(^{11}\); Fann et al., 1980 \(^{42}\); Klawans, 1973 \(^{67}\); and chapter 5 in this volume). This supersensitivity of the dopamine receptors becomes most obvious when the drug is reduced or eliminated, terminating the blockade. The overactive, unblocked receptors produce the TD symptoms. Undoubtedly, a great deal more must be learned about the neuropathology of both these drug-induced diseases, which probably involve multiple neurotransmitter system abnormalities. However, if health care providers were to stop prescribing these drugs to patients, the problem would virtually disappear.

More recent studies have indicated that TD may be the result of complex interactions between dopamine and the cholinergic system, which becomes more active when the suppressive or balancing effect of the dopaminergic system is blocked by the neuroleptics. In addition, the neuroleptics are directly toxic to neurons by means of disrupting a number of separate biochemical pathways (chapter 5).

### 4.9 Children and Neuroleptics

In recent years, unscrupulous physicians have been pushing for the increased prescribing of neuroleptic drugs to children. The main justification has been the diagnosis of bipolar disorder in children, a complete sham based on nothing more than the assumption that certain common childhood behaviors, such as anger and agitation, are precursors to adult bipolar disorder. These drug advocates have largely ignored the manifold serious risks associated with giving neuroleptics to children, including tardive dyskinesia (see previous discussion), brain cell damage and brain shrinkage (chapter 5), obesity, and diabetes. Nor have these drug advocates considered the difficult-to-measure risks
associated with bathing the growing brain in toxins.

In an editorial titled “Gaining: Pediatric Patients and Use of Atypical Antipsychotics,” published in the American Journal of Psychiatry in December 2006, Tobin [97] stated:

“Recent studies of overall pediatric use have shown a 6- to 20-fold increase in prescription of atypical antipsychotics in four state Medicaid programs and, nationally, a sixfold increase in pediatric visits that included prescriptions of antipsychotic medication, more than 90% of which were prescriptions for atypical antipsychotics.”

Tobin claims that there are some good justifications for prescribing antipsychotic drugs to children but warns about the drugs causing excessive weight gain and type II diabetes. After showing this concern, does the editorial recommend cutting back on prescribing atypical antipsychotic drugs to children? No. Does the editorial recommend stopping the drug when children and adolescents begin to show signs of drug-induced weight gain? No. The editorial recommends continuing the neuroleptic while adding the highly experimental and potentially dangerous drug metformin (Klein et al., 2006 [68]), which is used for treating type II diabetes. As a result of its determination to prescribe neuroleptic drugs to tens of thousands of children, psychiatry has created a major public health threat to the physical health of America’s youth.

There has also been an increase in children displaying manic-like symptoms consistent with a manic episode or bipolar disorder. Prior to the advent of Prozac in 1989, I never saw a child with genuine manic symptoms. Since then, I have seen an increasing number. Why? Every single case of childhood bipolar disorder or mania that I have seen has resulted from an adverse drug reaction, usually to the newer antidepressants such as Prozac or Paxil, and on fewer occasions, to stimulants like Ritalin and Adderall. In no case have the offending health care providers admitted that the disorder was caused by their prescribed medications. At the most, they told parents that the drug had unmasked a preexisting bipolar disorder, a claim wholly lacking in scientific foundation.

As a result of the increased prescription of drugs like Zyprexa, Risperdal, and Geodon to children, I am seeing an increasing number of TD cases in young people. I have personally evaluated well over a dozen cases involving Risperdal and an additional number caused by Zyprexa and Geodon, several of which I describe in detail in Medication Madness (in press).

In my experience, TD is no less frequent in children than in adults, and it can be more severe, often involving the torso and causing difficulties with gait (see Breggin, 1983b [17], for a review). As already mentioned, children seem more resilient than adults, and I have seen several cases that have improved dramatically and a limited few that have gone into remission after withdrawal of the drug. Sometimes the gradual improvement has required many months, subjecting the child to a lengthy disability.

The stigmatizing consequences of TD are even more devastating to children than to adults. I evaluated one 10-year-old child who largely recovered from a severe case caused by Risperdal, leaving her only with an occasional abnormality of her eye muscles that caused her eyes to briefly roll up inside her head, showing the whites. Imagine how she is going to feel when she develops an interest in boys and realizes, on her own or through humiliating experiences, that little boys will not feel comfortable watching a little girl’s eyes roll up inside her head.

4.9.1 Treating Childhood Tourette’s with Neuroleptics

One of the most tragic situations in the treatment of children today involves the use of neuroleptics for the control of Tourette’s disorder. Tourette’s involves a combination of tics and spontaneous, inappropriate vocalizations, such as curse words. While claims have been made for biological origin,
none has been demonstrated. On the other hand, it extremely well documented that neuroleptics frequently produce TD in children with far more disabling tics, spasms, and other abnormal movements.

The devastating effects of neuroleptics in children diagnosed with Tourette’s often go unrecognized. Dulcan (1994) \(^{39}\) reported that the symptoms of Tourette’s can be exacerbated for several months following withdrawal from neuroleptics. Brun (1988) \(^{19}\) reviewed 208 cases. She found that 34 suffered from drug-induced dysphoria that appeared in the form an “organic affective syndrome,” 9 from a drug-induced worsening of their Tourette’s, 5 from aggression and hostility, 3 from “fog states,” and from “frank psychomotor seizures”. A number of the children endured drug-induced akathisia, which worsened their emotional and neurological condition. The author also noted the appearance of withdrawal dyskinesias. Three of the children developed symptoms of TD, which, the author reported, resolved over a period of weeks or months.

I have evaluated several children and young adults who developed severe cases of tardive dyskinesia following neuroleptic treatment for Tourette’s. One, a 20-year-old man who had been treated with Risperdal, eventually recovered from Tourette’s. However, his drug-induced severe abnormal tongue movements and jaw spasms have required treatment with Botox, and he may never fully recover from them. He had been able to live a happy and largely unimpaired life with Tourette’s; but the TD has severely impaired his school, occupational, and social life.

The use of neuroleptics for the treatment of Tourette’s does not meet a reasonable medical standard in terms of its risk:benefit ratio.

### 4.9.2 The Food and Drug Administration Opens the TD and NMS Floodgates for Children

On October 6, 2006, the FDA \(^{45}\) announced its approval of Risperdal for the treatment of “extreme irritability” in autistic children. The only way Risperdal can reduce this so-called extreme irritability (anger and temper tantrums) is by deactivating the frontal lobes, limbic system, and reticular activating system, causing a chemical lobotomy with emotional blunting. Since Risperdal is a potent dopamine blocker, it has this capacity.

A primary effect will be the further impairment of the autistic child’s already limited ability to care about and relate to other people. Risperdal will make children more autistic. In many cases, it will also worsen the child’s so-called irritability by causing agitation and akathisia. But in the process of making children more robotic, it will make some seem less troublesome.

Worst of all, the FDA’s limited approval of the drug for treating extreme irritability in autistic children will further encourage the widespread, off-label use of this devastating drug in large numbers of children with behavior problems. Risperdal is already frequently prescribed off label with no scientific justification to a wide range of children, usually with the aim of suppressing unwanted behaviors. The FDA’s action will greatly encourage this abusive use of the drug, ultimately causing a new wave of TD, tardive dementia, and tardive psychosis among children.

After I had written these concerns about the increasingly widespread use of Risperdal for treating children, the FDA (2007d, August 22 \(^{46}\)) took an even more reckless step when it made this announcement:

> “The U.S. Food and Drug Administration today approved Risperdal (risperidone) for the treatment of schizophrenia in adolescents, ages 13 to 17, and for the short-term treatment of manic or mixed episodes of bipolar I disorder in children and adolescents ages 10 to 17. This is the first FDA approval of an atypical antipsychotic drug to treat either disorder in these age groups.”
Risperdal, with its potent capacity to block dopamine $D_2$ receptors, is the least “atypical” of all the so-called atypicals. Most of the cases of TD in children that I have evaluated have been caused by Risperdal. As you read in chapters 5-2 about the devastating toxicity of the “antipsychotic” drugs, keep in mind that America’s drug watchdog agency has, turned on its children by unleashing one of the worst iatrogenic disorders upon them.

4.10 Hurrying Death

Until the advent of neuroleptic drugs, it was observed that patients diagnosed with schizophrenia lived normal life spans, unless subjected to the violent and unhealthy environments of state mental hospitals (Breggin, 1991c [14]). Since the advent of neuroleptics, almost every patient in the Western world diagnosed with schizophrenia ends up being afflicted with a variety of neurological disorders induced by neuroleptics as well as the risk of many other serious disorders, such as stroke, heart disease, obesity, and diabetes.

In 2006 Joukamaa [64] and colleagues, in the British Journal of Psychiatry, examined the mortality rates for patients diagnosed with schizophrenia in a representative population sample of 7,217 Finns aged 30 and over. A comprehensive health and psychiatric examination, including previous medical records, was utilized, and the patients were followed up for 17 years. At that time, 39 of 99 individuals had died. The relative mortality risk between those with schizophrenia and others was 2.84 (95% confidence interval [CI] 2.06-3.90). According to the authors, “the number of neuroleptics used at the time of the baseline survey showed a graded relation to mortality”. Still short of willing to face the reality, the authors concluded, “There is an urgent need to ascertain whether the high mortality in schizophrenia is attributable to the disorder itself or the antipsychotic medication.”

There cannot be any question whether the lethal agent is schizophrenia or the neuroleptics. There are no known physical disorders, not even any abnormal lab tests, associated with the diagnosis of schizophrenia, whereas the neuroleptic drugs are cytotoxic and cause numerous physical disorders of the brain and body from diabetes and liver disease to unexplained sudden death. They also produce apathy and indifference as their primary effect, greatly reducing the capacity of an individual to respond to the early onset signs of heart disease, stroke, and other illnesses that require immediate treatment. In April 2005, the FDA (2005b) [44] issued a public health advisory that the use of atypical antipsychotics to treat elderly patients with dementia was associated with an increased risk of death in placebo-controlled clinical trials. In June 2005, Health Canada issued a similar warning. The trials that provided the data involved risperidone, olanzapine, quetiapine, and aripiprazole. Mortality was approximately 1.6 to 1.7 times higher when compared to placebo.

In 2007 [48], Gill et al. examined antipsychotic use and mortality in older adults with dementia in Ontario, Canada, over a 5-year period (see also Medline Plus, 2007[78]). A total 27,259 matched pairs were identified. Comparisons were made between atypical neuroleptic exposure and no antipsychotic drug exposure and between atypical neuroleptic drug exposure and conventional antipsychotic drug exposure. Patients were in community or in long-term care. The risk of death was assessed at 30, 60, 120, and 180 days after the initial dispensing of the antipsychotic drug. Both the older and the atypical neuroleptics were associated with an increased risk of death at all assessment times, including 180 days, by a factor of 1.31-1.55 times. Conventional antipsychotics had a greater risk than atypicals at all points in time. The authors concluded,

“Our study provides further evidence that use of atypical antipsychotics is associated with a small but significant increase in mortality among older patients with dementia. In addition, the risk of death associated with antipsychotics is apparent after as little as 1 month of use and may persist for six months.”
4.11 Conclusion

The widespread use of neuroleptics has unleashed an epidemic of neurological disease on the world. Even if TD were the only irreversible disability produced by these drugs, this would be among the worst medically induced disasters in history. In reality, the antipsychotic drugs also reduce the quality of life, cause multiple severe and potentially lethal physical disorders, and shorten the life span.

Meltzer (1995) [79] urged that attempts be made to remove long-term patients from neuroleptics and tried to demonstrate its feasibility. Gualtieri (1993) [53], warning about the extreme dangers, suggested that neuroleptics be viewed as a necessary evil and a therapy of last resort. I believe that the profession should make every possible effort to avoid prescribing antipsychotic drugs. Meanwhile, the FDA-driven escalation in prescribing these drugs to children and adolescents should be stopped.

As a step toward a more ethical psychiatry, the use of any neuroleptics in the treatment of children should be prohibited. In the long run, if psychiatry entirely gave up the use of neuroleptics, it would find that psychosocial approaches are much less risky and much more genuinely effective. Chapter 5 will examine some of these better alternatives.
Bibliography


