

Recognition of Movement Disorders: Extrapyramidal Side Effects and Tardive Dyskinesia. Would You Recognize Them If You See Them?



Elizabeth Pulsifer Anderson



Edward B. Freeman

Anti-emetic, anti-spasmodic and prokinetic medications commonly used in gastroenterology are neuroleptics, a class of drugs which includes anti-psychotics used for schizophrenia. These medications are capable of causing serious and potentially permanent side effects. The manifestation of neuroleptic drug side effects may range from dramatic and debilitating to very subtle. It has been demonstrated repeatedly that these side effects often go unrecognized. Doctors prescribing prokinetics, anti-emetics and anti-spasmodics need to be able to recognize these side effects. A full description of the most common movement side effects and the corresponding medical term is included as a resource list for professionals and patients.

BACKGROUND

Any drug capable of causing Extra Pyramidal Side effects (EPS) and Tardive Dyskinesia (TD) is *by definition* a neuroleptic, Latin for “seize the neuron.” It is widely assumed that only patients

Elizabeth Pulsifer Anderson, Director, Pediatric Adolescent Gastroesophageal Reflux Association, Inc. (PAGER). Edward B. Freeman, M.D., Psychiatrist, Private Practice, Killeen, Texas.

who are being treated for psychiatric disorders such as schizophrenia are at risk for neuroleptic side effects, yet several gastroenterology drugs have the same side effect profile as Thorazine. Patients taking these medications need to be monitored carefully to prevent potentially irreversible side effects.

Psychiatrists have long been trained to recognize the signs and symptoms of EPS and TD and a great deal of physician education has been aimed at them,

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Because it is impossible to predict which patients may develop symptoms, familiarity with the numerous GI drugs capable of causing neuroleptic reactions is essential.

EPS and TD are documented with the use of metaclopramide, domperidone, cisapride, promethazine, prochlorperazine, perphenazine, hycosamine sulfate and other belladonna alkaloids, ranitidine, chlorpromazine, thiethylperazine maleate, trimethobenzamide, ondansetron hydrochloride, phenothiazines, baclofen and rabeprazole. Symptoms suggestive of EPS or isolated reports of movement disorders are associated with scopolamine, olsalazine, mesalamine and balsalazide disodium, cimetidine, esomeprazole, omeprazole and pantoprazole.

yet it has been well documented that they often miss the symptoms. In some studies, experts in the field pick up twice as many cases of tardive as newly trained psychiatrists.

Most other physicians have never been trained to recognize the many different manifestations of EPS and TD. These conditions can be particularly difficult to recognize in children, even for those with specific training.

The relationship between neuroleptic medications and movement disorders is extremely complex and confusing. A neuroleptic may cause movement symptoms in a patient, but the same drug can also temporarily suppress the symptoms or delay the onset of symptoms for the same patient. Symptoms often first appear during withdrawal of the medication. Movement symptoms can occur spontaneously, but they are often clearly induced by medication. The best way to avoid permanent movement disorders is to use neuroleptics very cautiously and to monitor patients closely for emerging symptoms.

TERMINOLOGY

There are two major classifications of movement disorders, dystonias and dyskinesias. There are also two time frames used to classify the onset of symptoms.

Dystonias are spasms of individual muscles or groups of muscles. They can be sustained or intermittent, sudden or slow, painful or painless. They can affect

any of the body's voluntary muscles including those of the vocal cords. The movements of dystonias can appear very bizarre and deliberate but are involuntary.

Dyskinesias are involuntary, often hyperkinetic movements of various types that have no purpose and are not fully controllable by the patient. Some are random, some rhythmic, most are very odd looking and socially stigmatizing. They can affect the ability to initiate or stop a movement as in Parkinson's. They can affect the smooth movement of a joint resulting in a jerky articulation. Abrupt and seemingly violent movements of a limb are common as are gyrations of any body part. Tics and involuntary vocalizations are related to dyskinesias.

Extrapyramidal Side Effects (EPS) describes movement side effects that begin during the early phases of treatment with a neuroleptic drug. Early onset symptoms tend to resolve quickly and completely when the patient is weaned from the offending medication(s). The word refers to symptoms originating in a specific part of the brain that refines and modulates movement.

Tardive Dyskinesia/Dystonia (TD) simply means late onset of the same EPS movement side effects. They can appear after months of trouble free treatment, or they can begin to appear as the dose is lowered or the drug is withdrawn. Symptoms generally appear shortly after drug withdrawal although they can appear months later. The previous cut off of three months post withdrawal is now being questioned. Tardive reactions may resolve quickly, but these late reactions are more likely to be persistent or permanent. Symptoms that persist for six to twelve months are considered to be permanent although they may diminish slightly over the course of several years.

Masking is the term used to describe the ability of the drug to cover the toxic symptoms it is producing.

EPIDEMIOLOGY

Studies of movement symptoms in patients taking neuroleptics for schizophrenia show prevalence rates ranging from .5% to nearly 70%. Studies examining this wide range of published prevalence rates show the discrepancies are most likely due to the skill of the

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observer. Movement disorders caused by motility and antispasmodic medications in the treatment of gastrointestinal diseases are widely believed to be rare. This assumption is probably dangerous and inaccurate. Small studies of metoclopramide in particular show EPS and TD in up to 30% of patients. Given the devastating and potentially permanent nature of TD, extreme care should be taken to use neuroleptic drugs only when absolutely necessary and in the lowest doses possible.

RISK FACTORS

Most risk assessment studies on EPS and TD have been conducted in patients with schizophrenia. In these patients, TD is associated with older age, higher medication doses and longer treatment periods; i.e. total exposure. Females also appear to be a higher risk.

Concomitant treatment with any additional drugs capable of causing neuroleptic side effects is likely to increase the risk of EPS and TD. This includes both traditional antipsychotics and the newer, "atypical" antipsychotics which still carry some risk. Substances as common as alcohol and cold medications have some risk of TD and EPS. Caution is needed as well with patients taking anticonvulsants, antihistamines, barbituates or antidepressants as some drugs in these categories have a high risk of EPS and TD.

Underlying "soft neurological" factors or mental retardation are significant risk factors in the development of TD.

Many experts caution that tapering down to drug free periods a few times a year is necessary to ascertain whether a patient has "covert" symptoms that are being masked by the continuing use of the drug. Other experts believe that this cycling on and off for "drug holidays" can provoke a tardive reaction and is an additional risk factor.

RECOGNIZING SIDE EFFECTS OF NEUROLEPTICS

Movement symptoms may be so subtle that a psychiatrist or neurologist who specializes in movement disorders may be the only expert to pick them up. But in many unfortunate patients, the symptoms are visible from blocks away.

Movement symptoms are generally not present during sleep, can worsen with stress, and patients can often suppress these symptoms for a short period of time through intense concentration. Movement symptoms may be present uniformly throughout the day, or they may have a diurnal pattern. Some specific movement symptoms are more troublesome during resting and abate during voluntary movement. Other specific symptoms are only problematic during voluntary movement.

Movement symptoms can wax and wane over time and deliberate provocation may be necessary to elicit the symptom in a clinical setting. This is typically done by distracting the patient with conversation or asking them to perform a mental task, such as math, that requires intense concentration. Tongue and facial symptoms are often the first to appear and a thorough neurological exam involves careful observation of the tongue in the mouth and sticking out.

EPS and TD can mimic disorders such as Parkinson's Disease, Tourette's Syndrome, Huntington's Chorea, tics, cerebral palsy, stroke and hyperactivity. They are often mistaken for psychiatric disturbances and patients may be shunned.

During episodes of dystonia, opposing muscles that should relax contract. This can result in a limb that appears distorted. One of the most common manifestations is an ankle that twists and won't bear weight. In some cases, muscle groups that should be uninvolved in the activity being attempted will get involved. The result can be shoulders that swing violently during walking or an entire arm and shoulder that cramp and contort while the hand is holding a pen. In some instances, the opposing hand/arm/shoulder may also contort in a perverse sympathy.

Some patients find quirky tricks that can short circuit a dystonia or dyskinesia. For example, a few patients with torticollis find that stroking their jaw or touching the back of the head can stop the muscle spasms. A case report describes one patient with a severe gait disturbance who found that tossing a small object from hand to hand allowed him to walk more normally. For this reason, patients should be asked about any odd mannerisms.

In addition to causing movement disorders, neuroleptics used in gastroenterology are capable of causing

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Localized Symptoms	
Body area	Associated movement symptoms
Neck/spine symptoms	Muscle spasms of the neck (cervical) which pull the head to the side (torticollis), forward and down (antecollis), or up (retrocollis) are often painful. An extreme bending at the waist is rare (Pisa Syndrome or pleurothotonus). The most extreme form of back arching can bring the entire body off the bed except the back of the head and the heels (opisthotonus). Pelvic rocking or gyrations (axial hyperkinesia) may appear to be self stimulating or sexual in nature. Jackknifing refers to abrupt bending at the waist.
Gait/walking disorder	A disorganized walk (ataxia) may be as subtle as a foot rolling in occasionally, or as dramatic and absurd as a Monty Python routine. The patient may appear clumsy, stumbling, clomping or drunk. An inability to start walking as if glued to the floor and then an inability to stop, or a shuffling walk are characteristic of tardive Parkinsonism.
Oral facial symptoms	Oral-mandibular/buccal-lingual symptoms include chewing motions (sometimes called 'Wrigley Sign'), biting with nose wrinkling ('Rabbit Syndrome'), tongue probing in the cheek ('Bon Bon Sign'), grimacing, pouting and repetitive swallowing. The jaw may open or shut or lock (trismus/lockjaw) making eating difficult. The tongue may protrude rapidly ('Fly Catcher') or hang flaccidly (tonic). The patient may make sucking/kissing/smacking/clicking noises. The patient may bite their own cheeks or tongue. Eyebrows may raise ('Spock eyebrows') or lower making the person appear haughty or angry. Symptoms confined to the lower face may be called Miegé's Syndrome. Tooth grinding (bruxism) may occur during sleep. Some symptoms can be aborted by touching the lips or other tricks. Some patients with tardive Parkinsonism lack facial expressions (mask-like facies) and they may drool.
Finger movements	Finger movements often resemble playing 'Air Guitar', 'Air Piano' or a particular movement called 'milkmaid grip'. Writer's cramp is a severe spasm of the entire hand or arm. The opposing arm may also cramp. This is more than fatigue and may be induced by fine motor activities other than writing. 'Pill rolling' finger movements (rubbing the thumb and fingers in a motion similar to the gesture meaning 'money') are more common in drug-induced Parkinsonism.
Limb symptoms	Flailing movements involving a whole limb may appear combative like a punch or karate kick (ballismus), or may appear like raising a hand to ask a question. This is one of the few movements that occur during sleep. Some patients with tardive Parkinsonism have limb movements that are jerky and have a ratchet-like quality (cog wheel rigidity).
Eye symptoms	Blinking of both eyelids (blepharospasms) may be so severe that the patient is legally blind. The eyes may be rolled in any direction (oculogyric crisis).
Vocalizations, breathing, swallowing	Vocal tics such as grunting, throat clearing, swearing (coprolalia), and echoing words or sounds (echolalia) are possible. The vocal cords may spasm (dysphonia) making the voice choppy, quavery, breathy or cause a hoarse sounding noise when breathing in (stridor). The vocal cords may clamp shut (Laryngospasm/obstructive apnea/dysepea). The speech may be slurred (dysarthria) or have a quality normally associated with brain damage (bulbar). Swallowing may be uncoordinated (dysphagia).

a host of other symptoms that may not be automatically connected with the drug: drooling, autonomic instability, depression, cognitive slowing, confusion, flat affect, agitation, restlessness, irritability, headaches, disordered thinking, memory changes, altered sensations or perceptions, word retrieval problems, and many others.

MONITORING MOVEMENT SYMPTOMS

The Abnormal Involuntary Movement Scale, (AIMS) is available online and provides one quick and systematic way to assess a variety of common movement symptoms. This scale is not useful for distinguishing between the many types of movement disorders and it

General Symptoms	
Medical Term	Description/examples
Akathisia	An inner feeling of restlessness, which compels the patient to pace, march, fidget or wiggle although some patients are able to sit still. In infants, this is more likely to look like air boxing or air cycling. Restlessness may manifest as insomnia. It may be perceived as an uncomfortable inner vibration. Patients may call akathisia anxiety.
Chorea/choreic	Dance-like movements of any body part or the whole body.
Myoclonus/ myoclonic	Involuntary movements that are sudden and violent in appearance as if struck by lightning or hit by an invisible assailant.
Tics	Gilles de la Tourette Syndrome may be drug induced.
Vermicular/ atreoid	Worm-like writhing movement of any body part or the entire body.
Bradykinesia	Slowing of voluntary movements (bradykinesia) can affect any body part or the whole body. In rare cases there can be a complete lack of movement (akinesia).
Resting Tremor	Shaking of a resting limb or tongue that tends to subside during deliberate movements. The opposite of alcohol induced tremors which are worse during intentional movement.
Neuroleptic Malignant Syndrome	The most dangerous side effect of anti-psychotics is Neuroleptic Malignant Syndrome. This potentially fatal reaction is characterized by "lead pipe rigidity," high fever, dehydration, sweating, elevated blood pressure, fast heart rate and respiration, agitation, elevated white blood cell count, difficulty swallowing and autonomic instability.
Paroxysmal	Very abrupt movements

cannot distinguish drug induced symptoms from spontaneous ones. Several other scales are commonly used and a full discussion of their merits and proper uses can be found in "Assessment of drug-related movement disorders in schizophrenia." Since different clusters of symptoms can suggest different treatments, a full exam by a movement specialist may be desired.

TREATMENT

Treatment of movement side effects that appear early during treatment (EPS) is generally accomplished by slowly withdrawing the drug or lowering the dose. When the drug is being used to treat a major psychiatric illness such as schizophrenia, withdrawal of the drug may not be feasible. Anticholinergic medications may be helpful in EPS, but generally are not. Beta blockers have also been tried.

Treatment of late onset (TD) movement symptoms and syndromes can be much more complex. Withdrawal of the drug may need to be undertaken very slowly and drugs to counteract the symptoms may be

tried. Unfortunately, anticholinergic drugs are generally not as helpful with late onset symptoms and may occasionally cause paradoxical exacerbation. Consultation with a movement disorders specialist may be helpful and in complex cases referral may be necessary.

The long list of drugs that may be used to reduce TD symptoms attests to the difficulty in treating this iatrogenic disease. Many cases of TD do not respond well to currently available treatments and there are many new treatments being investigated including vitamins that act as free radical scavengers. Vitamin E and vitamin B₆ have both shown benefit in preventing the development of TD although they have not been effective in treating the disorder once it has developed. Research is being conducted on the use of branch chain amino acids.

PEDIATRIC CONSIDERATIONS:

Recognition of movement side effects in children is particularly problematic. Infants are more likely to have box-
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ing arm movements, cycling leg movements or generalized hypertonia, all of which are uncommon in adults. A gait disturbance may not be apparent in a child who is just learning to walk. Motor restlessness in a pre-schooler can look like urinary urgency. Early onset EPS or TD can look like cerebral palsy. How do you distinguish between biting due to a dystonia and a temper tantrum?

Back and neck arching in an infant may be due to pain, an infantile spasm, a seizure, acid reflux induced Sandifer Syndrome or dystonia. A pediatric movement disorders specialist may need to examine the child in order to make a definitive diagnosis.

Non-movement side effects of neuroleptics are also more difficult to recognize in children. Small children can't tell us that they have a headache, that they are having memory trouble, that their senses are not functioning correctly, or that they are suffering from a mood change. How do you distinguish hormonal changes of puberty from the hormonal changes (gyncomastia, amenorrhea) due to prolactin fluctuations caused by a neuroleptic? How do you distinguish drug-induced muscle pain (arthralgia) from the pain of the disease you are treating? How do you recognize psychosis, dementia or even a sleep disorder in a baby? There is a wide range of developmental levels within the range of "normal" making subtle deficits difficult to spot. One author (Anderson) recently met a toddler who was believed to be profoundly retarded while on metaclopramide. His "intractable seizures" stopped the day after withdrawal and he was walking and talking after several months of intense therapy (personal communications with parents and doctor).

To further complicate matters, children metabolize many drugs differently. Children have an undeveloped blood-brain barrier which can leave them more susceptible to CNS involvement where none would be expected in an adult. Children with acute illness or dehydration seem to be at additional risk for dystonias. Many common medications can exacerbate neuroleptic side effects. In addition, pediatric formulations of some drugs contain alcohol which can exacerbate or precipitate movement symptoms and many other side effects. Of particular concern is the alcohol in pediatric ranitidine. One of the side effects of ranitidine is an interference with the normal clearance of alcohol that can magnify the effects of the alcohol by a factor of ten.

Children and the elderly are recognized to be at additional risk of EPS and TD from neuroleptics used for psychiatric illnesses. It is reasonable to assume that they are at increased risk when using neuroleptics for gastrointestinal ailments. The lack of recognition means that any estimates about the rarity of side effects are suspect. A few pediatric gastroenterologists no longer use neuroleptics for just this reason.

LEGAL CONSIDERATIONS

There have been many lawsuits filed by patients experiencing TD. *The Journal of the American Academy of Psychiatry and the Law* and *the Journal of Clinical Psychiatry* have both printed review articles describing the many legal issues raised. According to "Tardive Dyskinesia: Tremors in Law and Medicine," most suits have alleged malpractice but there have also been suits alleging failure to obtain written informed consent, torts violations, failure to monitor, inappropriate reassurance that the TD/EPS symptoms were not drug related, failure to follow standards of care, failure to refer to a neurologist, product liability, etc. Institutionalized psychiatric patients have filed suits alleging civil rights violations. This article is written jointly by a forensic psychiatrist and an attorney. It summarizes the circumstances, arguments and rulings from dozens of individual cases and is available online.

"Update on Legal Issues Associated with Tardive Dyskinesia," a section of a the *Journal of Clinical Psychiatry Supplement on TD*, contains a history of the use of neuroleptics and is more medically oriented. It explains concepts such as determining when the statute of limitations clock is likely to start in language accessible to doctors. It gives practical guidelines for physicians who want to avoid lawsuits. The author explains that, "In determining causation, the law is more interested in the straw that broke the camel's back than in all the straws already piled on its back." He includes a quote from a 1984 article; "The impending flood of tardive dyskinesia litigation has begun. I think that there is an enormous backlog of cases that is going to plague us for years." He also warns that the pendulum is swinging in the direction of trying to link all movement disorders to neuroleptics. Indeed, there are now class action law suits for patients who took metaclopramide and were damaged.

RECOMMENDATIONS

To avoid EPS and potentially irreversible TD, neuroleptics must be used at the lowest possible doses, for the shortest possible duration, only when clearly indicated and when there is no safer alternative. Patients should be monitored closely and frequently for emerging symptoms using standardized movement rating scales. Possible side effects should be fully disclosed via written informed consent documents and the doctor should initiate an ongoing dialog about this topic with the patient. The doctor should consider alerting family members since they often become aware of movement disorders before the patient does.

Resources

Journal of Clinical Psychiatry, 2000, Volume 62, Supplement 4, "Update on Tardive Dyskinesia" contains 9 articles (57 pages) on aspects of TD. CME credit is available. This supplement includes the article, "Update on Legal Issues Associated with Tardive Dyskinesia." The supplement may be ordered on line at <http://www.psychiatrist.com/order.htm>

Psychotropic Drug Directory, 2001, Stephen Bazire and William Benfield Jr., Quay Books, Mark Allen Publishing. This book contains a full list of drugs capable of causing movement disorders, mood disorders, sleep disorders, etc., (Chapters 5.8-5.9) with citations for each entry. It also has a section on the treatment of movement disorders (Chapters 1.20-1.22) with citations to relevant articles for each entry. Order online at <http://www.markallengroup.com/quaybooks/>

"Tardive Dyskinesia: Tremors in Law and Medicine," Neil S. Kaye, MD, FAPA, and Thomas J. Reed Esquire. *Journal of the American Academy of Psychiatry and the Law*, 1999; Volume 25, No 2. Viewable online at <http://www.courtpsychiatrist.com/tardive.html>

Details of pediatric hypertonia symptoms are available in "Classification and Definition of Disorders Causing Hypertonia in Childhood," *Pediatrics*, 2003; Vol 11, No 1. Available in PDF format online at <http://pediatrics.aappublications.org/cgi/reprint/111/1/e89.pdf>

"Assessment of drug-related movement disorders in schizophrenia," Maurice Gervin and R.E. Thomas *Barnes Advances in Psychiatric Treatment*, 2000; 6: 332-341. This article contains a discussion of several movement rating scales and reviews methods of conducting them that can reduce the variability of the results. Available online at <http://apt.rcpsych.org/cgi/content/full/6/5/332>

WE MOVE

(Worldwide Education and Awareness for Movement Disorders)
204 W. 84th Street
New York, NY 10024
Tel: 212-875-8312

Fax: 212-875-8389

www.wemove.org and www.mdvu.org

Dystonia Medical Research Foundation

One East Wacker Drive, Suite 2430

Chicago, Illinois 60601-1905

Tel: 312-755-0198

In Canada: 800-361-8061

Fax: 312-803-0138

dystonia@dystoniafoundation.org

(information packet, videos, list of movement disorders clinics and tardive experts available for a donation)

National Institute of Neurological Disorders and Stroke

6001 Executive Blvd.

Rm. 8184, MSC 9663

Bethesda, MD 20892-9663

nimhinfo@nih.gov

http://www.ninds.nih.gov/health_and_medical/disorders/tardive_doc.htm

Tel: 301-443-4513 TTY: 301-443-8431

Fax: 301-443-4279

American Psychiatric Association Task Force on Late Neurological Effects of Antipsychotics Drugs. Copies of the report are available from APA, Publications/Sales Department, 1700 18th Street, NW, Washington, DC 20009. Cost is \$11.00 for 204 page report.

There are currently at least 16 books on tardive that appear on internet searches.

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Patients and professionals who suspect movement symptoms in patients taking any medications should file a MedWatch report with the FDA. Medical professionals are not required to file reports so consumers are urged to file their own with the information available to them. MedWatch reports are compared to prevent double counting of events if multiple reports are filed. Contact the FDA at www.fda.gov/medwatch or 800-FDA-1088.