Antipsychotic Drug-Induced Movement Disorders

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ABSTRACT: Very early in the process of diagnosing abnormal involuntary movement (AIM) disorders, one can be rewarded by keeping a high index of suspicion for possible drug-induced causes, not only through a complete list of current medications, but also identification of the drugs the patient used to take and other possible offending medications that might be available from family members and other sources. Among drug-induced movement disorders, antipsychotic drugs and other dopamine receptor blocking agents occupy a central place. Their various acute and tardive motor complications provide the template of this short review. Movement disorders caused by antidepressants, lithium, antiemetics, antiparkinsonian agents, anticonvulsants, calcium channel blockers, sympathomimetics and others are only briefly covered in table form.

RÉSUMÉ: Troubles du mouvement induits parles antipsychotiques. L'une des questions fondamentales dans le diagnostic et la prise en charge des troubles du mouvement est de déterminer si une médication est en cause. Ceci nécessite de toujours rester sur ses gardes et d'obtenir non seulement une liste complète de la médication actuelle mais aussi une histoire pharmacologique détaillée de la médication antérieure ou disponible auprès des proches ou d'autres sources. Les antipsychotiques et autres bloqueurs des récepteurs dopaminergiques occupent une place dominante au sein des troubles du mouvement iatrogènes. Les complications motrices tant aiguës que tardives qu'ils engendrent sont au coeur de cette courte revue. Les troubles du mouvement causés par les antidépresseurs, le lithium, les anti-émétiques, les anti-parkinsoniens, les anti-épileptiques, les bloqueurs des canaux calciques, les sympathomimétiques et divers autres agents sont abordés seulement sous forme de tableau.

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The true cause of movement disorder may well be overlooked completely unless a physician has a good understanding of the many possible offending medications. One can approach the topic of drug-induced movement disorders in two ways: starting with the movement disorder itself and trying to think of possible offending drugs, or starting with the offending drug to identify possibly related movement disorders (see Table). In most reviews on this topic, side effects from neuroleptic (a term derived from the Greek "which takes the nerves" proposed in 1955 by Delay and Deniker) drugs receive special attention due to the high prevalence and long recognition of abnormal involuntary movements (AIMs) in patients using these medications. This article is no exception and provides a description of acute and tardive drug-induced AIMs and their different phenomenologic subtypes. The interested reader is referred to *A Guide to the Extrapyramidal Side-Effects of Antipsychotic Drugs* by Owens for more details.[1]

Acute dystonic reactions

An acute dystonic reaction consists of sustained, often painful muscular spasms, producing twisting abnormal postures. Approximately 50% of reactions occur within 48 hours of initiation of a dopamine receptor blocking agent, 90% within five days.[2] These reactions are more common with parenteral than oral medications. The incidence rate of acute dystonic reactions with high-potency classical antipsychotics has been difficult to estimate from retrospective studies and reported figures are quite variable. Recent studies suggest that they are not uncommon and affect 30-40% of patients exposed to classical antipsychotic drugs.[3-4] Haloperidol and the long-acting depot fluphenazines have the highest incidence of these reactions. They are 15 times more common in the young than old[5] and, contrary to traditional teaching, not necessarily more common in males than females.[3-4] A relation between drug potency, dose, rapidity of titration and acute dystonia has also been proposed on clinical grounds, but a clear correlation between the clinical manifestations and drug blood concentrations is lacking.[6] The rate and rapidity of receptor

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Table: Drug-induced movement disorders: main offending drugs.

Movement disorders	Drugs
Parkinsonism	Presynaptic monoamine depleters
	Reserpine, tetrabenazine
	Dopamine receptor blocking agents
	"Classical" antipsychotics
	"Atypical" antipsychotics (low incidence)
	Antiemetics/antivertigo (metoclopramide, prochlorperazine, promethazine, thiethylperazine)
	Trifluoperazine/isopropamide (Stelabid™)
	Calcium channel blockers
	Flunarizine, cinnarizine
	Acetylcholine release stimulant
	Cisapride
	Selective serotonin reuptake inhibitor
	Fluoxetine
	Miscellaneous (often anecdotal)
	Amiodarone
	Valproic acid
	Lithium
	Methyldopa
	Vincristine
Dyskinesias (acute/tardive)	Dopamine receptor blocking agents (see above)
	Levodopa
	Dopamine agonists (low incidence)
	Anticholinergics
	Antidepressants
	Lithium (usually in toxic range)
	Anticonvulsants (esp. with co-existing brain lesions)
	Benzodiazepines
Tremor – resting	Dopamine receptor blocking agents
	Calcium channel blocking agents
	Amiodarone
Tremor – postural	Antidepressants
	Lithium
	Valproic acid
	Sympathomimetics (bronchodilators)
	Cimetidine
	Thyroxine
	Steroids
	Antineoplastics
Tremor – action/intentional	Anticonvulsants
	Benzodiazepine withdrawal
	Antiarrhythmics
	Cyclosporine
	Antibiotics (ofloxacine, cotrimoxazole)
Myoclonus	Antibiotics
	Sulfamides
	Anticonvulsants
	Antidepressants
	Tricyclic
	Lithium
	Monoamine oxidase inhibitors
	Calcium channel blocking agents
	Levodopa
	Amantadine
	Theophylline
	H_1 or H_2 antihistaminics toxicity
	Isoniazide
	Baclofen
	Opiates
	Anesthetics
Dystonia	"Classical" antipsychotics
	Antiemetics
	Antidepressants
	Anticonvulsants (rare)
	Levodopa
Akathisia	"Classical" antipsychotics
	Benzodiazepine withdrawal
	Antidepressants
	Anticonvulsants
	Lithium
	Calcium channel blockers
Tics (rarely iatrogenic)	Antipsychotics (chronic use and drug withdrawal)
	Stimulants (methylphenidate)

occupancy in the brain is probably more relevant. The risk is higher in patients with a prior history of a similar reaction or a family history of dystonia.[7]

Acute dystonic reactions vary greatly in intensity and are often part of a spectrum of neurobehavioral and affective manifestations including vague prodromal symptoms of nervousness and restlessness that may progress to feelings of stiffness and tension, unpleasant motor uneasiness, or painful sensations, followed by objective motor signs familiar to neurologists. According to retrospective data,[8] the most frequent types include torticollis (30%), and glossal dystonia (17%), trismus (15%), oculogyric crisis (6%), opisthotonos (3.5%). Trunk movements can include scoliosis, flexion (including the so-called Pisa syndrome consisting of lateral trunk flexion),

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retrocollis, or dystonic gait. Rarely, life-threatening laryngeal adductor spasms can occur. The movements may then fluctuate over hours and temporarily abate in response to reassurance. This can lead to an inappropriate diagnosis of hysteria. They may last from minutes to hours without treatment. Occasionally the movements are more choreiform. They are more typically generalized in young patients and more focal in older patients.

Oculogyric crisis usually occurs as a side effect of antipsychotic drug treatment. It is the most common of the ocular dystonic reactions (which include blepharospasm, periorbital twitches, and protracted staring episodes). The clinical spectrum though is poorly understood, leading to the frequent mislabel of a psychogenic disorder. It is often not realized that, in addition to the acute presentation, oculogyric crisis can develop as a recurrent syndrome, triggered by anxiety. The onset of a crisis may be sudden or stuttering over several hours. Initial symptoms include restlessness, agitation, malaise, or a fixed stare, followed by the more characteristically described maximal upward deviation of the eyes in a sustained fashion. The eyes may also converge, deviate upward and laterally, or deviate downward. The most frequently reported associated findings are backward and lateral flexion of the neck, widely opened mouth, tongue protrusion, and ocular pain.

The pathophysiology of acute dystonic reaction secondary to antipsychotics remains unknown. A deficit in central dopamine transmission results in overactive striatal acetylcholine release,[9] consistently reversed by anticholinergic drugs to alleviate acute dystonia. The “miss-match” theory, whereby the acute blockade of postsynaptic dopamine receptors is overcome by the compensatory increase in dopamine turnover as drug levels decline, is not supported by experiments conducted in antipsychotic drug-exposed monkeys with acute dystonia, showing worsened dystonia with co-administration of the tyrosine hydroxylase inhibitor α-methyl-para-tyrosine, and improvement with dopaminergic drugs.[10] Other neurotransmitter systems may well be involved.

The treatment[5] consists of the administration of parenteral anticholinergics (e.g. benztropine 2 mg I.V., repeated q. 15 min if needed for a maximum cumulative dose of 6 mg). If the reaction persists, procyclidine 5 mg I.V. or diphenhydramine 10 mg I.V. may be given. Diazepam 5 mg I.V. can also be effective. Anticholinergics should be continued orally for 48-72 hours depending on the half-life of the offending drug used. If the antipsychotic treatment is to be continued, usually the anticholinergic can be safely tapered over two to three weeks. Some evidence suggests that long-term concomitant anticholinergics predispose to tardive dyskinesia (TD). Routine prophylaxis with these medications would be appropriate in patients with a previous proven risk for dystonic reactions.

Acute akathisia

Akathisia (inability to sit still) was a term introduced to describe restlessness in psychiatric patients and later to describe restlessness resulting from encephalitis lethargica. It is now used to describe the restlessness observed in patients secondary to antipsychotics, typically manifested by excessive voluntary movements. The movements are stereotyped motor patterns such as pacing, body rocking, or foot tapping. Occasionally akathisia can result in repetitive vocalizations. Some authors now describe these movements as “stereotypies” associated with an abnormal subjective sensation. The movements seen can mimic a variety of other movement disorders. The key in the diagnosis is the history of irresistible restlessness or inner urge to move. These movements tend to decrease in amplitude with distraction (like tics) and seem less bothersome when lying down (unlike tardive stereotypies). The body movements involved in akathisia tend to be more in caudal body parts as opposed to tardive stereotypies, which are more prominent rostrally. Occasionally the inner subjective feeling of restlessness is absent. The term “pseudoakathisia” has been used in this situation.

Akathisia is common with prevalence and incidence rates in the order of 20-30%.[2,11] The symptoms typically starting within days of exposure but may be delayed as long as several weeks (evident in the first two to three months in 90% of cases). There is no age or sex predisposition. Akathisia may slowly subside with continued therapy but often persists, resulting in poor medication compliance. This condition is often misdiagnosed as increased agitation, resulting in higher doses of antipsychotics further aggravating the situation.

It is thought that the mesocortical dopamine tracts may be involved in the genesis of akathisia. Blockade of the mesocortical dopaminergic system results in similar hyperactivity in rat models. The role of other neurotransmitters including GABA, opioids, and serotonin is uncertain. The pathophysiology of acute akathisia must be different from tardive akathisia since increasing the dose of the antipsychotic makes acute akathisia worse while often improving tardive akathisia.

The key in the clinical approach is prevention, and failing that, early recognition. When akathisia is distressing, decreasing the dose of the offending medication should be the first approach. When this is not possible, switching to an antipsychotic drug of a lower potency would be favored. If this fails, treatment with the beta-blocker propranolol or an anticholinergic may help to a variable degree up to 50% of patients.[1] In cases lacking coexistent parkinsonian features, propranolol is the first drug of choice and the dose administered is usually low (20-60 mg/day) but varies. Anticholinergic drugs, commonly given to prevent acute dystonia especially in high-risk patients, are controversial as some feel long-term prophylaxis increases the risk of tardive AIMs. Benzodiazepines and amantadine are acceptable third-line choices.

Drug-induced parkinsonism

Drug-induced parkinsonism (DIP), albeit variable in delay of onset, typically occurs early following antipsychotic drug initiation or dose escalation. The symptoms occur within one month of starting the drug in about 40% of cases and within three months in 90% in those treated with a classical antipsychotic,[2] and within 9-12 months in those using calcium channel blockers. This is probably the most easily-understood side effect of dopamine transmission blocking agents, but problems with definition, recognition, distinction from depression or the negative symptoms of schizophrenia, as well as pre-existing parkinsonian features in drug-naive subjects, have made prevalence estimates practically impossible to establish. At least

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15% of antipsychotic-exposed patients develop DIP. It is not infrequent to see DIP, akathisia, and other dyskinesias simultaneously. Minor extrapyramidal features can be identified on examination as early as the fourth day of treatment in elderly patients. The drugs most often provoking DIP are listed in the Table.

Clinical phenomenology is indistinguishable from Parkinson's disease.[12] Drug-induced parkinsonism is more likely to be symmetric and less likely to be associated with tremor. However, a clearly asymmetric pattern may be seen in about one-third of older patients[13] and tremor-dominant cases have been described. One sign is a low frequency oral-facial-nasal type of tremor termed "rabbit syndrome". This occurs in 3% of cases.[14] The earliest feature is akinesia with loss of arm swing. The rigidity tends to lack the cogwheel phenomenon. Tremor, when it does occur, is more likely to be seen with posture and action as opposed to just at rest. There is a higher prevalence (exceeding 50%) of this complication in elderly patients. It is reportedly twice as common in females than males. Concomitant structural brain pathology likely constitutes a predisposing factor in some cases. About two-thirds of patients will recover within two months on average but some may take over six months for their parkinsonian signs to resolve.[12] Milder parkinsonism can persist in 11% of cases in the elderly.[12] Patients with incomplete recovery following drug withdrawal may actually have idiopathic Parkinson's disease.[15]

Drug-induced parkinsonism is caused by underactive dopamine transmission along the nigrostriatal circuitry. One explanation for the higher incidence of parkinsonism in elderly patients implicates the age-dependent loss of dopamine neurons. The management of DIP focuses on the offending drug which should be reduced, discontinued, or switched to a less potent drug. Palliative approaches have not been studied thoroughly. Anticholinergics such as procyclidine or trihexyphenidyl are traditionally prescribed. Treatment should be reassessed periodically to clarify the persistence of the problem. Amantadine, acting primarily as a noncompetitive antagonist at glutamate N-methyl-D-aspartate receptors at therapeutic dosing,[16] has produced antiparkinsonian benefit[17] with a favorable adverse effect profile in psychiatric patients, and may be preferred in the elderly. Dopaminergic drugs (levodopa, agonists) have not attracted much interest because of fear of exacerbating psychosis. However, the absolute risk appears low[18-19] and these drugs may be carefully administered in selected cases as third-line agents.

TARDIVE DYSKINESIAS (TD)

Movement disorders of delayed onset during chronic antipsychotic drug therapy have been recognized since the late 1950s but the term TD was not introduced until the mid-60s. In the past TD specifically referred to the classical rhythmic oro-facial movements, with lip smacking and puckering, chewing movements, and slow writhing movements of the tongue in the floor of the mouth ("buccolinguomasticatory dyskinesia"). It is also used to describe the more generalized involuntary movements following antipsychotics. More recently the term "tardive stereotypies" has been used for classical, patterned oro-facial movements. Stereotypies can be defined as an involuntary, coordinated, patterned, repetitive, purposeless movement or utterance. Stereotypies can be seen in a variety of medical conditions including autism, mental retardation, Rett's syndrome, restless legs syndrome and akathisia. Up to 15% of nonmedicated schizophrenic patients are thought to have involuntary movements,[20] the prevalence reaching 50% in older institutionalized subjects.[21] It is also reported that 1-4% of the normal elderly develop "spontaneous" orofacial dyskinesias.[22,23] Careful characterization of such cases is lacking.

The prevalence of TD among patients chronically treated with antipsychotic drugs varies between 0.5-56% in the literature, with an average estimate of 25%. The incidence in young adults is about 4-5% per year.[24] The aging process, affecting pharmacokinetic and pharmacodynamic parameters in many ways, is the most consistent and significant risk factor affecting TD development. Many other debated variables have been reported to influence risk including female gender, affective disorders, organic brain dysfunction, high cumulative drug exposure (dose x duration), the presence of early extrapyramidal side effects following treatment initiation, the use of high potency antipsychotics (haloperidol, fluphenazine) or depot preparations, and the concomitant use of anticholinergics. Diabetes has been reported to increase the risk of TD.[25]

Scattered information about genetic vulnerability leading to an increased risk of AIMs has been emerging over the years. Metabolism of most drugs influences their pharmacological and toxicological effects. Genetic polymorphisms have been described for many drug-metabolizing enzymes. Two of the most important enzymes for metabolism of antipsychotic drugs and other psychoactive drugs are the cytochrome P450 2D6 and 1A2. Tardive dyskinesia was found with a higher incidence in patients that were heterozygous carriers of 2D6 mutated alleles than in patients without CYP2D6 mutations.[26] Recent genetic studies have also confirmed a small contribution to the risk of TD associated with dopamine D_3 receptor gene Ser9Gly polymorphism.[27]

According to DSM-IV criteria, the minimal length of antipsychotic drug exposure necessary to link dyskinesia with the drug is three months for those under age 60, and one month in those age 60 and older, acknowledging the fact that elderly individuals are more prone to TD induction for reasons that remain elusive. The course of TD is uncertain and unpredictable, and reported remission rates are extremely variable. It may improve over the years, sometimes at the expense of worsening of parkinsonism in psychiatric inpatients who remain on antipsychotic drug treatment.[28] The risk of persistent AIMs directly correlates with the duration of antipsychotic drug exposure: the longer the tardive movements are present, the less likely they will resolve.

It has been recognized that reduction or abrupt discontinuation of antipsychotics can produce new movement disorders or exacerbate pre-existing ones. These disorders are described as "withdrawal dyskinesia" or "withdrawal emergent dyskinesia". Others describe this phenomenon as "reversible tardive dyskinesia". Although a continuum from withdrawal dyskinesia to TD may be present, this has so far not been proven. Withdrawal emergent dyskinesia occurs mainly in children with a prevalence around 20%.[1] The minimal length of use or dosage of antipsychotics required to produce withdrawal emergent

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dyskinesia is unclear. The dyskinesia typically occurs within two weeks following dose reduction or discontinuation. This is then followed by rapid improvement over several weeks or rarely two to three months. To date there is no definite proof that patients who have demonstrated withdrawal emergent dyskinesia are at a higher risk of going on to develop TD.

The most common and typical tardive stereotypies are the repetitive orofacial and lingual movements that resemble chewing, lip smacking, tongue protrusion ("fly-catching") or lateral tongue movements in the floor of the mouth ("bonbon sign"). Often the patient is unaware of these early movements which are often predictive of further development. Other examples of tardive stereotypies include repetitive and patterned hand waving, toe waving, body rocking, and head bobbing. More complex movements consist of leg crossing, standing and sitting, picking at clothes, rubbing the face and head, shifting weight, as well as marching. Abdomen and pelvic muscle involvement can produce pelvic rocking ("copulatory stereotypy"). Vocal stereotypies include humming, moaning, and altered breathing patterns ("respiratory stereotypy"). Facial stereotypies improve when protruding the tongue and tend not to involve the upper face, distinguishing these movements from those seen in Huntington's disease. Tardive stereotypies are accentuated by distraction such as writing or performing rapid alternating movements and they may be suppressible but to a much lesser degree than tics.

Tardive dystonia has a special place among TD manifestations because of the disability and pain it may produce, and its distinctive pathophysiological and therapeutic features. Tardive dystonia is indistinguishable clinically from idiopathic torsion dystonia except that it has a higher incidence of retrocollis and opisthotonic posturing. Unlike typical idiopathic dystonia, tardive dystonia may improve with action and is usually not helped by sensory tricks. Tardive dystonia differs from TD for an earlier age of onset and male predominance (2:1 ratio). The onset of tardive dystonia can occur as early as three weeks and 20% of patients are affected within the first year of exposure to the antipsychotic. The exact prevalence rate is unknown but appears much lower than for typical TD, ranging from 1-2%[29] to 13%.[30] However, these patients are far more likely to be referred to neurologists for management. The overall remission rate is low, around 14%, and may occur late after stopping the offending drug.[31] Most patients progress for the first few months to a year and then stabilize. The pharmacological substrate for tardive dystonia is also different than that in TD as anticholinergics are beneficial in 45% of these patients.

Tardive akathisia is another late and persistent complication of antipsychotic drug treatment similar to acute akathisia, albeit less distressing and uncomfortable in its chronic form. The pharmacological approach to acute and tardive akathisia is clearly different, tardive akathisia often behaving like TD. A withdrawal-emergent subtype can emerge within six weeks of drug discontinuation or substantial dose reduction. Aside from treatment regime issues (potency, dosage, route), no definite predisposing factors have been identified. Approximately one-quarter of patients chronically exposed to typical antipsychotics show persistent akathisia. Leg and/or trunk movements are commonly observed.

Other unusual chronic antipsychotic drug-induced movement disorders include: 1) tardive chorea; 2) tardive tics; 3) tardive myoclonus, typically postural and treated with clonazepam; 4) tardive tremor, a coarse postural and action tremor sensitive to tetrabenazine.[32]

The pathophysiology of TD is not understood but striatal dopamine (D_2) receptor supersensitivity has been the traditional and oversimplistic explanation, based on the pharmacological blockade and substantia nigra pathology documented in a Danish postmortem study.[33] There are several problems with this hypothesis: 1) the late appearance of AIMs, yet receptor supersensitivity is seen early; 2) dopamine receptor supersensitivity is likely present in all patients but only 25 % get tardive AIMs; 3) tardive movements often persist after drug withdrawal even though there is a resolution of supersensitivity; 4) TD is not seen with presynaptic dopamine depleting agents that can also induce dopaminergic receptor supersensitivity. Other transmitter systems are likely involved.[34]

A gamma amino butyric acid (GABA) hypothesis has been suggested whereby antipsychotics induce the destruction of a sub-population of GABA neurons in the striatum which might result in an imbalance between the so-called direct and indirect striato-pallidal efferent pathways to promote the development of TD. Although such process has never been clearly demonstrated, animal studies have correlated a decrease in the (external) pallidal levels of mRNAencoding glutamic acid decarboxylase, the rate-limiting enzyme in GABA synthesis, with the presence of oral movements in rats chronically treated with haloperidol.[35] This suggests reduced GABA outflow from the external pallidum that should, in principle, cause parkinsonism. Other rat studies still suggest that conventional antipsychotic drugs have more widespread and potent effects on GABA transmission in the basal ganglia than newer antipsychotics associated with a lower incidence of TD.[36] These physiological abnormalities may affect thalamocortical neural pathways to promote TD.

A third hypothesis is related to an excess of free radicals producing cytotoxic damage. Typical antipsychotics can induce reactive oxygen species in cell culture,[37] induce lipid peroxidation and decrease forebrain levels of antioxidant defence enzymes in rats.[38] There are some studies suggesting free radical scavengers, including vitamins E and B6, may be helpful in management. A meta-analysis combining studies published in the '90s demonstrated that a significant subgroup showed improvement in AIMs with vitamin E.[39] Unfortunately, a prospective, double-blind, randomized controlled trial for up to two years with vitamin E (1600 IU/day) has shown no benefit.[40] The hypothesis remains attractive and evidence of the antidyskinetic efficacy of high doses of melatonin (10 mg/day) in a recent placebo-controlled pilot trial[41] will certainly fuel the search for other potent antioxidants as prophylactic and palliative agents in TD.

Some investigators hypothesize that antipsychotic drugs enhance striatal glutamatergic neurotransmission by blocking presynaptic dopamine receptors, causing neuronal damage as a consequence of oxidative stress. Cerebrospinal fluid from schizophrenic patients with TD had significantly higher concentrations of N-acetylaspartate, N-acetylaspartylglutamate, and aspartate than patients without TD.[42] These findings suggest that changes in glutamate homeostasis and transmission may be relevant to the pathophysiology of TD. Improvement in TD

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scores in some patients with amantadine[43,44] suggests that overactive glutamatergic pathways participate in TD production and that it is possible to manage TD with such drugs without exacerbation of psychosis. Research has also demonstrated abnormalities in a variety of other peptide systems including cholecystokinin, neurotensin, and opiates. Further work is needed to delineate the significance of these neurochemical findings in TD.

As TD can be disabling, potentially persistent and refractory to all approaches, the emphasis needs to be placed on prevention rather than treatment. Patients on chronic therapy need to be advised of the risks and, in view of their possible lack of awareness of the problem, reviewed periodically to screen for early and mild manifestations. The prospective use of clinical rating scales, such as the Abnormal Involuntary Movement Scale and the more recent and extensive Extrapyramidal Symptoms Rating Scale, is extremely helpful in the rigorous assessment and prevention of TD and should be stimulated.

In general, antipsychotics should be used only when psychosis is present and ideally should not be used for anxiety, depression, or insomnia. Chronic use of drugs such as metoclopramide should be avoided. There are alternative medications with a far lower risk of tardive movement disorders. If antipsychotics are to be used chronically, the lowest effective dose should be used and the need for these medications should be reassessed every four to six months. Frequent antipsychotic drug holidays are now believed to increase the risk of persistent TD and are not generally recommended. Chronic concomitant use of anticholinergics also appears risky. This may increase the incidence of TD.

The first step in the management of disabling TD is to attempt to withdraw the offending drug, if possible. This can transiently increase TD severity. If discontinuation of the antipsychotic is impossible, switching to a less potent drug would be the next option. The risk of AIMs with the second generation (so-called "atypical") antipsychotics is much less than with conventional drugs. The patient with withdrawal dyskinesia can be reassured that the condition usually disappears within a few weeks; if the patient's movements become so severe that they impair day-to-day activity, the clinician may decide to reintroduce the antipsychotic drug at a lower dose and taper more slowly. Another option, particularly when anxiety is prominent, could be to prescribe benzodiazepines for a short period of time.

If TD persists despite the above interventions, the drug of choice is tetrabenazine (Nitoman™), a presynaptic depletor of monoamines interfering with the vesicular monoamine transporter type 2; it is effective in controlling these movements in up to 50% of cases. Its half-life is short (6.5 hrs) but its main metabolite (hydroxytetrabenazine) is also pharmacologically active with a half-life of 10 hrs, so that a BID-TID regimen is sufficient.[45] The maximum recommended dose is 150 mg/day. Main side effects include drowsiness, parkinsonism, hypotension, depression, anxiety, insomnia and akathisia.[46] Thus, patients with affective disorders may not respond favorably. Combination with clonazepam is sometimes more effective. Tetrabenazine is also effective against tardive dystonia and tardive akathisia. Tardive dystonia may also benefit from a trial of anticholinergics, and clonazepam and baclofen have had some success. For focal dystonias intramuscular botulinum toxin is an excellent option.[47] Other medications with some potential in individual cases include baclofen, valproic acid, and the noradrenergic drugs clonidine and propranolol. Calcium-blocking agents (verapamil, diltiazem) have also been used in TD but no reliable conclusions can be drawn from the sparse literature about their efficacy according to a recent review by the Cochrane Schizophrenia Group. Alpha-tocopherol (vitamin E), as mentioned above, has shown some therapeutic effect in a subgroup of patients. Pyridoxine (vitamin B6) has also ameliorated TD at daily doses of 300-400 mg.[48]

The success of posteroventral pallidotomy and high-frequency deep brain stimulation against levodopa-induced dyskinesia in patients with Parkinson's disease has spurred interest in neurosurgical interventions for disabling and medically resistant TD.[49-51] Limited accounts on different procedures (lesioning vs stimulation) and targets (thalamus vs internal pallidum) are available but evidence gathered thus far suggests that the internal pallidum is likely to become the target of choice in such cases.

Dental prosthetic therapy is a nonpharmacological approach that should not be neglected in the control of orofacial TD.[52] Any team approach in TD management should include an interested general dentist or prosthodontist. Finally, one option in the case of the elderly patient, or in a patient who would not tolerate or respond favorably to the medications listed above, would be to simply return to the prior antipsychotic agent at a somewhat higher dose. In this approach, the physician and patient accept the potential (but not inevitable) risk of development of more severe movements in the future.

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