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Drug-induced tardive motor syndromes

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Drug-induced tardive motor syndromes (TMS) is a group of disorders, characterized by involuntary movements of the tongue, face, lips, trunk and extremities, occurring after long-term exposure to a variety of pharmacological agents, mostly neuroleptics. The diagnosis of TMS requires exposure to dopamine receptor blocking agents for a period at least of 3 months, although for people over 60 years old the necessary exposure period is limited to 1 month. The exact pathophysiology still remains obscure. The aim of this article is to review the phenomenology, epidemiology and treatment options of the TMS, as clinically distinct movement disorders. TMS include tardive dyskinesia, which is the most common movement disorder, tardive dystonia, tardive akathisia, tardive Tourettism, tardive tremor and tardive myoclonus as well as some specific syndromes less often presented such as Pisa, Meige and Rabbit syndromes. Prevention remains the cornerstone in good clinical practice. Preventive approach requires thorough diagnostic process with frequent reviews in order to determine the necessity of use and dosing of neuroleptic treatment. Clinical vigilance for early detection of signs of TMS as well as recording of early extrapyramidal side-effects in the patient's history is needed, as these may predict the occurrence of TMS. In case of occurrence of TMS, gradual discontinuation of the offending agent is required. Therapeutic interventions include the administration of the following agents: atypical antipsychotics (mainly clozapine), benzodiazepines, vitamin E, reserpine, tetrabenazine, anticholinergics, botulinum toxin A. The early management of TMS is crucial for the patients' better clinical outcome and improved quality of life.

Key words: Tardive motor syndromes, tardive dyskinesia, tardive dystonia, tardive akathisia, tardive tourettism, tardive tremor, tardive myoclonus, Rabbit syndrome, Meige syndrome.

Introduction

Drug-induced tardive motor syndromes (TMS) is a group of disorders, characterized by involuntary movements of the tongue, face, lips, trunk and extremities, occurring after long-term exposure to a variety of pharmacological agents, mostly neuroleptics. They have been associated with chronic blockade of D2 dopamine receptors in nigrostriatal pathway, although various pathophysiological mechanisms have been proposed.

The most relevant compounds associated with the occurrence of tardive motor syndromes are summarised in table 1.

The diagnosis of TMS requires exposure to dopamine receptor blocking agents for a period of 3 months, although for people over 60 years old the necessary exposure period is limited to 1 month.¹

TMS include tardive dyskinesia, which is the most common movement disorder, tardive dystonia, tardive akathisia, tardive Tourettism, tardive tremor and tardive myoclonus as well as some specific syndromes less often presented i.e. Pisa, Meige, and Rabbit syndromes.

In this article, we discuss the phenomenology, epidemiology and treatment options of the TMS, as clinically distinct movement disorders.

Tardive dyskinesia

History

The term tardive dyskinesia (TDk) and their symptoms, as a side effect, were first described in the 1950s, with the introduction of neuroleptics for the treatment of psychotic symptoms and was, broadly, used to describe all the late-onset movement disorders. Most recent articles suggest the division into phenomenological distinct TMS, limiting the term TDk to the prototype oral-buccal-lingual involuntary movements.

Other terms describing the symptoms of TDk include "Bucco-linguo-masticatory syndrome", "Terminal extrapyramidal insufficiency syndrome", "Rhythmical chorea".

Early, on the introduction of the term, there was a debate on whether TDk is a distinct clinical entity or part of the acute early-onset movement

Table 1. Medications associated with the occurrence of tardive motor syndromes.

Neuroleptics	Butyrophenones: Droperidol, Haloperidol Dibenzodiazepines: Loxapine Diphenylbutylpiperidines: Pimozide Indolones: Molindone Phenothiazines: Chlorpromazine, Fluphenazine, Mesridazine, Perphenazine, Thioridazine, Trifluoperazine Thioxanthenes: Thiothixene
Atypical antipsychotics	Risperidone, Olanzapine, Amisulpride, Aripiprazole, Ziprazidone, Quetiapine
Antidepressants	Tricyclic antidepressants: Amitriptyline, Amitriptyline and perphenazine combination, Imipramine, Doxepin, Amoxapine Trazodone Monoamine oxidase inhibitors (MAOIs): Phenelzine Selective serotonin reuptake inhibitors (SSRIs): Fluoxetine, Sertraline
Mood stabilizers	Lithium, Carbamazepine
Antiepileptic drugs	Phenobarbital, Phenytoin, Ethosuximide
Anticholinergics	Biperiden, Benzhexol, Orphenadrine, Ethopropazine, Procyclidine
Antiparkinson agents	Levodopa, Levodopa and carbidopa, Bromocriptine
Antihistamines	Antihistaminic decongestants Combinations of antihistamines and sympathomimetics
Anxiolytics	Alprazolam
Antiemetics	Metoclopramide, Prochlorperazine
Antimalarials	Chloroquine
Oral contraceptives	Estrogens
Stimulants	Amphetamine, Methylphenidate

disorders, which were already associated with the use of neuroleptics. Furthermore, there was a discussion about the association of TDk with the use of antipsychotic drugs or whether these symptoms were within the context of the psychotic disorder itself.^{2,3}

Clinical description

TDk is characterized by repetitive, involuntary, purposeless movements. The typical signs include chewing, tongue protrusion, vermicular tongue activity, lip smacking, puckering, and pursing, choreoathetoid movements in the limbs and trunk, guitar or piano playing movements and other flexion and extension movements of the fingers and/or wrists. Very rarely TDk produces aerophagia, irregular respiratory rates and grunting noises. As far as the limbs are concerned, there may be repetitive movement, flexion and extension of the toes and tapping, or flexion and extension of the thighs in the supine position. These symptoms may co-exist or overlap with other movement disorders (i.e. tardive dystonia or tremor).

TDk is present at rest and diminishes or subsides when the affected body part is activated. Furthermore, the symptoms exacerbate when the patient's attention is distracted away from the movements, although the patient is likely to be unaware of the movements.

Various instruments have been developed in order to measure the presence and severity of TDk symptoms. Amongst them, the most widely used is the Abnormal Involuntary Movement Scale (AIMS).

Diagnosis

Criteria for diagnosis¹ of TDk according to the severity of the motor symptoms and the time they are developed were proposed by Shooler & Kane:¹

- A person who has taken neuroleptics for at least 3 months (1 mo if older than 60 y) develops at least 2 movements of at least "mild" severity while taking a neuroleptic.
- A person who has taken neuroleptics for at least 3 months (1 mo if older than 60 y) develops at least 1 movement of at least "moderate" severity while taking a neuroleptic.
- A person who has taken neuroleptics for at least 3 months (1 mo if older than 60 y) develops at least 2 movements of at least "mild" severity within 4 weeks of the discontinuation of the neuroleptic.
- A person who has taken neuroleptics for at least 3 months (1 mo if older than 60 y) develops at least 1

movement of at least "moderate" severity within 4 weeks of the discontinuation of the neuroleptic.

- A person who has taken neuroleptics for at least 3 months (1 mo if older than 60 y) develops at least 2 movements of at least "mild" severity within 8 weeks of the discontinuation of a depot neuroleptic.
- A person who has taken neuroleptics for at least 3 months (1 mo if older than 60 y) develops at least 1 movement of at least "moderate" severity within 8 weeks of the discontinuation of a depot neuroleptic.

Research criteria for neuroleptic-induced tardive dyskinesia proposed by the American Psychiatric Association (DSM-IV) are shown in table 2.

Classification of TDk

The following classification of TDk has been suggested in order to study better the epidemiology, etiology, and treatment of TDk patients.

Table 2. Research criteria for neuroleptic-induced tardive dyskinesia (DSM-IV).

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- A. Involuntary movements of the tongue, jaw, trunk, or extremities have developed in association with the use of neuroleptic medication.
 - B. The involuntary movements are present over a period of at least 4 weeks and occur in any of the following patterns.
 1. Choreiform movements (i.e., rapid, jerky, nonrepetitive)
 2. Athetoid movements (i.e., slow, sinuous, continual)
 3. Rhythmic movements (i.e., stereotypies)
 - C. The signs or symptoms in Criteria A and B develop during exposure to a neuroleptic medication or within 4 weeks of withdrawal from an oral (or within 8 weeks of a withdrawal from a depot) neuroleptic medication.
 - D. There has been exposure to neuroleptic medication for at least 3 months (1 month if age 60 years or older).
 - E. The symptoms are not due to a neurological or general medical condition (e.g., Huntington's disease, Sydenham's chorea, spontaneous dyskinesia, hyperthyroidism, Wilson's disease), ill-fitting dentures, or exposure to other medications that cause acute reversible dyskinesia (e.g., L-dopa, bromocriptine). Evidence that the symptoms are due to one of these etiologies might include the following: the symptoms precede the exposure to the neuroleptic medication or unexplained focal neurological signs are present.
 - F. The symptoms are not better accounted for by a neuroleptic-induced acute movement disorder (e.g., Neuroleptic-Induced Acute Dystonia, Neuroleptic-Induced Acute Akathisia)
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- Probable TDk includes:
- A history of at least 3 months of total cumulative neuroleptic exposure.
- Presence of at least “moderate” abnormal involuntary movements in one or more body areas or of “mild” movements in two or more body areas.
- Absence of other conditions that might produce abnormal involuntary movements. It is worth noting that to be “probable” the dyskinesia is observed only on one occasion.
- Masked Probable TDk: patients with previous probable TD in whom either reintroducing or increasing the dose of the neuroleptic drug results in disappearance of significant dyskinesia.
- Persistent TDk: patients who meet the criteria for probable TD and continue to do so for 3 months. This is qualified by concurrent neuroleptics, neuroleptic-free, or unspecified if the patient has received neuroleptics for only part of the 3-month period.
- Masked Persistent TDk: patients who meet the criteria for persistent TDk but in whom significant dyskinesia disappears within 3 weeks of introduction or increase in the neuroleptic dose.
- Transient TDk: patients with previous probable TDk who on reexamination within 3 months, no longer have significant dyskinesia without reintroduction or increasing the neuroleptic dose.
- Withdrawal TDk: patients who develop significant dyskinesia within 2 weeks following discontinuation of neuroleptics.

Epidemiology

The prevalence of TDk varies broadly due to methodological issues. In many studies, the term “tardive dyskinesia” is indiscriminately used for all tardive syndromes. Other confound factors include special populations at risk (e.g. inpatients, elderly patients, children and adolescents, comorbidity with organic illness)

Realistically, TDk prevalence rates are approximately 15–30% of persons who receive long-term treatment with neuroleptics^{4,5} and TDk incidence is about 3–5%.^{6,7} Prevalence is higher in cigarette smokers⁸ although this finding might be a

result of higher neuroleptic dosages that this special population is receiving.⁹

Risk factors

- Older age appears to be a significant risk factor in developing TDk.¹⁰ It occurs in 5–10% of patients younger than 40 years old, reaching rates of 50–70% in patients older than 65 years old.¹¹ Recent longitudinal studies from geriatric populations show TDk incidence rates of 26–31% after only 1 year of exposure to conventional antipsychotics.¹² Children are also at higher risk for TDk symptoms. The reported rates vary between 22–48%.¹³
- Women seem to be more vulnerable, presenting TDk in an odds ratio of 1.7 compared to men.¹⁴ However, Richardson et al¹⁵ suggested that the occurrence of TDk symptoms is equal in men and women until the age of 64, after which there is a higher rate in women.
- African-Americans present the highest rates of TDk symptoms compared to Caucasians and Asians.¹⁶ This is attributed to low metabolizers, higher doses of oral neuroleptics, higher rate of parenteral depot neuroleptics and the use of antipsychotics for disorders other than psychotic illnesses (i.e. bipolar disorder, panic attacks, obsessive-compulsive disorder).¹⁷
- Typical neuroleptics have been associated with higher risk for extrapyramidal side-effects.¹⁸ As a result, in order to minimize the acute and long-term movement disorders, they are no longer used as first-line treatment for psychosis. As far as the atypical neuroleptics are concerned, the evidence based data have ranked them from lower to high risk in inducing TDk as follows: clozapine < quetiapine < aripiprazole < olanzapine = ziprasidone < risperidone.¹⁹
- Patients suffering mood disorders are at higher risk of developing TDk after exposure to neuroleptics than schizophrenics.^{20,21}
- Patients with family history positive for TDk are more vulnerable to develop TDk symptoms.²²
- Patients with early onset psychosis and medication naive schizophrenic patients.²³
- Patients with clinically significant neuroleptic-induced parkinsonism are at greater risk of

developing TDK²⁴ than patients without such a history.

- Presence of negative symptoms.²³
- Patients with cognitive impairment.^{22,23}

Differential diagnosis

The differential diagnosis of TDK can be a difficult challenge. This disorder is a subset of a large variety of abnormal involuntary movements, some of which may resemble TDK. It includes hereditary and acquired forms of movement disorders, psychogenic movement disorders, or the stereotypic movements of schizophrenia. Involuntary movements may be idiopathic, be caused by many other drugs, or occur as part of neurodegenerative diseases, or other medical illnesses. A thorough history, including past and present drug use, and a complete physical, neurological, and psychiatric examination, accompanied by appropriate laboratory tests, are often necessary to make the correct differential diagnosis of dyskinesias²⁵ (table 3).

Course and prognosis

TDK progresses quite faster than other movement disorders, such as tardive dystonia. It is also more common to appear after withdrawal from neuroleptic medication.

Longitudinal studies' outcomes vary between a persisting nature,²⁶ improvement²⁷ and an unpredicted course of TDK.

Studies, which at baseline include both patients with TDK as well as symptoms-free patients, demonstrate worsening of TDK, mainly due to the occurrence of new incidents of TDK, which significantly outweigh the improvement of the already existing cases. Younger patients are more likely to improve.¹⁰

Tardive dystonia

History

The term "Tardive Dystonia" (TDt) was used by Burke et al., in 1982, who provided a detailed description of the operational definition, phenomenology and epidemiology of this TMS.²⁸

Table 3. Differential diagnosis of tardive dyskinesia

Drug-induced (other than antipsychotics): Antidepressants, antihistamines, antimalarials, diphenylhydantoin, heavy metals, levodopa, sympathomimetics
Dental problems (e.g., ill-fitting denture)
Spontaneous, idiopathic, senile dyskinesias
Schizophrenic mannerisms and stereotypes
Psychogenic movements
Post encephalitic dyskinesias
Huntington's disease
Sydenham's chorea
Pregnancy (chorea gravidarum)
CNS anoxia associated movements
Cerebrovascular accidents
Brain tumors
Wilson's disease
Thyroid hyperactivity
Parathyroid hypoactivity
Systemic lupus erythematosus
Polycythemia vera
Hepatic failure
Renal failure

Clinical manifestations

TDt is a sustained muscular contraction that takes different forms and affects different parts of the body. It may be localized, involving one or more body parts or generalized.

Focal dystonia implies that a single body part is affected. Such focal locations include torticollis, anterocollis, and retrocollis (dystonic movements of the neck), blepharospasm (dystonic movement of the eyelid), writer's cramp (dystonic movements of the arm), oromandibular (dystonic movements of the mouth), dystonic adductor dysphonia (larynx spasm). Involvement of the laryngeal and pharyngeal muscles may lead to serious problems, such as respiratory distress and asphyxia, dysphagia and choking.

Segmental dystonia can be cranial, axial, brachial, or crural. Cranial dystonia refers to movements in the head and neck region. Axial dystonia comprises of both neck and trunk involvement. A specific sub-division of segmental axial dystonia is Pisa syndrome, a condition in which there is sustained involuntary flexion of the body and head to one side and slight rotation of the trunk so the person

appears to lean like the Leaning Tower of Pisa. Brachial dystonia can affect arms or one or both arms plus a contiguous axial structure (neck, trunk or both). Crural dystonia is present in both legs with or without the participation of the trunk, or one leg and the trunk.^{29–31} Although it may present with dystonia in any distribution, craniocervical types seem to be most common.³²

TDt is less recognized and less understood than acute dystonia. The motor presentations are similar to those seen in acute dystonia, and are clearly distinguishable from them only by their duration. There was a considerable clinical overlap with TDk, until Burke et al³² referring to this type of “dyskinesia” as TDt, described the clinical features of the TDt as distinct entity, along with similarities and differences between TDt and classic TDk.

A rare syndrome of cranial dystonia is the Meige syndrome. The two forms of the syndrome are: Meige I syndrome (blepharospasm) characterized by involuntary spasm of the musculature of the upper face, and Meige II syndrome (Brughel’s syndrome) which is a disabling spasm of facial musculature, consisting of primary blepharospasm, followed by abnormal facial movement, as yawning, jaw opening and abnormal tongue movements. Tardive blepharospasm is the presence of repetitive sustained contractions of musculature for at least 1 month, developing during or within 3 months of discontinuation of treatment with dopamine antagonists (in the absence of other disease or familial causes). Dyskinetic blinking may occur. Symptoms of tardive blepharospasm fluctuate. Fatigue, anxiety, work, and light exacerbate tardive blepharospasm, while rest and sleep relieve it.³³

Diagnosis

The following 4 criteria were proposed for the diagnosis of TDt.³⁴

- The patient must have dystonic movements defined as sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures.
- The dystonia must develop either during or within 3 months of a course of neuroleptic treatment. The 3-month cut-off recognizes the fact that neuroleptics may suppress TDk, which often does

not become apparent until some time after drugs are discontinued.

- No other neurologic signs should be present to suggest one of the many known causes of secondary dystonia, such as Wilson’s disease.
- The patient must have a negative family history for dystonia. In the presence of positive family history, knowing whether the affected individual has neuroleptic-induced dystonia or simply expresses an inherited form that is coincident with neuroleptic use is not possible.

Burke²⁸ also proposed a 5th criterion: “If other involuntary movements (such as dyskinesia, akathisia) are present, the dystonia is the most prominent”, but this one has received criticism from other investigators since many movement disorders can coincide and overlap.

Epidemiology

The prevalence of TDt varies from 0,4 to 4% of neuroleptic treated patients.^{35–37} Generally, the prevalence of TDt depends on the criteria used for diagnosis. Some studies raise the rate of TDt up to 21%, when they were based on specific populations. Owens³⁸ suggested that the increasing awareness and skills in recognition of TDt would increase prevalence rates because a large number of static dystonic postural abnormalities are seen in the long-term psychotic population. Another possible explanation is that in earlier studies mainly, only patients with moderate to severe forms of DTt were considered cases, whereas in later studies the diagnosis was also applied to mild cases.³⁹

Risk factors

- Age: There is conflicting data about the influence of age in the presentation of TDt. Although no large population exists, TDt appears to have an earlier mean age of onset than other related dystonic conditions.³⁹
- Gender: The literature shows a higher prevalence in men. The mean ratio that derives from several studies is estimated at 2.4 men to every woman.⁴⁰ Men develop the tardive dystonia with a shorter length of exposure to neuroleptics than women.

- Exposure: A number of studies have consistently reported a shorter mean duration of neuroleptic exposure for TDt patients as compared to TDk.⁴⁰
- Brain injury: Brain injury may influence the onset of dystonia in neuroleptic-treated patients⁴¹
- Past history of acute dystonia.⁴²

Differential Diagnosis

Differentiating tardive dystonia from other causes of dystonia is important. Other causes include:

- Idiopathic (primary) child or adult onset dystonias: They are autosomal dominant.^{43,44}
- Secondary dystonias with hereditary neurological syndromes^{45,46} (Dopa-responsive dystonia, Rapid-onset dystonia-parkinsonism, Huntington's disease, Familial basal ganglia calcifications, Wilson's disease, Metachromatic leukodystrophy, Homocystinuria, Hallervorden-Spatz disease, Dystonic lipidosis, Lesch-Nyhan syndrome, Leber's disease, Ataxia-telangiectasia, Neuroacanthocytosis)
- Dystonias due to degenerative disorders of unknown etiology (Parkinson's disease, progressive supranuclear palsy, Cortico basal ganglionic degeneration).^{47,48}
- Dystonias due to exogenous causes (Perinatal cerebral injury, Encephalitis, Multiple sclerosis, Head trauma, Cervical cord injury or lesion, Stroke, Tumor).⁴⁶

Course and prognosis

TDt has an insidious progress over months or years, until it becomes chronic. It causes emotional and physical disability. The daily living activities of the patients are affected, causing social embarrassment. Disability is moderate to severe in 70% of patients with TDt. For the most part, it affects one single body part and progressively multiple regions are involved. About 2/3 cases' onset is in the face, neck or both. The severity of TDt can increase with fatigue and stress, but tends to be suppressed through relaxation and sleep. Complete remission is unlikely within 6 months of neuroleptic withdrawal with improved patients having a shorter history of exposure to antipsychotics.^{35,39,42}

Tardive akathisia

History

Akathisia has most frequently been considered as an acute motor syndrome, but it can also be a tardive one in patients receiving antipsychotic treatment. Tardive Akathisia (TA) refers to an abnormal state of subjective symptoms of inner restlessness and the inability to remain still. There are no marked differences in the motor phenomena of acute and chronic akathisia, although it has been suggested that the accompanying subjective sense of restlessness may be less intense in the latter.⁴⁹

Since the term involves both subjective experience and objective clinical manifestations, there has been confusion regarding the classification of akathisia.^{49,50} Some authors consider akathisia to be strictly a subjective abnormal state, so the movement disorders are not considered to have characteristic pattern.⁵¹ On the other hand, some consider the presence of the movements alone as sufficient evidence for the diagnosis of akathisia. This entity constitutes a specific form, called pseudoakathisia (typical motor features of akathisia occurring in the absence of subjective experience).⁵²

Another classification of TA is as follows.⁵³

- Objective akathisia (pseudoakathisia): subtype of akathisia, in which motor signs (tapping, squirming, marching movements) are present but there is a lack of subjective awareness of inner restlessness.
- Subjective akathisia: refers to akathisia in which inner restlessness, urge to move, and a feeling of unease are present without any characteristics of motor signs.
- Mixed akathisia: both subjective and motor aspects are clinically present.

Clinical manifestations

TA includes the presence of subjective symptoms of restlessness and the urge to move. It refers to the inability to sit down or remain still. People with tardive akathisia exhibit constant pacing and moving of the hands and feet. The motor features most commonly involve the lower limbs, and included marching in place and crossing and uncrossing the legs when sitting. They typically shift weight from one foot to the other when standing and swing legs when sitting. Other movements include trunk

rocking, respiratory grunting or moaning and complex hand movements, such as face rubbing, scratching, and rubbing the thighs. In a relatively small number of individuals, repetitive, restless movements are observed. TA may co-exist with other movement disorders, such as drug-induced parkinsonism, oral-buccal-lingual dyskinesia and tardive dystonia.^{49–52,54}

Epidemiology

Studies suggest that a significant number of patients receiving long-term neuroleptic treatment develop TA. The prevalence deriving by systematic studies is between 20 and 50%.⁵⁵

Risk factors which have been associated with TA are old age, female sex, iron-deficiency, cognitive dysfunction and affective disorders, although there are conflicting results and further research is warranted.^{51–55}

Differential diagnosis

TA, stereotypies, some cases of chorea, tardive ticks, and tardive myoclonus are in some circumstances indistinguishable motor syndromes.⁵⁴

- Some cases of chorea can be classified as akathisia and stereotypy, while other cases of chorea can be classified as myoclonus. In addition, some cases of tics can also be classified as myoclonus. Some cases of dystonia can be classified as akathisia.
- Restlessness legs syndrome (Ekbom syndrome): The clinical features of Ekbom syndrome, that distinguish it from TA are the sensory dyskathesias, the almost exclusive involvement of the legs and the presence of symptoms during the night, in opposition to TA, which is present throughout the day
- Motor tics. Major differences are: (a) in TA, one of the prominent symptoms is the sense of inner restlessness and the inability to remain still, which are uncommon in motor tics (b) The diversity of tics, in contrast to the characteristic movements of TA (c) Complex vocal tics (formed words) do not occur in TA.

Tardive tourettism

Tardive Tourettism (TT) was initially described in 1978 by Klawans et al and until now, only few cases

of adult patients have been reported. It resembles Tourette syndrome and presents during exposure to neuroleptic treatment or after the process of cessation.^{56–58} Typically, TT begins in individuals older than 21 years, while Tourette syndrome commonly presents by age 7 years. This condition is characterized by frequent, multiple motor and vocal tics, echolalia, echopraxia, coprolalia, and copropraxia. Symptoms occurred after 2–24 years of exposure to neuroleptics or within 2 weeks – 1 year after their discontinuation.⁵⁶

In nearly half the cases^{57–59} TdK was observed concomitantly with TT, indicating that these two entities may share similar pathophysiologic mechanism. In other cases, TdK was developed in patients with TT after treatment with neuroleptics was stopped.⁶⁰ The majority of patients were receiving treatment for chronic schizophrenia and in most cases, dopamine antagonists are used as treatment for symptom relief. A recent report of the effectiveness of clozapine implies a possible involvement of D1/D4 dopamine receptors in the pathophysiology of TT, as well as serotonergic and cholinergic mechanisms. Clonidine, alone or combined with mesoridazine, has been occasionally used to good effects.⁵⁷

Tardive tremor

Tardive Tremor (TTr) was initially described by Stacy and Jankovic.⁶² It refers mainly to large amplitude postural and resting tremor (involuntary, rhythmic, oscillatory movements), involving the upper extremities, after treatment with dopamine receptor blocking drugs.

Patients exhibited tremor with minimal or no parkinsonian features in the reported cases. In opposition to parkinsonian tremor, TTr occurs after prolonged use of neuroleptic drugs but persists long after their discontinuation (for an average of 6 years after discontinuation of neuroleptic medication). It also differed from parkinsonian one in that it is predominantly postural and kinetic and is not accompanied by other parkinsonian signs.

Additionally, in TTr, suppression of symptomatology rather than exacerbation is observed when treated with a dopamine depleting agents or dopamine

receptor antagonists, unlike Parkinsonian tremor. In most cases, comorbidity with TdK has been described.⁶³

Alonso-Navarro et al⁶⁴ report four cases of patients who developed orthostatic tremor after exposure to dopamine blocking drugs, but improved after gradual withdrawal of the offending drugs. They proposed, "This tardive orthostatic tremor could be considered within the spectrum of drug-induced movement disorders".

Tardive myoclonus

Myoclonus is a brief involuntary muscular contraction, causing a jerk-like movement. In literature, there are scarce reports of myoclonus after prolonged use of neuroleptics.^{65,66}

Tics and chorea are suppressible, whereas myoclonus is not suppressible.⁶⁷

When myoclonus and TdK co-exist, the term "myoclonic dystonia" has been proposed.⁶⁸

Rabbit syndrome

Rabbit Syndrome (RS) characterized by fine, rapid, rhythmic movements along the vertical axis of the mouth, at a frequency of approximately 5Hz, resembling the chewing movements of a rabbit.⁶⁹

It is a movement disorder, associated with long-term exposure to typical and newer neuroleptic medication considered as a distinct neuroleptic-induced extrapyramidal syndrome. Different from other types of oral dyskinesias such as buccolingual and buccolinguo-masticatory syndromes, in which the tongue is involved, making slower and less regular movements, RS can be associated with drug-induced parkinsonism.⁷⁰

Its prevalence ranges from 2.3% to 4.4% in the use of typical antipsychotics. The syndrome is associated with middle-aged and elderly populations and with increased vulnerability of the female sex.⁷¹

In most reported cases of RS regarding second generation antipsychotics, Risperidone is involved, with some isolated reports that link the disorder to Clozapine, Olanzapine, or Aripiprazole.⁷²

In fact, RS may be due to a hypercholinergic state resulting from the neuroleptic blockade

of dopaminergic neurons in the extrapyramidal system. This would explain the response of RS with anticholinergic agents, whereas TdK would be worsened by such treatment. Thus, the importance of the differential diagnosis between these two entities is underlined.⁷³

Pathophysiology of tardive syndromes

a. The hypersensitivity theory

The prominent explanatory model of TMS has traditionally been the hypersensitivity of dopamine (D2) receptors in the nigrostriatal system. According to this model, long-term blockade of post-synaptic D2 receptors with dopamine antagonists (i.e. neuroleptics and/or antipsychotics) results in denervation supersensitivity with up-regulation of D2 receptors.⁷⁴

This theory has some flaws:

- Although a dopaminergic hypersensitivity, which can be shown by an increased D2 receptor supersensitivity occurs quite early, TMS appear significantly later on in the course.
- Parkinsonism and TdK can occur simultaneously, in different regions or in the same region.
- The D2 receptor supersensitivity in animals develops in all cases and after one single dose, whereas TMS develop in only some patients and only after long-term treatment.
- During long-term stable, decreased, or increased neuroleptic and/or antipsychotic treatment, TMS may decrease, in contrast to dopaminergic hypersensitivity.
- TMS may persist, even after the resolution of D2 receptor hypersensitivity.

These observations indicate that the dopaminergic hypersensitivity theory cannot fully explain the pathophysiology of TMS. Therefore, other additional theories should be considered.

b. Serotonin-dopamine antagonist hypothesis

An enhanced model of the dopamine-receptor hypersensitivity involves D1 receptor, mainly due to the effect of clozapine, which rarely produces movement disorders. Clozapine has higher affinity for D1 and 5-HT2 receptors as well as lower affinity

for D2 receptors. By selectively blocking D2 receptors in the nigrostriatal system, chronic treatment with conventional neuroleptics disrupts the normal coordinated balance of D1- and D2- mediated striatal outputs. However, the D2 blockade in the nigrostriatal system is overcome by increased release of dopamine secondary to serotonin blockade in this area.^{75,76}

c. Dopamine-GABA hypothesis

According to another hypothesis, gamma-aminobutyric acid (GABA) insufficiency is involved in the neuroanatomical loop controlling movements.^{77,78} This hypothesis derived from decreased glutamic acid decarboxylase, the GABA synthesizing enzyme, observed in dyskinetic animals, compared to similarly medicated with neuroleptics, who did not present TDk.

Moreover, there seem to be two types of GABA receptors enervated by DA. The first type (derived from the anterior striatum to the lateral globus pallidus, is inhibited by DA), while the second type (derived from the posterior striatum to substantia nigra and to the median globus pallidus is excited by DA). Since neuroleptics block these pathways, by blocking DA receptors, GABA neurons projecting to the lateral globus pallidus are facilitated, while the GABA neurons projecting to substantia nigra and median globus pallidus are inhibited. From animal studies it is known that increased GABA activity in lateral globus pallidus induces parkinsonism in animals, while the decreased GABA function in the medial globus pallidus and in reticular zone of the substantia nigra seems to be associated with hyperkinetic movements. This fact suggests that DA receptors blockade has distinct effect depending on their localization in the brain.^{79,80}

d. Free radical hypothesis

According to another hypothesis it is suggested that tardive dyskinetic symptoms be due to neurotoxic effects of free radical biproducts from catecholamines metabolism, induced by neuroleptic drugs.⁸¹ This model has been used as a rationale for the administration of vitamin E for the management of neuroleptic-induced movement

disorders, especially in the early phase, when effects are potentially reversible.

e. Genetic hypothesis (animal model)

More recent evidence involves the adenosinergic receptor system in the development of TDk in rodents.⁸² The polymorphisms of *D2* gene,⁸³ *D3*⁸⁴ the dopamine transporter⁸⁵ and the manganese superoxide dismutase gene⁸⁶ have been proposed to participate in the development of TMS.

In brief, the exact pathophysiology still remains obscure. Despite the extensive data, there is not direct evidence about the mechanism of action behind tardive syndromes. Further studies are required in order to reveal the nature of this complex spectrum of tardive movement disorders.

Treatment of Tardive Syndromes

Prevention remains the cornerstone in good clinical practice. Having in mind the possibility of TMS, the prudent clinician should take into account the risk-benefit ratio, before administering neuroleptics to a patient.

Preventive approach requires thorough diagnostic process with frequent reviews in order to determine the necessity of neuroleptic treatment, clinical vigilance for the early detection of signs of TMS and recording of early extrapyramidal side-effects (EPSEs) in the patient's history, as these may predict the occurrence of TMS.⁸⁷

The introduction and wide-spread use of second-generation antipsychotics has reduced the occurrence of TMS.^{88,89} In case of occurrence of TMS, gradual discontinuation of the offending agent is required,⁹⁰ having in mind that symptoms might initially exacerbate. If there is need for antipsychotic medication due to the underlying illness, an atypical antipsychotic should be administered. The decision should take into account patients' clinical profile as well as the agent's specific side-effects and pharmacological profile.⁹¹

Worth of note is the fact that TMS (as part of EPSEs) are one of the main reasons of non-adherence with the medication, leading in its turn to higher rates of relapse, hospital admissions and mortality. Consequently, the management of TMS is crucial

for better clinical outcome and improved quality of life. Frequent monitoring, while noting patients' subjective experiences, remains the most effective way of managing TMS.

1. Medication

a. Atypical antipsychotics

Clozapine: Clozapine (CLZ) has very low risk of TMS and the reports which link clozapine to TMS involve movement disorders that can not be solely attributed to the way of action of this antipsychotic agent.⁹² CLZ effect has been demonstrated in several studies. In most of them, there was a significant improvement in the severity of TD symptoms. CLZ appears also to be effective in cases of TDt,⁹³ which is a very promising outcome, since TDt is hard to treat.

The clinical effectiveness of CLZ regarding tardive movement disorders may be attributed to its pharmacological profile. CLZ exhibits higher D1 and lower D2 affinity, 5-HT₂ antagonism, remarkable binding to dopamine receptor D₄, α₂-antagonism and activity at M1 muscarinic receptor.⁹⁴ Thus, it is an important advance in the treatment of TMS. However the administration of CLZ should take into account the side-effects, such as agranulocytosis and lower seizure threshold.

Risperidone: It has been in longer clinical use than any other atypical antipsychotic, after clozapine. It caused less parkinsonism, dystonia and akathisia than haloperidol⁹⁵ (10 mg/day). In double blind studies, risperidone significantly lowered dyskinesia's scores compared to placebo. Nevertheless, risperidone has been implicated as a causative agent for TDk in patients never previously exposed to traditional neuroleptics. Issues like whether risperidone causes, masks or ameliorates tardive movement disorders and whether the effect is dose-related need further investigation.

Olanzapine: Olanzapine was found to be effective according to various case reports, in the improvement of TDk,⁹⁶ and TDt.^{97,98} Although olanzapine has been associated with the occurrence of tardive movement disorders, it seems to be a quite safe treatment option for patients vulnerable to TMS.

Aripiprazole: Aripiprazole is a D₂ partial receptor agonist. The effectiveness of this novel antipsychotic agent regarding the treatment of TMS has not yet been established as reports indicate controversial results.⁹⁹

Quetiapine: Quetiapine seems quite safe in the treatment of TMS, an outcome that is attributed to its pharmacologic profile, which is similar to clozapine's.¹⁰⁰ Nevertheless, there are reports linking quetiapine to tardive dyskinesia.¹⁰¹

Ziprazidone: Some reports associate ziprazidone with the occurrence or re-emergence of TMS, although the evidence is scarce for a reliable conclusion.¹⁰²

Amisulpride: There are conflicting results on the role of amisulpride, as far as TMS are concerned. Further trials are warranted.^{103,104}

b. Benzodiazepines (BZD)

Their role in the management of TMS is important, although limited controlled research has been published. Despite the extensive use of BZDs, a recent review indicates that the treatment with BZD remains "experimental".¹⁰⁵ Clonazepam (1–4 mg/day) and Diazepam (6–25 mg/day) are the most widely used.¹⁰⁶

c. Vitamin E

The use of alpha-tocopherol (vitamin E) for the treatment of TMS is based on the hypothesis that neuroleptics contribute to increase lipid peroxidation and free radical production, which is decreased by administering the anti-oxidant vitamin E. Several trials have found vitamin E effective, especially in the early stages of neuroleptic treatment.¹⁰⁷ It seems that alpha-tocopherol has a protective role in neuronal damage. Doses range between 400–1600 IU/day

d. Catecholamines depleters

Reserpine: Reserpine proved to be effective in patients with severe tardive dyskinesia, along with the discontinuation of neuroleptics.¹⁰⁸ Side-effects, like worsening of depression, parkinsonism and hypotension should be taken into account.

Tetrabenazine: Tetrabenazine has been shown to deplete cerebral monoamines and is currently used to treat hyperkinetic movement disorders, like chorea in Huntington's disease, tics in TS and TDK¹⁰⁹ in doses between 25–200 mg/day

e. Anticholinergics

It seems that anticholinergics are more effective in cases of TDt.¹¹⁰

f. Botulinum toxin

Botulinum toxin type A (BTTA) is an acetylcholine receptor inhibitor, which produces neuromuscular blockade by inhibiting the calcium ion-mediated release of acetylcholine at the motor nerve terminals and by diminishing endplate potential. These result in paralysis of the affected muscles. BTTA seems particularly effective in the treatment of various forms of dystonia. The effect of BTTA lasts for 3–4 months. Patients who are resistant to BTTA may improve with Botulinum Toxin Type F, but the duration of the benefit is shorter.^{106,111}

g. Miscellaneous treatments

- Catecholamines agonists (Apomorphine, hydergine, methylphenidate, bromocryptine): Bromocryptine possesses both dopamine agonist and antagonist activities. In doses 0.75–7.5 mg/day, it failed to improve TDt in small open and double-blind studies.¹¹²
- Cholinergics (Deanol): Deanol is an orally administered putative cholinergic drug. It has been involved in numerous studies, among which only one of the double-blind studies showed it to be significantly superior to placebo.¹¹³
- GABAergic drugs (Muscimol, progabide, sodium valproate, gabapentine): The inhibiting effect of GABA on dopamine neurons provides the rationale for treating TDK with drugs that increase GABAergic influences.¹¹⁴ Muscimol is the first specific GABA-agonist that has been tried for TDK and produced a 48% decrease in TDK symptoms in doses up to 9 mg/day in a placebo – controlled trial. Progabide achieved 40–60% improvement in TDK symptoms in one open and two double-blind clinical trials.¹¹⁵ Sodium valproate is thought to increase the production and prevent the breakdown

of GABA in the brain, via GABA-transaminase inhibition. Double-blind studies in which 900–2500 mg sodium valproate, was used, showed no improvement in TDK symptoms.¹¹⁶

- Calcium channel antagonists: Animal experiments had shown that calcium-channel blockers possess dopamine antagonist properties.¹¹⁷ Adequately controlled, long-term studies are due. There are, however, serious limitations: hypotension, increased anxiety, hostility and depression and the dissipation of antidyskinetic effect after 1–3 months.
- Lithium: Systematic open and double-blind studies revealed modest benefit. There was a trend in these studies for serum lithium levels to be <0.8 mEq/L in order to reduce TDK. Some reported worsening of existing TDK symptoms, especially at toxic lithium levels.^{118,119}
- Aminoacids: aminoacids are precursors of neurotransmitters that may be involved in the pathophysiology of TDK. Recent studies have shown remission of TDK symptoms by the use of aminoacids in the daily dietary.¹²⁰
- Levetiracetam: there are two published studies regarding its effectiveness in treating TDK symptoms.¹²¹
- Naltrexone: it may be effective when added to benzodiazepines.¹²²
- Pyridoxine: vitamin B6 has been considered for the treatment of TDK because of its role in the metabolic breakdown of L-DOPA. Doses up to 400 mg/day¹²³ have to administer.

2. Somatic treatments

- ECT: Electroconvulsive therapy has not been systematically studied for the treatment of TDK.¹²⁴
- Transcranial magnetic stimulation
- Pallidotomy

These two latest methods are mainly applied in patients with disabling TMS due to neurological disorders (primary dystonias) unresponsive to other therapies. There is no adequate evidence even in most severe forms of drug-induced TMS.^{32,46}

Φαρμακο-επαγόμενα όψιμα κινητικά σύνδρομα

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Τα όψιμα κινητικά σύνδρομα (ΟΚΣ) είναι μια ομάδα διαταραχών που χαρακτηρίζονται από ακούσιες κινήσεις της γλώσσας, του προσώπου, των χειλέων, του κορμού και των άκρων που συμβαίνουν μετά από μακρόχρονη έκθεση σε ποικίλους φαρμακολογικούς παράγοντες, κυρίως νευροληπτικά φάρμακα. Η διάγνωση των ΟΚΣ απαιτεί έκθεση σε παράγοντες που δεσμεύουν τους υποδοχείς ντοπαμίνης για περίοδο τουλάχιστον 3 μηνών, αν και για άτομα άνω των 60 ετών η περίοδος έκθεσης περιορίζεται στον 1 μήνα. Η ακριβής παθοφυσιολογία των ΟΚΣ παραμένει ακόμη ασαφής. Σκοπός αυτού του άρθρου είναι η ανασκόπηση της φαινομενολογίας, επιδημιολογίας και των θεραπευτικών επιλογών για τα ΟΚΣ, ως κλινικά διακριτές κινητικές διαταραχές. Τα ΟΚΣ περιλαμβάνουν την όψιμη δυσκινησία, η οποία είναι η πιο συνήθης κινητική διαταραχή, την όψιμη δυστονία, την όψιμη ακαθισία, το όψιμο σύνδρομο Tourette, τον όψιμο τρόμο και τον όψιμο μυόκλονο, όπως επίσης, και διάφορα ειδικά σύνδρομα που εμφανίζονται σπανιότερα, π.χ. τα σύνδρομα Pisa, Meige και Rabbit. Τα συνηθέστερα ΟΚΣ είναι η όψιμη δυσκινησία, η όψιμη δυστονία και η όψιμη ακαθισία. Η κλινική εικόνα της όψιμης δυσκινησίας χαρακτηρίζεται από επαναλαμβανόμενες ακούσιες και άσκοπες κινήσεις που αφορούν το στόμα, τη γλώσσα και το πρόσωπο όπως και χοριοαθροσικού τύπου κινήσεις των άκρων, των δακτύλων και του κορμού. Η όψιμη δυστονία είναι μια κατάσταση επίμονης μυϊκής σύσπασης που μπορεί να αφορά διάφορα μέρη του σώματος ή σπανιότερα περισσότερα του ενός μέρη του σώματος. Συχνές είναι οι εντοπίσεις στο πρόσωπο και τον αυχένα με τη μορφή του ραιβόκρανου, του οπισθόκρανου ή του βλεφαρόσπασμου. Ακόμη μπορεί να αφορά σπασμό των μυών της γραφής ή σπασμό των λαρυγγικών και των φαρυγγικών μυών με αποτέλεσμα δυσφωνία και δυσκαταποσία. Η όψιμη ακαθισία εμφανίζεται ως αντικειμενική ακαθισία όταν ο ασθενής δεν συνειδητοποιεί το πρόβλημα της ανησυχίας και της αδυναμίας να παραμείνει σε μια σταθερή θέση και ως υποκειμενική ακαθισία όταν ο ασθενής ενώ δεν παρουσιάζει τα κινητικά προβλήματα παραπονείται για εσωτερική ανησυχία και τάση για κινητικότητα. Στη μεικτή μορφή υπάρχει συνδυασμός των παραπάνω καταστάσεων. Η πρόληψη παραμένει ο ακρογωνιαίος λίθος στην καλή κλινική πρακτική. Η προληπτική προσέγγιση απαιτεί προσεκτική διαγνωστική διαδικασία με συχνές επανατοποθετήσεις προς τον σκοπό του καθορισμού της ανάγκης της λήψης φαρμακευτικής αγωγής αλλά και της ανάγκης της ελαχίστης δοσολογίας της. Η κλινική εγρήγορηση για την πρώιμη επισήμανση σημείων ΟΚΣ και η καταγραφή πρώιμων εξωπυραμιδικών ανεπιθυμητών ενεργειών στο ιστορικό του ασθενούς θεωρείται σημαντική, καθώς αυτές αποτελούν πιθανό προβλεπτικό παράγοντα για την εμφάνιση ΟΚΣ. Στην περίπτωση εμφάνισης ΟΚΣ, η προοδευτική μείωση ή και η διακοπή του φαρμακευτικού παράγοντα που ενοχοποιείται κρίνεται απαραίτητη. Οι θεραπευτικοί χειρισμοί περιλαμβάνουν τη χορήγηση των παρακάτω σκευασμάτων: ορισμένα άτυπα αντιψυχωσικά φάρμακα (κυρίως κλοζαπίνη), βενζοδιαζεπίνες, βιταμίνη Ε, ρεζερίπνη, τετραμπεναζίνη, αντιχολινεργικές ουσίες, αλλαντική τοξίνη Α. Η έγκαιρη αντιμετώπιση των ΟΚΣ θεωρείται σημαντική και αποσκοπεί στην καλύτερη κλινική έκβαση και τη βελτίωση της ποιότητας ζωής του ασθενούς.

Λέξεις ευρετηρίου: Όψιμα κινητικά σύνδρομα, όψιμη δυσκινησία, όψιμη δυστονία, όψιμη ακαθισία, όψιμο σύνδρομο Tourette, όψιμος τρόμος, όψιμος μυόκλονος, σύνδρομο Rabbit, σύνδρομο Meige.

References

- Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. *Arch Gen Psychiatry* 1982, 39:486-487
- Tardive dyskinesia: summary of a Task Force Report of the American Psychiatric Association. By the Task Force on Late Neurological Effects of Antipsychotic Drugs. *Am J Psychiatry* 1980, 116:3-1172
- Tarsy D. History and definition of tardive dyskinesia. *Clin Neuropharmacol* 1983, 6:91-99
- Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. *Arch Gen Psychiatry* 1982, 39:473-481
- Halliday J, Farrington S, Macdonald S, MacEwan T, Sharkey V, McCreadie R. Nithsdale Schizophrenia Surveys 23: movement disorders. 20-year review. *Br J Psychiatry* 2002, 181:422-427
- Glazer WM, Morgenstern H, Doucette JT. Predicting the long-term risk of tardive dyskinesia in outpatients maintained on neuroleptic medications. *J Clin Psychiatry* 1993, 54:133-139
- Kane JM, Woerner M, Weinhold P, Wegner J, Kinon B, Borenstein M. Incidence of tardive dyskinesia: five-year data from a prospective study. *Psychopharmacol Bull* 1984, 20:387-389
- Binder RL, Kazamatsuri H, Nishimura T, McNiel DE. Smoking and tardive dyskinesia. *Biol Psychiatry* 1987, 22:1280-1282
- Yassa R, Lal S, Korpassy A, Ally J. Nicotine exposure and tardive dyskinesia. *Biol Psychiatry* 1987, 22:67-72
- Smith JM, Baldessarini RJ. Changes in prevalence, severity, and recovery in tardive dyskinesia with age. *Arch Gen Psychiatry* 1980, 37:1368-1373
- Jeste DV. Tardive dyskinesia in older patients. *J Clin Psychiatry* 2000, 61(Suppl 4):27-32
- Woerner MG, Alvir JM, Saltz BL, Lieberman JA, Kane JM. Prospective study of tardive dyskinesia in the elderly: rates and risk factors. *Am J Psychiatry* 1998, 155:1521-1528
- Campbell M, Grega DM, Green WH, Bennett WG. Neuroleptic-induced dyskinesias in children. *Clin Neuropharmacol* 1983, 6:207-222
- Smith JM, Dunn DD. Sex differences in the prevalence of severe tardive dyskinesia. *Am J Psychiatry* 1979, 136:1080-1082
- Richardson MA, Pass R, Craig TJ, Vickers E. Factors influencing the prevalence and severity of tardive dyskinesia. *Psychopharmacol Bull* 1984, 20:33-38
- Morgenstern H, Glazer WM. Identifying risk factors for tardive dyskinesia among long-term outpatients maintained with neuroleptic medications. Results of the Yale Tardive Dyskinesia Study. *Arch Gen Psychiatry* 1993, 50:723-733
- Littlewood R. Psychiatric diagnosis and racial bias: empirical and interpretative approaches. *Soc Sci Med* 1992, 34:141-149
- Dolder CR, Jeste DV. Incidence of tardive dyskinesia with typical versus atypical antipsychotics in very high-risk patients. *Biol Psychiatry* 2003, 53:1142-1145
- Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry* 2004, 161:414-425
- Mukherjee S, Rosen AM, Caracci G, Shukla S. Persistent tardive dyskinesia in bipolar patients. *Arch Gen Psychiatry* 1986, 43:342-346
- Nasrallah HA, Churchill CM, Hamdan-Allan GA. Higher frequency of neuroleptic-induced dystonia in mania than in schizophrenia. *Am J Psychiatry* 1988, 145:1455-1456
- Wegner JT, Catalano F, Gibraltar J, Kane JM. Schizophrenics with tardive dyskinesia neuropsychological deficit and family psychopathology. *Arch Gen Psychiatry* 1985, 42:860-865
- Waddington JL, Youssef HA. Late onset involuntary movements in chronic schizophrenia: relationship of "tardive" dyskinesia to intellectual impairment and negative symptoms. *Br J Psychiatry* 1986, 149:616-620
- Kane JM, Woerner M, Lieberman J. Tardive dyskinesia: prevalence, incidence, and risk factors. *J Clin Psychopharmacol* 1988, 8:52S-56S
- Granacher RP, Jr. Differential diagnosis of tardive dyskinesia: an overview. *Am J Psychiatry* 1981, 138:1288-1297
- Wegner JT, Kane JM. Follow-up study on the reversibility of tardive dyskinesia. *Am J Psychiatry* 1982, 139:368-369
- Klawans HL, Tanner CM, Barr A. The reversibility of "permanent" tardive dyskinesia. *Clin Neuropharmacol* 1984, 7:153-159
- Burke RE, Fahn S, Jankovic J, Marsden CD, Lang AE, Gollomp S et al. Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. *Neurology* 1982, 32:1335-1346
- Suzuki T, Matsuzaka H. Drug-induced Pisa syndrome (pleurothotonus): epidemiology and management. *CNS Drugs* 2002, 16:165-174
- Villarejo A, Camacho A, Garcia-Ramos R, Moreno T, Penas M, Juntas R et al. Cholinergic-dopaminergic imbalance in Pisa syndrome. *Clin Neuropharmacol* 2003, 26:119-121
- Suzuki T, Koizumi J, Moroji T, Sakuma K, Hori M, Hori T. Clinical characteristics of the Pisa syndrome. *Acta Psychiatr Scand* 1990, 82:454-457
- Kang UJ, Burke RE, Fahn S. Natural history and treatment of tardive dystonia. *Mov Disord* 1986, 1:193-208
- Marsden CD. Blepharospasm-omandibular dystonia syndrome (Brueghel's syndrome): a variant of adult-onset torsion dystonia? *J Neurol Neurosurg Psychiatry* 1976, 39:1204-1209
- American Psychiatric Association. Diagnostic and statistical manual of mental Disorders. 4th ed. Text Revision. Washington, DC. *American Psychiatric Association*, 2000:807
- Wojcik JD, Falk WE, Fink JS, Cole JO, Gelenberg AJ. A review of 32 cases of tardive dystonia. *Am J Psychiatry* 1991, 148:1055-1059
- van Harten PN, Matroos GE, Hoek HW, Kahn RS. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia The Curanao Extrapyramidal Syndromes Study. *Schizophr Res* 1996, 19:195-203
- Raja, M. Tardive dystonia: prevalence, risk factors and comparison with tardive dyskinesia in a population of 200 acute psychiatric inpatients. *Eur Arch Psychiatry Clin Neurosci* 1995, 245:145-151
- Owens DG. Dystonia: a potential psychiatric pitfall. *Br J Psychiatry* 1990, 156:620-634
- Yassa R, Nair V, Iskandar H. A comparison of severe tardive dystonia and severe tardive dyskinesia. *Acta Psychiatr Scand* 1989, 80:155-159
- van Harten PN. Tardive dystonia: male:female ratio. *Br J Psychiatry* 1991, 159:440
- Lee MS, Rinne JO, Ceballos-Baumann A, Thompson PD, Marsden CD. Dystonia after head trauma. *Neurology* 1994, 44:1374-1378
- Sachdev P. Clinical characteristics of 15 patients with tardive dystonia. *Am J Psychiatry* 1993, 150:498-500
- van Harten PN, Kahn RS. Tardive dystonia. *Schizophr Bul* 1999, 25:741-748
- Shanga H, Clercb N, Langc D, Kaelin-Langb A, Burgunderb JM. Clinical and molecular genetic evaluation of patients with primary dystonia. *Eur J Neurol* 2005, 12:131-138

45. Molho ES, Feustel PJ, Factor SA. Clinical comparison of tardive and idiopathic cervical dystonia. *Mov Disord* 1998, 13:486–489
46. Bressman SB. Dystonia update. *Clin Neuropharmacol* 2000, 23:239–251
47. Rosenblatt A, Leroi I. Neuropsychiatry of Huntington's disease and other basal ganglia disorders. *Psychosomatics* 2000, 41:24–30
48. Kidron D, Melamed E. Forms of dystonia in patients with Parkinson's disease. *Neurology* 1987, 37:1009–1011
49. Barnes TR, Braude WM. Akathisia variants and tardive dyskinesia. *Arch Gen Psychiatry* 1985, 42:874–78
50. Braude WM, Barnes TR. Late-onset akathisia-an indicant of covert dyskinesia: two case reports. *Am J Psychiatry* 1983, 140:611–612
51. Van Putten T, May PR, Marder SR. Akathisia with haloperidol and thiothixene. *Psychopharmacol Bull* 1984, 20:114–117
52. Burke RE, Kang UJ, Jankovic J, Miller LG, Fahn S. Tardive akathisia: an analysis of clinical features and response to open therapeutic trials. *Mov Disord* 1989, 4:157–175
53. Kim JH, Byun HJ. Prevalence and characteristics of subjective akathisia, objective akathisia, and mixed akathisia in chronic schizophrenic subjects. *Clin Neuropharmacol* 2003, 26:312–316
54. Gervin M, Barnes TRE. Assessment of drug-related movement disorders in schizophrenia. *Advances in Psychiatric Treatment* 2000, 6:332–343.
55. Sachdev P. The epidemiology of drug-induced akathisia: Part II. Chronic, tardive, and withdrawal akathisias. *Schizophr Bull* 1995, 21:451–461
56. Reid SD. Neuroleptic-induced Tardive Tourette treated with clonazepam: a case report and literature review. *Clin Neuropharmacol* 2004, 27:101–104
57. Bharucha KJ, Sethi KD. Tardive tourettism after exposure to neuroleptic therapy. *Mov Disord* 1995, 10:791–792
58. Mueller J, Aminoff MJ. Tourette-like syndrome after long-term neuroleptic drug treatment. *Br J Psychiatry* 1982, 141:191–193
59. DeVeugh-Geiss J. Tardive Tourette syndrome. *Neurology* 1980, 30:562–563
60. Singh SK, Jankovic J. Tardive dystonia in patients with Tourette's syndrome. *Mov Disord* 1988, 3:274–280
61. Jaffe E, Tremeau F, Sharif Z, Reider R. Clozapine in tardive Tourette syndrome. *Biol Psychiatry* 1995, 38:196–197
62. Stacy M, Jankovic J. Tardive tremor. *Mov Disord* 1992, 7:53–57
63. Tarsy D, Indorf G. Tardive tremor due to metoclopramide. *Mov Disord* 2002, 17:620–621
64. Alonso-Navarro H, Orti-Pareja M, Jimenez-Jimenez FJ, Zurdo-Hernandez JM, de Toledo M, Puertas-Munoz. Orthostatic tremor induced by pharmaceuticals. *Rev Neurol* 2004, 39:834–836
65. Little JT, Jankovic J. Tardive myoclonus. *Mov Disord* 1987, 2:307–311
66. Fukuzako H, Tominaga H, Izumi K, Kojima T, Nomoto M, Hokazono Y et al. Postural myoclonus associated with long-term administration of neuroleptics in schizophrenic patients. *Biol Psychiatry* 1990, 27:1116–1126
67. Meidinger AL, Milltenberger RG, Himle M, Omvig M, Trainor C, Crosby R. An investigation of tic suppression and the rebound effect in Tourette's disorder. *Behav Modif* 2005, 29:716–745
68. Obeso JA, Rothwell JC, Lang AE, Marsden CD. Myoclonic dystonia. *Neurology* 1983, 33:825–830
69. Schwartz M, Hocherman S. Antipsychotic-induced rabbit syndrome: epidemiology, management and pathophysiology. *CNS Drugs* 2004, 18:213–220
70. Schwartz M, Weller B, Erdreich M, Sharf B. Rabbit syndrome and tardive dyskinesia: two complications of chronic neuroleptic treatment. *J Clin Psychiatry* 1995, 56:212
71. Yassa R, Lal S. Prevalence of the rabbit syndrome. *Am J Psychiatry* 1986, 143:656–657
72. Catena Dell'osso M, Fagiolini A, Ducci F, Masalehdan A, Ciapparelli A, Frank E. Newer antipsychotics and the rabbit syndrome. *Clin Pract Epidemiol Ment Health* 2007, 11:3–6
73. Deshmukh DK, Joshi VS, Agarwal MR: Rabbit syndrome: a rare complication of long-term neuroleptic medication. *Br J Psychiatry* 1990, 157:293
74. Gerlach J, Casey DE. Tardive dyskinesia. *Acta Psychiatr Scand* 1988, 77:369–378
75. Huttunen M. The evolution of the serotonin-dopamine antagonist concept. *J Clin Psychopharmacol* 1995, 15(Suppl 1):4S–10S
76. Trungram JM, Ledbetter R, Zalis ME, Burgdorf RO, Wooten GF. Treatment of severe axial tardive dystonia with clozapine: case report and hypothesis. *Mov Disord* 1994, 9:441–446
77. Monteleone P, Maj M, Ariano MG, Iovino M, Fiorenza L, Steardo L. Prolactin response to sodium valproate in schizophrenics with and without tardive dyskinesia. *Psychopharmacology* 1988, 96:223–226
78. Thaker GK, Nguyen JA, Tamminga CA. Saccadic distractibility in schizophrenic patients with tardive dyskinesia: functional evidence for subcortical GABA dysfunction. *Biol Psychiatry* 1989, 25:49–59
79. Stevens JR. Dopamine regulation in the mesolimbic system: the GABA connection. *Brain Res Bull* 1980, 5(Suppl 2):231–236
80. Thaker GK, Nguyen JA, Strauss ME, Jacobson R, Kaup BA, Tamminga CA. Clonazepam treatment of tardive dyskinesia: a practical GABA-mimetic strategy. *Am J Psychiatry* 1990, 147:445–451
81. Lohr JB, Cadet JL, Lohr MA, Larson L, Wasli E, Wade L et al. Vitamin E in the treatment of tardive dyskinesia: the possible involvement of free radical mechanisms. *Schizophr Bull* 1988, 14:291–296
82. Bishnoi M, Chopra K, Kulkarni SK. Involvement of adenosinergic receptor system in an animal model of tardive dyskinesia and associated behavioural, biochemical and neurochemical changes. *Eur J Pharmacol* 2006, 552:55–66
83. Kaiser R, Tremblay PB, Klufmoller F, Roots I, Brockmoller J. Relationship between adverse effects of antipsychotic treatment and dopamine D2 receptor polymorphisms in patients with schizophrenia. *Mol Psychiatry* 2002, 7:695–705
84. Steen VM, Lovlie R, MacEwan T, McCreadie RG. Dopamine D3-receptor gene variant and susceptibility to tardive dyskinesia in schizophrenic patients. *Mol Psychiatry* 1997, 2:139–145
85. Lee SH, Oh DY, Jung SC, Kim YM, Cho HK, Koh JK et al. Neuroleptic drugs alter the dopamine transporter-mediated uptake and release of dopamine: a possible mechanism for drug-induced tardive dyskinesia. *Pharmacol Res* 1997, 35:447–50
86. Hori H, Ohmori O, Shinkai T, Kojima H, Okano C, Suzuki T et al. Manganese superoxide dismutase gene polymorphism and schizophrenia: relation to tardive dyskinesia. *Neuro-psychopharmacology* 2000, 23:170–177
87. Tenback DE, van Harten PN, Slooff CJ, van Os J. Evidence that early extrapyramidal symptoms predict later tardive dyskinesia: a prospective analysis of 10,000 patients in the European Schizophrenia Outpatient Health Outcomes (SOHO) Study. *Am J Psychiatry* 2006, 163:1438–1440

88. Kane JM. Tardive dyskinesia circa 2006. *Am J Psychiatry* 2006, 163:1316–1318
89. Tarsy D, Baldessarini RJ. Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? *Mov Disord* 2006, 21:589–598
90. Simpson GM. The treatment of tardive dyskinesia and tardive dystonia. *J Clin Psychiatry* 2000, 61(Suppl 4):39–44
91. Margolese HC, Ferreri F. Management of conventional antipsychotic-induced tardive dyskinesia. *J Psychiatry Neurosci* 2007, 32:72
92. Tarsy D, Baldessarini RJ. Epidemiology of tardive dyskinesia: is risk declining with modern antipsychotics? *Mov Disord* 2006, 21:589–598
93. Trungram JM, Ledbetter R, Zalis ME, Burgdorf RO, Wooten GF: Treatment of severe axial tardive dystonia with clozapine: case report and hypothesis. *Mov Disord* 1994, 9:441–446
94. Tandon R. Neuropharmacologic basis for clozapine's unique profile. *Arch Gen Psychiatry* 1993, 50:158–159
95. Peuskens J. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-center, double-blind, parallel-group study versus haloperidol. *Br J Psychiatry* 1995, 166:712–26 & 727–733
96. Fernandez HH, Friedman JH. Classification and treatment of tardive syndromes. *Neurologist* 2003, 9:16–27
97. Havaki-Kontaxaki BJ, Kontaxakis VP, Christodoulou GN. Treatment of tardive pharyngolaryngeal dystonia with olanzapine. *Schizophr Res* 2004, 66:199–200
98. Lucetti C, Bellini G, Nuti A, Bernardini S, Dell'Agnello G, Piccinni A et al. Treatment of patients with tardive dystonia with olanzapine. *Clin Neuropharmacol* 2002, 25:71–74
99. Zacher JL, Hatchett AD. Aripiprazole-induced movement disorder. *Am J Psychiatry* 2006, 163:160–161
100. Gourzis P, Polychronopoulos P, Papapetropoulos S, Assimakopoulos K, Argyriou AA, Beratis S. Quetiapine in the treatment of focal tardive dystonia induced by other atypical antipsychotics: a report of 2 cases. *Clin Neuropharmacol* 2005, 28:195–196
101. Ghaemi SN, Ko JY. Quetiapine-Related Tardive Dyskinesia. *Am J Psychiatry* 2001, 158:1737
102. Correll CU, Leucht S, Kane JM. Lower Risk for Tardive Dyskinesia Associated with second-generation antipsychotics: a systematic review of 1-year studies. *Am J Psychiatry* 2004, 161:414–425
103. Fountoulakis KN, Panagiotidis P, Siamouli M, Kantartzis S, Mavridis T, Iacovides A, Kaprinis G. Amisulpride-induced tardive dyskinesia. *Schizophr Res* 2006, 88:232–234
104. Masdrakis VG, Papadimitriou GN, Papageorgiou C, Kouzoupis A, Gailoglou D, Soldatos CR. Development of tardive dyskinesia in a patient taking amisulpride. *Prog Neuropsychopharmacol Biol Psychiatry* 2007, 31:586–587
105. Bhoopathi PS, Soares-Weiser K. Benzodiazepines for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev* 2006 19, 3:CD000205
106. Havaki-Kontaxaki B, Kontaxakis VP, Margariti MM, Paplos KG, Christodoulou GN. Treatment of severe neuroleptic-induced tardive torticollis. *Ann Gen Hosp Psychiatry* 2003, 2:9
107. Zhang XY, Zhou DF, Cao LY, Xu CQ, Chen DC, Wu GY. The effect of vitamin E treatment on tardive dyskinesia and blood superoxide dismutase: a double-blind placebo-controlled trial. *J Clin Psychopharmacol* 2004, 24:83–86
108. Fahn S. A therapeutic approach to tardive dyskinesia. *J Clin Psychiatry* 1985, 46:19–24
109. Paleacu D, Giladi N, Moore O, Stern A, Honigman S, Badarny S. Tetrabenazine treatment in movement disorders. *Clin Neuropharmacol* 2004, 27:230–233
110. Skidmore F, Reich SG. Tardive dystonia. *Curr Treat Options Neurol* 2005, 7:231–236
111. van Harten PN, Hovestadt A. Botulinum toxin as a treatment for tardive dyskinesia. *Mov Disord* 2006, 21:1276–1277
112. Lenox RH, Weaver LA, Saran BM. Tardive dyskinesia: clinical and neuroendocrine response to low dose bromocriptine. *J Clin Psychopharmacol* 1985, 5:286–292
113. Alphs LD, Davis JM. Cholinergic treatments for tardive dyskinesias. In: Bannet J, Belmaker RH (eds) *New directions in tardive dyskinesia research*. Modern problems in pharmacopsychiatry. Basel, Karger, 1983, 21:168–186
114. Thaker GK, Ferraro TN, Hare TA, Tamminga CA. Pathophysiology and therapy of tardive dyskinesia: the GABA connection. In: Wolf ME, Mosnaim AD (eds) *Tardive dyskinesia-Biological mechanisms and clinical aspects*. Washington DC: American Psychiatric Press, 1988:199–215
115. Casey DE. Tardive dyskinesia: In: Meltzer HY (ed) *Psychopharmacology: The third generation of progress*. New York, Raven Press, 1987:1411–1419
116. Linnola M, Viukari M, Hietala O. Effect of sodium valproate on tardive dyskinesia. *Br J Psychiatry* 1991, 158:503–510
117. Borison RL, McLarnon MC, DeMartines N, Diamond B. Calcium channel antagonists: interaction with dopamine, schizophrenia and tardive dyskinesia. In: Wolf ME, Mosnaim AD (eds) *Tardive Dyskinesia: biological mechanisms and clinical aspects*. Washington DC, American Psychiatric Press, 1988:217–231
118. Gerlach J, Thorsen K, Munkvad I. Effect of lithium on neuroleptic-induced tardive dyskinesia compared with placebo in a double-blind cross-over trial. *Pharmakopsychiatr Neuropsychopharmacol* 1975, 8:51–56
119. Simpson GM, Lee JH, Voitashevsky A, Zoubok B. Lithium in tardive dyskinesia. *Pharmakopsychiatr Neuropsychopharmacol* 1976, 9:76–80
120. Richardson MA, Bevans M, Weber J, Gonzales J, Flynn C, Amira L. *A dietary intervention decreases TD symptoms*. 149th APA Annual Meeting. New York, NY, 1994
121. McGavin CL, John V, Musser WS. Levetiracetam as a treatment in tardive dyskinesia: a case report. *Neurology* 2003, 61:419
122. Wonodi I, Adami H, Sherr J, Avila M, Hong LE, Thaker GK. Naltrexone treatment of tardive dyskinesia in patients with schizophrenia. *J Clin Psychopharmacol* 2004, 24:441–445
123. Lerner V, Miodownik C, Kaptsan A, Cohen H, Matar M, Loewenthal U, Kotle M. Vitamin B6 in the treatment of tardive dyskinesia: a double blind, placebo controlled, crossover study. *Am J Psychiatry* 2001, 158:1511–1514
124. HayDP, HayL, Blachwell B, Spiro HR. ECT and tardive dyskinesia. *J Geriatric Psychiatr Neurol* 1990, 3:106–109

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