Tardive Syndromes

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Abstract

Dopamine receptor blocking antipsychotics, first introduced to clinical practice in 1952, were hailed as a panacea in the treatment of a number of psychiatric disorders. Within 5 years however, this notion was to be shattered by the recognition of both acute and chronic drug-induced movement disorders which can accompany their administration. Tardive syndromes, denoting the delayed onset of movement disorders following administration of dopamine receptor blocking (and also other) drugs, comprise diverse manifestations ranging from the classic oro-bucco-lingual dyskinesia, through dystonic craniocervical and trunk posturing to abnormal breathing patterns.

Despite having been an important part of clinical movement disorder practice for over 60 years, the pathophysiologic basis of tardive syndromes remains poorly understood and the optimal treatment approach remains unclear. This review summarises the current state of knowledge relating to tardive syndromes, and provides clinicians with pragmatic, clinically focused guidance with which to tackle the disorder.

Introduction

Movement disorders occurring as a direct iatrogenic consequence of the administration of dopamine receptor blocking neuroleptic drugs were first reported in 1957, five years after their introduction into psychiatric practice. The year 1964 saw their first collective description as a 'tardive' (drawn from the latin *tardus*, meaning late) phenomenon [1], reflecting their delayed onset following medication administration, in contrast to 'acute' dystonic reactions, which can also occur following dopaminergic blockade. This term was rapidly adopted, and in the following decades, a flurry of publications were to expand the phenotypic spectrum of the disorder. Concurrently, theories aiming to explain disease pathogenesis began to emerge, and a number of therapeutic strategies were explored. This review provides physicians with a pragmatic, clinically-based platform with which to approach tardive syndromes. In addition,

we explore some recent developments in our understanding of disease pathophysiology, discuss how to approach treatment of tardive syndromes and try to dispel some commonly held myths along the way.

A necessary preamble to this review is a brief foray into nosology. Indeed, tardive syndromes (TS) are plagued by inconsistent use of descriptive language. The term 'Tardive dyskinesia', when first introduced, was intended to subsume the range of diverse movements which can emerge in a delayed fashion following long-term neuroleptic administration. However, more recently, a less confusing approach which classifies tardive movements according to their individual clinical phenomenologies, has been promoted, and will be used in this review. Accordingly, 'Tardive syndrome' is employed as the umbrella term for any/all potential tardive movement disorders. Meanwhile, 'Tardive dyskinesia' is reserved as a descriptor of a specific clinical entity, namely that of the characteristic oro-bucco-lingual choreiform movements (see below).

The scale of the problem

Tardive syndromes (TS) are a predictable, sometimes permanent, disabling consequence of medication administration. They are predominantly encountered in the psychiatric population, where they exacerbate the burden of social stigma and are linked to poorer quality of life and increased morbidity and mortality[2,3]. Antipsychotics are by far the most common offenders, though numerous other drugs have also been implicated (table 1).

Table 1: Examples of Medications known to cause Tardive syndromes[4–11]

Antipsychotics	**Risk of Tardive Syndrome***
· 'Typical'	
Haloperidol	High
Droperidol	High

Loxapine	High
Chlorpromazine	High
Fluphenazine	High
Thioridazine	High
Trifluoperazine	High
Sulpiride	High
Zuclopenthixol	High
Perphenazine	Moderate
Molindone	Moderate

- 'Atypical'

Quetiapine	Low
Olanzapine	Low
Risperidone	Low
Paliperidone	Low
Clozapine	Very Low
Amisulpiride	Low
Ziprasidone	Low/Moderate
Aripiprazole	Very Low
Lurasidone	Moderate

Antidepressants

- ***MAOIs***
  - Phenylzine — Low/moderate
- ***SSRIs***
  - Citalopram — Low
  - Escitalopram — Low
  - Fluoxetine — Low
  - Fluvoxamine — Low
  -
- ***SNRIs***
  - Venlafaxine — Low
  - Duloxetine — Low
- ***TCAs***
  - Amitryptiline — Low
  - Imipramine — Low

Antiemetics

- Metoclopramide — Low/Moderate
- Prochlorperazine — Low/Moderate

Anticholinergics

- Benzhexol — Low
- Orphenadrine — Low
- Procyclidine — Low

Antiepileptics

- Carbamazepine — Low
- Phenytoin — Low
- Ethosuximide — Low

Mood Stabilisers

- Lithium — Low/moderate

Antimalarials

- Chloroquine — Low
- Amodiaquine — Low

Antihistamines

- Hydroxyzine — Low

Anxiolytics

- Alprazolam — Low

Calcium Channel blockers

- Amlodipine — Low

Stimulants

- Amphetamines — Low
- Methylphenidate — Low

Dopamine Depletors

- Tetrabenazine — Very low

* The risk of developing tardive syndromes, as they relate to individual medication administration is a complex issue. It depends not only on the medication itself, but on a variety of other factors including medication dosage and duration of administration, co-administration with other medications capable of producing tardive syndromes, patient comorbidities and critically, the age of the patient. As such, this expression of 'risk' is intended purely as a general guide, and each case must be assessed on its merits.

The condition affects between 20-50% of patients receiving neuroleptic drugs[12]. Advancing age is the most robust risk-factor for the development of TS, with yearly incidence rates increasing from 5% in those under 40 years of age to 12% or higher in older age groups[12–14]. Risk increases cumulatively with duration of exposure and cumulative dose, culminating in an incidence of 20-25% after 5 years of exposure[15,16].[17]. These statistics must also be interpreted in the knowledge that medication compliance rates among the schizophrenic population are around 50%, so these figures may well be an underestimate[18].

Numerous other factors may increase one's risk further, including history of an affective disorder, previous organic brain damage, diabetes mellitus, female sex (oestrogen perhaps being protective pre-menopausally) and race[19]. Indeed, Asians have on average have lower (roughly 20%) and African Americans on average higher disease prevalence as compared to Caucasians [19–21].

Disease Pathophysiology

The pathophysiologic basis of tardive syndromes remains poorly understood. This uncertainty is reflected in the great number of theories which purport to explain the delayed development of these movement disorders.

The earliest theory to gain popular acceptance was the so-called dopamine receptor hypersensitivity theory. This suggested that administration of dopamine blocking neuroleptics led to compensatory up-regulation and/or hypersensitivity of post-synaptic dopamine (particularly D2) receptors [22,23]. Hypersensitivity of these receptors, which are expressed on indirect pathway medium spiny neurons and are inhibitory, would have the net effect of pallidal and subthalamic nucleus dis-inhibition, producing abnormal hyperkinetic movements[22]. This hypothesis was largely based on clinical observations, such as the greater likelihood of TS in patients receiving potent D2 blockers and the apparent improvement in tardive dyskinesia with additional dopaminergic

blockade, as well as on some animal studies[22,23]. However, evidence in humans for such alterations is lacking. There is no correlation between in-vivo striatal D2 receptor ligand binding assessed by PET and TD severity. Equally, post-mortem studies have not demonstrated significant differences in D2 receptor numbers in those with and without TS[22]. Moreover, this theory fails to explain why many patients fail to recover following cessation of the offending medication- if the only problem was receptor up-regulation/hypersensitivity, one would expect this to normalize following drug withdrawal.

An alternative hypothesis is that TS actually represents a neurodegenerative disorder of striatal interneurons induced by oxidative stress. This theory, which is supported somewhat by animal and human neuropathological studies[24,25], holds that dopaminergic receptor blockade causes increased dopamine turnover and oxygen free radical production by monoamine oxidase[22]. These free radicals are thought to be toxic to striatal interneurons, causing gliosis within the basal ganglia, explaining the persistence of symptoms after medication discontinuation. The significant and sustained improvement sometimes observed following deep brain stimulation for TS may argue somewhat against this idea however.

A further theory implicates damaged or dysfunctional striatal GABAergic neurons in the pathogenesis of TD. These neurons synapse on the soma of medium spiny neurons, providing potent feedforward inhibition, balancing activity in the direct and indirect basal ganglia pathways and providing surround inhibition[22,23]. Selective lesioning of these neurons has been shown to produce dyskinesia[26]. Long-term D2 agonism, in theory, has the potential to damage GABAergic interneurons via glutamate-mediated excitotoxicity and increased oxidative stress from dopamine turnover[27].

Finally, altered NMDA-mediated synaptic plasticity has been suggested as a somewhat unifying theory. Antipsychotics are known to influence NMDA

receptor mediated synaptic plasticity. In this setting, patterns of abnormal neurotransmission e.g. secondary to D2 receptor hypersensitisation could be abnormally potentiated, perpetuating a cycle of abnormal sensorimotor integration and abnormal tardive movements[22].

Of course, not everyone who is exposed to neuroleptic drugs will develop a tardive syndrome, implying that other, possibly genetic factors are at play, conferring increased vulnerability to TS. Genome wide association studies have identified some potential candidate genes, though their relevance to clinical practice remains to be determined[28].

Making the diagnosis-the devil is in the detail

The following section describes both the typical (or perhaps simply better recognized!) and less typical presentations of TS. One must be mindful however that individual components of the syndrome rarely occur in isolation. Rather, they generally coexist to greater or lesser degrees (though one may be dominant), and it is often the identification of multiple movement phenomenologies compatible with TS which allows a confident diagnosis to be made. A vital part of the evaluation is therefore not only identification of a movement which is potentially tardive in aetiology, but actively searching for the presence of other compatible abnormalities. Failing notice clues such as a fidgety patient (akathisia) who sighs deeply (respiratory dyskinesia) and moves his legs back and forth during the consultation (stereotypies), can rapidly lead one down the wrong diagnostic path.

Though diagnostic criteria for TS have been developed (table 2), in clinical practice, there are really only two questions which matter:

1. Is there a history of dopamine receptor blocking (or other TS-causing) drug administration (either prescription medication, over the

counter/traditional remedies, or poisoning), and what is the temporal relationship of this to the onset of the movement disorder?

2. Is the clinical phenomenology compatible with a tardive syndrome (see below)?

Table 2: Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) definition of tardive syndromes

Tardive syndromes are movement disorders distinguished by their late emergence in the course of treatment and their potential persistence for months to years, even in the face of neuroleptic discontinuation or dosage reduction.

Symptoms develop in association with the use of a neuroleptic medication for at least a few months.

Symptoms may develop after a shorter period of medication use in older persons.

The 'typical' tardive syndrome

'Classic' tardive dyskinesia involves stereotyped choreoathetoid movements predominantly involving the lips, tongue and perioral region. The movements tend to predominate in the lower face, with frontalis involvement being unusual. Patients often move the tongue in a writhing motion inside the mouth, are prone to frequent rapid tongue protrusion ('flycatcher tongue'), and pushing of the tongue against the inside of the cheek, creating a bulge ('bonbon sign'). Chewing and/or grimacing movements, lip smacking and puckering are typical. This may

be accompanied by low amplitude choreiform movements of the distal limbs, the so-called 'piano player' dyskinesia, due to their resemblance to finger movements on piano keys[29]. Patients are often unaware of these involuntary movements, though those involving the lips and tongue may cause problems with feeding.

Tardive dyskinesia is usually accompanied by one or more of the following tardive phenomena:

-*Tardive akathisia*, which is an uncomfortable sense of inner restlessness, requiring the affected individual to repeatedly move about in order to ease this unpleasant sensation. This can include rocking in place when seated, marching when standing, repetitive scratching or rubbing or indeed just appearing generally 'fidgety' during the consultation.

-*Tardive stereotypies:* these are patterned, purposeless, repetitive and somewhat ritualistic movements which may appear as truncal rocking, pelvic thrusting, to-and-fro leg movements, hand wringing or crossing/uncrossing of the legs. They may resemble akathisia but in contrast, stereotypies are not accompanied by inner restlessness.

-*Tardive dystonia*: As with most tardive syndromes, tardive dystonia adopts distinct phenomenological characteristics which are easily identified by the trained observer. The disorder frequently involves the craniocervical region, often manifesting as retrocollis. Dystonia may extend to the trunk, as opisthotonic posturing, while in the arms, abduction, internal rotation and wrist flexion is the classically adopted posture[29]. Blepharospasm may also emerge. In contrast to other TS, tardive dystonia appears particularly prevalent in young men around the age of 40 years[24]. Remission is also less likely than with tardive dyskinesia, particularly with drug exposure beyond 10 years [24].

The following tardive disorders are less well defined, with only a handful of cases reported in the literature.

-*Tardive Tourettism* is a rare disorder characterized by the emergence of multiple motor and verbal tics following exposure to dopamine receptor blocking drugs. The tics are generally similar to those of primary tic disorders, exhibiting suppressibility, build up of tension prior to the tic and release of tension upon performance of same[30,31].

-*Tardive tremor*

The entity of tardive tremor was first proposed in a 1992 report of five patients with a 3-5Hz postural and action greater than rest tremor without coexistent parkinsonism[32]. Though bearing some similarities to parkinsonian tremor, tardive tremor is said to be differentiated from the former by its postural and kinetic (rather than rest) predominance, its coarse disabling nature, its lack of responsiveness to levodopa and its occasional improvement with further dopaminergic blockade or tetrabenazine[32,33]. The syndrome generally persists despite DRBA withdrawal.

-*Tardive myoclonus*

Tardive myoclonus describes brief, upper-limb predominant postural myoclonic movements which are said to be a consequence of long-term dopaminergic blockade[34,35]. The literature on this entity is highly limited however, and therefore should be interpreted with caution.

-The phenomenon of *Tardive Gait* has also been described. Though poorly characterized and not uniform, gait disturbances have been described as 'dancing' (multiple short steps followed by a long step) or 'duck-like' (broad based with short stride length and some steppage features). Other abnormalities include initial floor contact with toes rather than heels, spastic qualities and abnormal armswing[36].

Some rather 'atypical' presentations

Patients with TS not infrequently exhibit other less recognized, but nonetheless characteristic features which point towards the diagnosis. Among these, respiratory phenomena, tardive pisa syndrome and withdrawal emergent dyskinesia are particularly important to be aware of.

-First described in 1964, *Respiratory Dyskinesia* involves periodic disturbances of respiratory rate, rhythm and amplitude, sometimes accompanied by respiratory pauses or forced inspiration against a closed glottis[37]. Patients may complain of dyspnoea, dysphonia, or may be seen to huff, grunt, gasp or take short, rapid breaths[38]. These respiratory phenomena often accompany other more classic tardive motor features.

-*Tardive Pisa syndrome*

Predominantly affecting older women, tardive pisa syndrome describes a drug-induced persistent truncal dystonia manifesting as tonic lateral flexion, occasionally accompanied by slight rotation [39]. The 'laterally leaning patient' is an important clue to a tardive aetiology.

-*Withdrawal emergent dyskinesia* is considered a variant of tardive dyskinesia which is generally observed following either abrupt discontinuation or significant dose reductions in neuroleptic medications[40]. The syndrome predominantly affects children, and usually manifests as generalized chorea (as opposed to the facial-predominant movements observed in classic TD). It is usually self-limiting after days to weeks[40].

-*Tardive oculogyric crises*

Originally described as a characteristic feature of encephalitis lethargica and now more commonly associated with medication-related acute dystonic reactions (as well as dopamine synthesis pathway defects), oculogyric crises can rarely occur as a tardive phenomenon in patients chronically exposed to antipsychotic medications[41,42]. Tardive oculogyric crises often accompany other tardive motor phenomena and may go unrecognized. They are not infrequently associated with transient recurrences of psychiatric symptoms ranging from anxiety, hallucinations and bizarre behavior to auditory hallucinations[41].

-A variety of *tardive pain syndromes* have also been described, temporally associated with neuroleptic use and often responding to standard TS treatments. Examples include tardive oral pain, which describes an uncomfortable, often burning sensation in the mouth and lips, and painful genital syndrome, with similar affliction of the genital region[43].

-*Tardive bruxism*
Bruxism, of either the grinding or mixed grinding-clenching type has been described as a side-effect of long-term neuroleptic exposure. It likely represents a forme fruste of tardive oromandibular dystonia[44]. Noise production is often a striking feature of the syndrome, at times so severe as to annoy roommates. The movements disappear during sleep.

Assessing TS severity

Prior to initiating a patient on dopamine receptor blocking drugs, clinicians should strive to document the presence of absence of abnormal involuntary movements. While both physician and nurse-led standardized assessment tools (such as the abnormal involuntary movement scale (AIMS) and Scanmove instrument, respectively) may not always be practical in the busy clinical setting[45,46], a focused examination is nevertheless important. It was recognized over 140 years ago that psychiatric patients may exhibit stereotypies,

chorea or abnormal facial grimacing as a result of their disease-failure to document this prior to treatment may lead to these later being mis-attributed to a drug effect[47,48].

There have also been publications suggesting that a certain number of older people develop spontaneous movements of the face as part of normal ageing. Whether this is true or merely represents the emergence of facial or cranio-cervical dystonic syndromes with age is yet to be resolved.

Facts and fallacies

Myth no. 1: Second generation antipsychotics, with their lower D2 binding affinity, have reduced the incidence of tardive syndromes

This has been a particularly contentious issue and making a definite statement in either direction is difficult. What can be said with certainty is that the introduction of second-generation antipsychotics has not done away with TS. Rather, due to rapid uptake in their prescription, including off-label use for mood disorders and sleep, they may ironically have contributed further to the problem.

While some studies suggest that the incidence of TS with second generation antipsychotics is not vastly dissimilar from that of their first generation counterparts[10,49], the largest literature review to-date involving 34, 555 patients treated with antipsychotics across 56 studies found an annualized incidence rate of 2.98% with second-generation antipsychotics versus 7.7% with first-generation antipsychotics, supporting the claim that SGA may indeed carry a lower risk[50]. This is also supported by a recent large meta-analysis of 57 studies on TS[9].

Myth no. 2: Prolonged exposure to a causative drug is necessary in order to be at risk of TS.

Though, as detailed above, the cumulative risk of TS increases year-on-year and most patients develop the disorder after at least 1-2 years of drug exposure[23,24], there are reports of its occurrence after just a single dose of neuroleptic. Prolonged drug exposure is therefore not a necessary pre-requisite.

Myth No.3 Some neuroleptics are safe

The recognition that first generation ('typical') antipsychotics were associated with a number of extrapyramidal side-effects prompted the development of newer compounds, termed 'atypical' antipsychotics, which were supposedly defined by the absence of extrapyramidal symptoms at therapeutic doses. Numerous mechanistic differences of these newer compounds, including effects on serotonergic signaling, more rapid dissociation from the D2 receptor, limbic selectivity, and in the case of aripiprazole, partial dopaminergic agonism were posited as the reason behind their more favourable side effect profiles.
While it is true that not every neuroleptic has the same propensity to cause tardive syndromes, none are devoid of risk. All classes of antipsychotics can produce tardive syndromes [20,51]. Nevertheless, newer 'atypical' agents probably carry about half the risk of producing later TS as compared to their 'typical' counterparts[9]. Furthermore, it is important to remember that it is not just neuroleptics which are implicated in the development of tardive syndromes (table 1).

Differential diagnoses not to miss, and how to spot them:

Differentiating spontaneous from drug-induced movement disorders in patients with psychiatric illness can be a challenging endeavor. It is nonetheless imperative to ensure that adequate thought has been given to exclude important differential diagnoses which can present with the combination of psychiatric

disease and abnormal movements[29]. The following conditions are important to keep in mind:

1. *Huntington's disease*

As a trinucleotide repeat expansion disorder with the cardinal manifestations of chorea, psychiatric disease and cognitive decline, HD is one of the most important differential diagnoses of tardive dyskinesia. Psychiatric disease (often requiring neuroleptic treatment), can precede the development of hyperkinetic movements in HD by a number of years. The emergence of the latter can therefore easily be mis-diagnosed as tardive by the inexperienced observer.
In this setting, some clinical clues can be particularly helpful[52]. These include:

a. The nature of the hyperkinetic movements: hyperkinetic movements in tardive dyskinesia tend to be stereotyped and semi-purposeful, as opposed to the random, flowing movements of chorea which typify HD.
b. Topographical distribution: in TS, movements tend to predominate around the lower face and axially (manifesting as retrocollis and opisthotonus). In contrast, HD patients often have significant limb chorea, which is unusual in TS. Hyperkinetic movements of the frontalis muscle are also common in HD, but uncommon in TS
c. Eye movements: Eye movement disorders are often a prominent, early feature of HD. They can involve disorders of saccadic initiation, broken pursuits and gaze impersistence. Eye movements are generally normal in TD, making a careful oculomotor examination an important part of the evaluation of all tardive syndromes.
d. Motor impersistence (of grip, tongue protrusion or gaze fixation) is a classic feature of HD, but is very uncommon in TD, and therefore a valuable clinical sign.
e. Other features of tardive syndromes such as akathisia and opisthotonus are highly suggestive of TS. Conversely, a family history suggesting dominant inheritance and caudate atrophy on MRI would point to a diagnosis of HD.

2. *Anti-NMDA receptor encephalitis*

   A number of autoimmune movement disorders can have co-existent neurobehavioural features-these are extensively reviewed elsewhere[53]. Anti-NMDA receptor encephalitis in particular however, could be confused with tardive dyskinesia, due to the prominent stereotyped perioral dyskinesia which typifies the disorder. The condition presents differently depending on age, with children having more 'neurological' (seizures, movement disorders) phenotypes, while adults tend to present with neurobehavioural syndromes, which can be mistaken for psychosis[54]. Sometimes, the neuropsychiatric features require neuroleptic treatment, creating an additional pitfall in the diagnostic pathway. A 'full house' of symptoms, including autonomic dysfunction, generally develops within 1 month[54]. Clinical suspicion should lead to testing for the causative antibody in serum and cerebrospinal fluid.
3. *Wilson's disease* should always be kept in the differential diagnosis of any movement disorder, especially in patients under the age of 40 years (though late presentations are reported). Psychiatric symptoms are common in Wilson's disease, and perioral movements are also classic. However, they tend to assume a more dystonic quality, frequently producing risus sardonicus. Dysarthria and drooling are also common in WD, but unusual in tardive dyskinesia.
4. *Edentulous dyskinesia* is a hyperkinetic movement disorder affecting 15% of the edentulous population[55] in which stereotyped, choreiform perioral and lip movements bear striking resemblance to the tardive oro-bucco-lingual dyskinesia. The disorder is present under conditions of partial or complete edentulism, and often resolves or significantly improves with the introduction of dentures to the mouth. Its pathogenesis is thought to relate to altered sensory feedback from oral structures as a result of malocclusion.
5. *Meige syndrome* is a primary dystonic disorder mostly affecting women in their 50s and 60s, characterized by the combination of blepharospasm and oromandibular dystonia. Differentiation from tardive conditions on purely clinical grounds can be particularly difficult, hence a history of

exposure to dopamine receptor blocking agents is critical to thoroughly explore in the history.

Treatment

Management of tardive syndromes should incorporate three key aspects.

First, prevention is always better than cure. As such, medications with documented potential for inducing TS should be used at the lowest possible dose for the shortest period of time possible. This may of course not always be possible.

Second comes the question of medication withdrawal. In actual fact, the evidence that withdrawing the offending drug significantly alters the natural history of tardive syndromes is not as strong as one might think[56]. Nevertheless, this is an intuitive move in clinical medicine-remove the thing which is causing the problem. Most movement disorder physicians would therefore advocate stopping the offending DRBA, or at least changing to a drug with less potential for tardive phenomena, if possible. The alternative drug of choice in this setting is often clozapine, both due to its proven efficacy in the treatment of, and its lower risk of inducing TS[57–59]. Close consultation with the psychiatric services is necessary prior to embarking on such a course of action. It is also important to realize that tardive symptoms may initially worsen following neuroleptic drug withdrawal, and that equally the symptoms may be suppressed by switching to a more potent dopamine receptor blocking agent[60].

Finally comes the question of symptomatic treatments for tardive syndromes. Numerous agents have been trialled in this regard, with varying evidence for their effectiveness.

As mentioned before, TS are often a complex medley of different movement disorders, and approaches which may be effective for one movement may worsen another. A tailored approach, focused on addressing the issue which is primarily bothersome for the patient is therefore paramount; generally, this will be either tardive dyskinesia or tardive dystonia.

Concerning tardive dyskinesia, the mainstay of medical treatment resides around the administration of vesicular monoamine transporter-2 (VMAT-2) inhibitors (tetrabenazine, deutetrabenazine, valbenazine-the latter two being the only FDA approved drugs for the treatment of TD), which act through pre-synaptic dopamine depletion. The main side effects of these medications are the development of reversible parkinsonism, as well as dose-dependent mood changes, particularly in the elderly; the side-effect profiles of deutetrabenazine and valbenazine appear significantly more favourable [61].

Other compounds which are worth a mention include Amantadine, which has shown antidyskinetic properties in multiple controlled and uncontrolled studies, and is supported by AAN guidelines for short-term treatment of tardive dyskinesia. Propranolol has surprisingly good data to support its use, though this is likely due to its effect of increasing neuroleptic drug levels[47]. Clonazepam also appears effective, though in the randomized controlled trial setting it appeared to lose its efficacy after 5-8 months and thus can only be tentatively recommended for short-term use. A number of antioxidants have also been trialled. Data surrounding their efficacy is largely inconclusive[60]. Other options such as additional dopaminergic blockade e.g. with haloperidol, have proven efficacy in reducing tardive dyskinesia, at least in the short-term. This however comes at the cost of an increase in akinetic rigid syndromes. Furthermore, there is insufficient data on the long-term effects of such approaches, and given that these agents have great propensity to cause TS, additional potent dopaminergic blockade is not recommended as a treatment strategy in TS[60].

For tardive dystonia, botulinum toxin is an effective option [23]. Trihexyphenidyl can also improve dystonic syndromes, though occasionally at the cost of worsening dyskinesia.

For both tardive dyskinesia and dystonia, an approach which is gaining increasing recognition is that of functional neurosurgery. Indeed, pallidal deep brain stimulation can be greatly beneficial, and early referral to a centre with experience in this procedure should be encouraged in refractory or debilitating cases[62]. Physicians may be reluctant to recommend this procedure due to the risk of worsening underlying psychiatric comorbidity, though in practice, this is seldom an issue, especially with pallidal targets[62]. Pallidotomy can also been considered in poor surgical candidates.

Tardive akathisia can be equally bothersome, but there is a dearth of evidence regarding its optimal treatment. Clonidine, moclobemide, benzodiazepines and even electroconvulsive therapy (ECT) has been used in some instances, with varying degrees of success[63–66]. Tardive pain syndromes often respond to VMAT-2 inhibitors, though other options such as ECT have been used[43]. Withdrawal emergent dyskinesia often settles spontaneously over a few weeks without treatment. Severe symptoms can however be managed by reintroduction of the offending drug, followed by a slower taper.

Patient outcomes

In an ideal world, patients developing TS would have their causative neuroleptic treatment stopped. Then, and only then, could the true reversibility of the syndrome be assessed. The nature of psychiatric disease however means that ongoing treatment is often necessary, making assessment of TS outcomes difficult. Predictors of poor outcome appear similar to those of developing TS in the first place, and include advanced age, longer duration of antipsychotic treatment and greater cumulative dose[67]. Once established, TS severity often

fluctuates over time, though in a significant proportion, the TS fails to resolve[56,68].

Key points

- Tardive syndromes often comprise a multitude of characteristic movement disorders. Each of these should be carefully examined for in suspect cases.
- Clozapine is the drug of choice for patients with TS who require ongoing neuroleptic treatment
- VMAT-2 inhibitors such as tetrabenazine, deutetrabenazine and valbenazine are the best medical treatment options for tardive dyskinesia
- Pallidal deep brain stimulation is an effective treatment option in refractory or debilitating tardive syndromes

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