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## Dystonia Secondary to Use of Antipsychotic Agents

Nobutomo Yamamoto and Toshiya Inada  
*Seiwa Hospital, Institute of Neuropsychiatry, Tokyo,  
 Japan*

### 1. Introduction

Following the introduction of first-generation antipsychotics (FGAs) in the early 1950s, there was a radical change in the therapeutic regimens for schizophrenia. However, it soon became apparent that these antipsychotic agents produced serious side effects including distressing and often debilitating movement disorders known as extrapyramidal symptoms (EPS). To prevent EPS, second-generation antipsychotics (SGAs) were developed and introduced, including risperidone in 1996, quetiapine, perospirone, and olanzapine in 2001, aripiprazole in 2006, and blonanserin in 2008. Clozapine was approved in 2010 in Japan with strict regulation of its use. These newer medications differ from FGAs, primarily on the basis of their reduced risk of inducing EPS. EPS lie at the interface of neurology and psychiatry and have generated a vast literature in both disciplines. EPS can be categorized as acute (dystonia, akathisia and parkinsonism) and tardive (tardive dyskinesia, tardive akathisia and tardive dystonia). Acute EPS has often been reported as an early sign of predisposition to tardive dyskinesia. Acute and tardive EPS may also adversely influence a patient's motor and mental performance and reduce compliance to treatment. Poor compliance leads to high relapse rates, with both ethical and economic consequences. Acute dystonic reaction is a common side effect of antipsychotics, but can be caused by any agents that block dopamine receptors, such as the antidepressant amoxapine and anti-emetic drugs such as metoclopramide.

Dystonia is characterized by prolonged muscle contraction provoking slow, repetitive, involuntary, often twisting, movements that result in sustained abnormal, and at times bizarre, postures, which eventually become fixed. Patients who have developed dystonic reactions often feel extremely uncomfortable, or suffer chronic pain. Dystonia is a symptom rather than a specific disease, and has many causes. This article reviews antipsychotic-induced acute and tardive dystonia (Inada et al, 1990).

### 2. Acute dystonic reaction

Antipsychotic-induced acute dystonic reaction often occurs within the first few days of antipsychotic treatment or when the dosage is increased. It has been reported that approximately 90% of these reactions occur within the first three to five days (Ayd, 1961; Lehan et al, 2004). If untreated, acute dystonic reaction may last hours or days. When the

cause is a long-acting depot injection, the duration of the acute dystonic reaction may be particularly long. This is often distressing and frightening for the patient, and may even be dangerous, possibly causing loss of drug adherence. Thus, acute dystonia continues to be a serious problem in the treatment of psychotic disorders. FGAs, such as butyrophenones, are the antipsychotics with the greatest likelihood of producing these complications (Lehan et al, 2004). As a result of the gradual increase in the use of SGAs in Japan, the incidence of antipsychotic-induced acute dystonic reaction has gradually decreased. Among all patients treated with antipsychotics, acute dystonic reactions occur in 2-10%, among whom the symptoms appear within days of therapy initiation in approximately 2-3% (Ayd, 1961). In Japan, there have been several reports on the prevalence of acute dystonic reactions. Kondo et al. (1999) reported that acute dystonic reactions developed in 51% of schizophrenic patients treated with nemonapride, and that 90% of them occurred within 3 days of therapy initiation. Yasui-Furukori et al. (2002) reported that acute dystonic reactions developed in 10 of 33 patients with acute schizophrenia treated with bromperidol. In a recent double blind study comparing the efficacy of blonanserin, an SGA developed in Japan, with that of risperidone, dystonia occurred in 2.8% of patients treated with risperidone and 4.5% of patients treated with blonanserin (Miura, 2008). Long-acting depot injections, such as haloperidol decanoate and fluphenazine decanoate, usually produce dystonic reactions within 72 hours after delivery (Tarsy, 1984). Data showed that the occurrence of acute dystonia could be lower in patients with schizophrenia receiving long-acting depot antipsychotics than in those receiving oral agents (Inada & Sasada, 2004). Miller and Jankovic (1990) reported that 24% of patients with antipsychotic-induced movement disorders had dystonia, but that such disorders were relatively rare in patients who received SGAs. Risperidone long-acting injectable (RLAI) was first approved in Japan as a long-acting depot SGA antipsychotic for the treatment of schizophrenia in 2009. Kamishima et al. (2009) reported that there was no significant difference between oral risperidone and RLAI. Kamishima et al. (2009) reported that dystonic reactions developed in 7.2% of patients with schizophrenia treated with RLAI within 48 weeks. In addition to the use of high-potency conventional antipsychotics, other risk factors for acute dystonic reactions include young age, male gender, high doses and intramuscular administration. A history of acute dystonic reaction has been identified as the most powerful predictor of a patient developing the condition. In a prospective study, cocaine use was also found to be a risk factor (Van Harten et al, 1998). The psychiatric aspects of acute dystonic reaction are related to the fear and anxiety associated with the unpredictable, sudden onset of involuntary movements and the loss of control of specific muscle groups. This can be particularly intimidating to psychotic patients with paranoid delusions about external forces attempting to control them.

Drug-induced dystonic movements are caused mainly by blockade of dopamine receptors. Dopamine is one of several transmitters that act on the central nervous system, and numerous dopamine receptor subtypes have been found in the extrapyramidal system. Dopamine D2 receptors are those most strongly associated with the efficacy of antipsychotics, and their blockade is at least partially responsible for the movement disorders like those in acute dystonia. Although also known to block other receptors, FGAs exert their therapeutic action primarily by blocking D2 receptors in the central nervous system, and have a high risk of inducing such side effects. SGAs are effective against psychosis and, at therapeutic doses, seldom cause EPS including acute dystonic reaction. Their therapeutic effects are attributable to central antagonism of both serotonin and

dopamine receptors, and also possibly to relatively loose binding to D2 receptors (Lehan et al., 2004). However, the exact mechanism responsible for acute dystonic reactions is not entirely understood. Although they are related to blockade of the D2 receptor, in common with all antipsychotics, the delay between receptor blockade and onset of clinical symptomatology suggests involvement of additional mechanisms, possibly secondary dopamine receptor hypersensitivity (Mazurek & Rosebush, 1996).

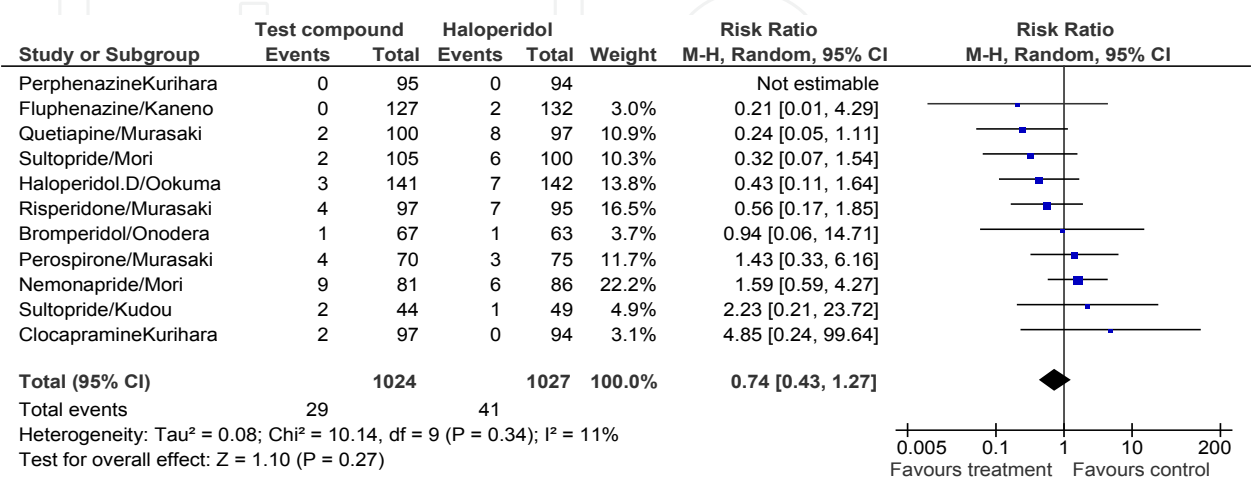


Fig. 1. Comparison of the occurrence of acute dystonic reactions in double-blind randomized controlled trials with haloperidol conducted in Japan (Inada T & Sasada K: Comparison of the efficacy of psychotropic drug at a glance Vol 3 Evidence of side effect and adverse events. Jiho Inc., Tokyo, 16-17 (Article in Japanese).

Acute dystonic reactions are sudden in onset and typically consist of bizarre movements involving tonic contractions of skeletal muscles. Common symptoms include intermittent or sustained muscular spasms. These dystonic reactions are most often localized in the face, neck and upper part of the body, while rarely involving the lower limbs. Laryngeal dystonia occurs only rarely, but may be life-threatening. The specific name of the reaction is derived from the specific anatomic region that is affected. Hence, the terms “torticollis,” “laryngospasm,” “oculogyric crisis,” and “opisthotonos” are used to describe dystonic reactions in the specific body regions. Although oculogyric crisis used to be seen most commonly in postencephalitic parkinsonism, it is now almost entirely attributable to neuroleptic exposure.

3. Tardive dystonia

Tardive dystonia has been considered a late-onset subtype of dystonic reaction characterized by a state of muscle hypertonus, seen in patients who have been receiving antipsychotic treatment for a prolonged period. Tardive dystonia has been considered a rare movement disorder. Although the prevalence of this condition in Japan has been estimated to be only 0.5-2.1% of all schizophrenic patients receiving long-term antipsychotic treatment (Harada 1989; Inada et al., 1991a; Inada et al., 1991b), the development of this condition still remains a potential treatment limitation factor. Van Harten and Kahn (1999) conducted a meta-analysis of 13 studies on the prevalence of tardive dystonia. The estimated prevalence, based on the mean value for all 13 studies, was 5.3%. However, they reported that these data

may have been inappropriate because not all of the studies had used the same criteria for defining tardive dystonia.

Tardive dystonia was first thought to be a subtype of tardive dyskinesia, since it often develops simultaneously with the latter. Burke et al. (1982a) demonstrated that it was correlated with frequent use of antipsychotics, and thereafter it became regarded as an entity independent of tardive dyskinesia. Inada et al. (1990) conducted a statistical trial in order to distinguish between tardive dyskinesia and tardive dystonia. The clinical features of tardive dystonia are usually divided into four categories: 1) focal (only a single body part affected), 2) segmental (two or more segments of a body part), 3) multifocal (two or more non-contiguous body parts), and 4) generalized (combined involvement of at least one leg, trunk and body part) (Fahn et al., 1987). Tardive dystonia often develops insidiously, and in about two-thirds of cases onset is observed in the face, neck, or both. Onset in an arm is less common, and onset in a leg is rare. In about three-quarters of patients, the dystonia progresses to a segmental state, but progression to a generalized state is uncommon. Patients with generalized dystonia are reportedly younger than those with focal dystonia (Van Harten and Kahn, 1999). Tardive dystonia can affect every body area, including twisting of the neck musculature in all directions, blepharospasm and oromandibular, laryngeal, arm, trunk and leg dystonia. The neck regions are most commonly involved, but arm involvement is also common. Blepharospasm is a common focal dystonia of the eyelids. Meige's syndrome is a segmental dystonia involving the eyelids, facial muscles and lower jaw. Both of these two forms are considered to belong to tardive dystonia, but are thought to be less severe than the typical neck or arm dystonia. "Pisa syndrome" is also a subtype of tardive dystonia, characterized by twisting and bending the neck and head to one side of the upper thorax. Oculogyric crisis is a common symptom of acute dystonic reaction, but a tardive form has also been reported (Sachdev, 1993). Tardive myoclonus has been considered a variant of tardive dystonia.

Tardive dystonia is a rare extrapyramidal adverse effect, and many studies have not distinguished it from tardive dyskinesia. Older age is the most firmly established risk factor for tardive dyskinesia. Other risk factors include mood disorders, organic brain dysfunction, diabetes mellitus, alcohol abuse, occurrence of extrapyramidal adverse effects during treatment, and use of high dosages of antipsychotics (Raja, 1998). Gender has also been considered a possible risk factor. Some studies have reported a male predominance whereas others have reported no gender difference. The onset of tardive dystonia seems to occur earlier in males than in females (Van Hatten and Kahn, 1999). In a study of the natural history of tardive dystonia in 107 patients, Kiriakakis et al. (1998) found that males were significantly younger than females at onset, and that the condition developed after a shorter period of drug exposure in men. Fatigue and stress exacerbate the severity of tardive dystonia or the subjective discomfort of affected patients. Relaxation and sleep can alleviate these to some extent. In some patients with bipolar disorder who develop tardive dystonia, their dystonia has been reported to become exacerbated during the depressive phase and to improve or disappear during the manic phase (Sachdev, 1989; Sandyk & Pardeshi, 1990; Yazici et al, 1991).

The pathophysiological background of tardive dystonia is unclear. It is thought to result from hypersensitivity of post-synaptic receptors associated with continuous blockade of dopaminergic neuronal transmission due to antipsychotic drugs (LeWitt, 1995). An anti-noradrenergic action may play an important role because the amount of noradrenaline has been shown to be reduced in the hypothalamus, mammillary body, and other areas



(Hornykiewicz et al., 1986). Go et al. (2009) reported that the prevalence rate of tardive dyskinesia was 20.3% (46 out of 277 patients) in a Filipino cohort of schizophrenia patients receiving SGA. In a recent double blind study comparing the efficacy of blonanserin, an SGA developed in Japan, with that of risperidone, dystonia occurred in 2.8% of patients treated with risperidone and 4.5% of patients treated with blonanserin (Miura, 2008).

#### 4. Diagnosis of dystonia

The differential diagnosis of drug-induced acute dystonic reactions must include cramps, contractures, tetany, acute dystonic reactions to non-antipsychotic agents, catatonia and restless legs syndrome. Catatonia, which is sometimes associated with mood disorder or schizophrenia, can be distinguished by a transient relationship with antipsychotic exposure and response to pharmacological intervention. Neuroleptic malignant syndrome can produce dystonia, but this differs in being also accompanied by fever and generalized rigidity. Acute dystonic reaction may sometimes be misdiagnosed as hysteria or related disorders. These reactions are distinguishable from tardive dystonia or tardive dyskinesia by their sudden onset. Lack of response to anticholinergic agents suggests an alternative diagnosis (Raja, 1998).

Tardive dystonia was first reported by Keegan and Rajput (1973). Burke et al. (1982a) demonstrated that it was correlated with frequent use of antipsychotics, and established the following four criteria for diagnosis of tardive dystonia: 1) presence of dystonic movements or postures; 2) their development during treatment with D2 receptor blockers or within 2 months of treatment discontinuation; 3) a negative family history for dystonia; 4) exclusion of other secondary dystonias, such as Wilson's disease, etc. Tardive dystonia may sometimes coexist with tardive dyskinesia or tardive akathisia. In such cases, the diagnosis should be made on the basis of the most predominant disturbance (Raja, 1998).

The differential diagnosis of tardive dystonia must include acute dystonic reactions, idiopathic dystonia, dystonia induced by other non-antipsychotic agents, Wilson's disease, tardive dyskinesia, etc. A progressive course and possibly a family history of dystonia would suggest idiopathic dystonia. Wilson's disease, an inborn error of copper metabolism, can be manifested as dystonia, but can be ruled out by the presence of a normal serum ceruloplasmin level and absence of a Kayser-Fleischer ring. Acute dystonic reaction almost always occurs within the first day of antipsychotic treatment and usually responds to anticholinergic agents, thus allowing distinction from tardive dystonia. Tardive dystonia, like the other dystonias, is involuntary and cannot be inhibited, thus differing from stereotypes, habit spasms or tics. Secondary dystonia resulting from infections, metabolic disorders, or structured lesions of the brain should be distinguished on clinical grounds (Raja, 1998). Although tardive dystonia can often be confused with tardive dyskinesia, it can be differentiated by the following features: 1) it has different phenomenological manifestations, 2) it has different demographic features: patients with tardive dystonia are younger at onset and lack the female predominance seen with tardive dyskinesia, and 3) it has reactions from those of anticholinergics: they can alleviate tardive dystonia but can exacerbate tardive dyskinesia (Burke, 1992; Greene 1997; van Harten and Kahn, 1999).

Dystonia can also be elicited by compounds other than antipsychotics, such as levodopa, carbamazepine, phenytoin, dextroamphetamine and diphenylhydantoin. Dystonia generally disappears after reduction of the dose or withdrawal of the causative drug. Idiopathic or

primary dystonia can often be differentiated from tardive dystonia by taking a careful medical history at onset of the dystonia in relation to the initiation of antipsychotics. Furthermore, the prevalence of idiopathic dystonia in the general population is only 0.03%, which is much lower than that of antipsychotic-induced dystonia (Van Hatten and Kahn, 1999).

The diagnosis and symptom severity of dystonia have been evaluated using the Drug-induced Extrapyrarnidal Symptoms Scale (DIEPSS), a standardized rating scale for evaluating antipsychotic-induced EPS in Japan. The DIEPSS was developed in Japan (Inada & Yagi, 1995, 1996; Inada, 2009) and has been used widely for the assessment of EPS in Japan. The DIEPSS is designed to evaluate the severity of drug-induced EPS occurring during treatment with antipsychotics, and consists of 8 individual items (gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia and dyskinesia) and one global item. The scale measures the severity of drug-induced EPS on a five-point scale (0-4). Raters should receive basic evaluation training on how to rate the severity of each DIEPSS item by attending DIEPSS workshops so that they can reproduce the stable data (Inada, 1996). Once an increase in muscle tone has been observed and the existence of dystonia has been confirmed, the severity of dystonia can be evaluated depending on the degree of impairment of daily living activity and the distress resulting from this painful condition during the observation period. The degree of abnormal movements resulting from the dystonia should be rated using the dyskinesia item of the scale.

## **5. Treatment of acute dystonic reaction**

The first approach for treating acute dystonic reactions, i.e., the therapeutic strategy initially considered for these conditions, has been reduction of the dosage, or withdrawal, of antipsychotics. Treatment strategies may include switching from a FGA to a SGA. Anticholinergic agents, dopamine agonists and benzodiazepines may often reduce the severity of the acute dystonic reaction.

### **5.1 Switching to a SGA**

The prevalence of acute dystonic reactions is lower in patients receiving SGAs than in those receiving FGAs at clinically effective doses. To date, the SGAs that have been released in Japan are risperidone, perospirone, quetiapine, olanzapine, aripiprazole, blonanserin and clozapine. As EPS, such as dystonia, may result in treatment refusal or non-compliance, the use of, or switching to a SGA with a significantly lower risk of EPS is very important. However, the risk of EPS cannot be ignored; emergence of EPS with risperidone at a dosage of over 6 mg per day has been reported (Lehan et al., 2004).

### **5.2 Anticholinergic agents**

Anticholinergic agents, which have central anticholinergic properties, are often used for the treatment of dystonic reactions. These agents, which are useful not only for curative but also diagnostic applications, usually result in improvement within 10 minutes of parenteral administration, and the peak benefit is evident at 30 minutes. The standard parenteral anticholinergic employed in Japan is intramuscular injection of biperiden 1 vial (5 mg). Intravenous injection of these agents may be considered for relief of life-threatening dystonias, such as laryngospasm. Improvement and peak benefit typically occur within 10

and 30 minutes, respectively, after oral administration. Once an acute dystonic reaction has been controlled, prophylactic use of oral anticholinergic agents is recommended for at least 4 weeks, especially in patients with a history of susceptibility to EPS and patients for whom antipsychotics are known to induce these effects (e.g., first-generation agents, high-dose risperidone) (Lehan et al., 2004). Biperiden and trihexyphenidyl have been released, but benztropine, commonly used for treating acute dystonic reactions in the USA, has not yet been approved in Japan.

The peripheral adverse effects of anticholinergic agents include dry mouth, constipation, blurred vision and urine retention. Anticholinergic agents may also impair memory, and thus worsen cognitive deficits in elderly patients, especially those with pre-existing symptoms of dementia. Anticholinergic agents should be avoided, if possible, in patients with prostatic hypertrophy, urine retention and narrow-angle glaucoma. If a patient cannot tolerate the anticholinergic adverse effects, the lowest effective dosage should be used, or the drug be replaced with a benzodiazepine.

### 5.3 Benzodiazepines

Benzodiazepines are an alternative therapeutic option for patients with acute dystonic reactions in whom anticholinergic agents are contraindicated. Representative benzodiazepines used in Japan include lorazepam, diazepam and clonazepam. Intravenous injection of 5-10 mg diazepam, the only available injectable benzodiazepine for this indication in Japan, can be used in especially severe cases.

### 5.4 Antihistaminic agents

Diphenhydramine, commonly used for treating acute dystonic reactions in the USA, is rarely used for this purpose in Japan. Instead, promethazine (15-50 mg 2-3 times per day) is sometimes used.

## 6. Treatment of tardive dystonia

There is no established therapy for tardive dystonia. Treatment of this condition has been considered even more difficult than that for tardive dyskinesia. Tardive dystonia shows a lower incidence of spontaneous remission than tardive dyskinesia (Raja, 1998).

The first approach for treating tardive dystonia is to evaluate the need for antipsychotics and to reduce their doses, if possible, because antipsychotics are often prescribed for non-psychotic conditions (Burke et al., 1982a, 1982b). Switching from a FGA to a SGA has been recommended in patients receiving FGAs, based on the clinical guidelines for the treatment of schizophrenia. Yamamoto (2005) reported a schizophrenic patient whose antipsychotic-induced Pisa syndrome improved after switching from olanzapine and risperidone to quetiapine. Imai and Ikawa (2011) also reported a case of antipsychotic-induced tardive oromandibular dystonia that improved after switching from sulpiride to aripiprazole. Clozapine, which has been reported to be effective for treatment-resistant schizophrenia, and has been available since 2009, may be the only antipsychotic with an established minimal risk of inducing tardive dyskinesia. Switching to clozapine may be potentially the first choice for patients showing tardive dystonia (Raja, 1998). In humans, clozapine can produce bradykinesia and mild akathisia, but no acute reaction or rigidity has been



reported, and tremor has only rarely. Clozapine has been approved for treatment-resistant or treatment-intolerant patients with schizophrenia. It can be used for treatment-intolerant schizophrenic patients with dystonia showing severity of 3 or higher in the dystonia item of the DIEPSS, after they have received two or more second-generation antipsychotics.

Tetrabenazine has been approved for the treatment of tardive dyskinesia in the United Kingdom. Fahn and Eldridge (1976) and others have reported that it may also be effective for tardive dystonia. However, tetrabenazine has yet to be released in Japan.

High dosages of anticholinergics, such as biperiden and trihexyphenidyl, are reportedly effective in some patients with tardive dystonia. Sugiyama et al. (1996) have reported that tardive dystonia was improved by treatment with trihexyphenidyl 18 mg/day in schizophrenic patients receiving antipsychotics. Benzodiazepines may also exert some benefits in patients with tardive dystonia. Yamamoto et al. (2007) reported a case of methamphetamine psychosis in which tardive dystonia was successfully treated with clonazepam. Treatment with dantrolene sodium is reserved for alternative situations in cases where clonazepam is not effective (Otsuki et al., 1991). Clonazepam should be administered carefully to avoid any adverse effects such as hepatotoxicity.

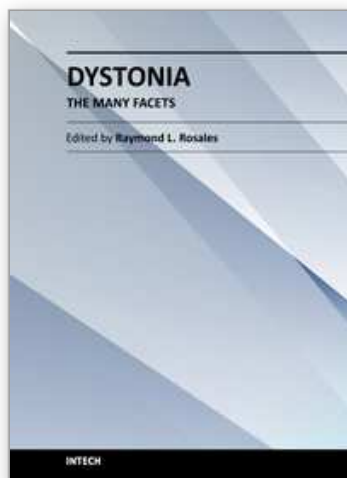
When tardive dystonia is relatively localized, as is the case for focal or mild segmental forms, botulinum toxin, which blocks release of acetylcholine at the neurotransmitter junction, can be considered. Local injections of botulinum toxin are reportedly very effective for treatment of focal dystonia (Jankovic & Brin, 1991). Injection of botulinum toxin in minute quantities into the contorted muscles induces prolonged muscle weakness without systemic toxicity. The therapeutic effects of botulinum toxin last on average 2-6 months as new nerve terminals develop. Excessive weakness of the injected muscle, which is the main adverse effect, is usually mild and transitory. Over 15% of patients may develop neutralizing antibodies in response to botulinum toxin treatment and become non-responders (Raja, 1998). In Japan, botulinum toxin A has been released, but other types of botulinum toxin have not. Kimura et al. (2005) have reported improvement of tardive dystonia in a schizophrenic patient after treatment with botulinum A toxin.

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## **Dystonia - The Many Facets**

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Dystonia has many facets, and among those, this book commences with the increasingly associated genes identified, including a construct on how biology interacts with the dystonia genesis. The clinical phenomenology of dystonia as approached in the book is interesting because, not only were the cervical, oromandibular/lingual/laryngeal, task-specific and secondary dystonias dealt with individually, but that the associated features such as parkinsonism, tremors and spasticity were also separately presented. Advances in dystonia management followed, and they ranged from dopaminergic therapy, chemodenervation, surgical approaches and rehabilitation, effectively complementing the approach in dystonia at the clinics. A timely critical pathophysiologic review, including the muscle spindle involvement in dystonia, is highlighted at the book's end.

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Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
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Phone: +86-21-62489820  
Fax: +86-21-62489821

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