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Managing Antipsychotic-Induced Acute and Tardive Dystonia

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Abstract

Antipsychotic-induced extrapyramidal adverse effects continue to be a serious problem in the treatment of psychotic disorders. While the pathophysiology of these adverse effects is not well understood, much recent research has focused on improving our ability to use available pharmacotherapy in the most effective and least toxic manner.

Acute dystonic reactions only occur within the first days of antipsychotic treatment. They are often distressing and frightening for the patient and may even be dangerous. However, they can be effectively prevented or reversed with anticholinergics. Furthermore, the growing use of the new atypical antipsychotics will lead to a significant decrease in the rate of acute dystonic reactions.

In contrast, tardive dystonia is a long-lasting menace in the course of antipsychotic treatment, for which there is no established therapy. Tardive dystonia is sometimes disabling or disfiguring and, like other tardive disorders, is potentially irreversible. Because, in most cases, patients need to continue taking the antipsychotic that has caused the adverse effect to prevent relapse of the mental illness, preventive measures are crucial. Antipsychotics should be prescribed only for patients affected by psychotic disorders, when definitely indicated and at the

lowest effective dosage. The use of clozapine and other novel antipsychotic agents is also likely to represent an important step in the prevention and treatment of tardive dystonia. Compared with traditional antipsychotics, most of the new antipsychotics are characterised by a low acute extrapyramidal adverse effects liability and they also bring the hope of reducing the risk of tardive disorders. If tardive dystonia has occurred, switching to clozapine or another atypical antipsychotic and treatment with tetrabenazine, reserpine and botulinum toxin are possible options.

1. Extrapyramidal Adverse Effects of Antipsychotics

The extrapyramidal adverse effects induced by antipsychotics remain one of the major problems in the treatment of psychiatric patients. The spectrum of extrapyramidal adverse effects is wide and includes acute dystonic reactions, parkinsonism, akathisia and tardive motor phenomena. Acute extrapyramidal adverse effects occur in up to 75% of patients treated with antipsychotics and they may be an early sign of a predisposition to development of tardive dyskinesia. They may also influence patients' motor and mental performance adversely[1,2] and reduce compliance to treatment.[3] Poor compliance leads to high relapse rates with both ethical and economic consequences. This article reviews acute and tardive dystonia, with emphasis on the issues of their clinical management.

Dystonia is characterised by prolonged muscle contraction provoking slow, repetitive, involuntary, often twisting, movements that result in sustained abnormal, at times bizarre, postures. Eventually, these postures become fixed. Dystonic movements typically interfere with motor performance by superimposing an unwanted posture on parts in use. If the muscle contraction is frequent and sustained, aching pain may be present. Dystonia generally increases during voluntary movements, nervousness, excitement and psychological stress, and decreases during quiet and relaxation, disappearing during sleep. The pathophysiology of dystonia is poorly understood.

Some primary dystonias are caused by specific genic mutations,[4,5] while others are currently being genetically mapped. Understanding the genetic basis of primary dystonias is likely to improve our comprehension of the pathophysiology of dystonic movements and could suggest effective means for treatment. However, it remains uncertain whether the distinct forms of dystonia caused by different aetiologies share a common pathophysiology.

Computerised searches of the MEDLINE databases were conducted covering the years from 1980 to 1997 and using the key words tardive dyskinesia, tardive dystonia, dystonia, clozapine, risperidone, olanzapine, sertindole, quetiapine, botulinum and tetrabenazine. In addition, the references in articles obtained from the computerised searches were checked to ensure that relevant articles not otherwise identified were included. Clinical trials, reviews, commentaries and case reports were considered.

2. Antipsychotic-Induced Acute Dystonic Reactions

Acute dystonic reactions typically occur within a few days of starting antipsychotic treatment (90% of acute dystonic reactions occur within the first 3 days), increasing its dosage or reducing the dosage of an anticholinergic drug used to treat or prevent extrapyramidal adverse effects. Acute dystonic reactions last from seconds to hours and their occurrence is more frequent in the afternoon and in the evening. In a sample of 200 patients taking antipsychotics for the first time, over 80% of the episodes of acute dystonic reactions occurred between 1200h noon and 2300h.[6] The observed circadian variation was not accounted for by sleep, fatigue or time elapsed from the last dose of medication.[6] Risk factors include young age, male gender, use of high-potency antipsychotics, high dose and parenteral administration.[7] Two recent studies found

that higher positive symptoms,[8] higher negative symptoms, and a lower Global Assessment Functioning Scale score[9] were predictors of acute dystonic reactions in patients with first-episode psychosis. A retrospective chart study[10] found that the prevalence of acute dystonic reactions was higher in patients with mania (26.1%) than in patients with schizophrenia (5.9%). However, prospective studies failed to support this finding.[9,11]

Acute dystonic reactions are most often localised in the face, neck and upper part of the body, while rarely involving lower limbs.[12] Acute dystonic reactions are often distressing and frightening, and can have serious consequences such as temporomandibular joint dislocation.[13] Laryngeal dystonias rarely occur but may be life-threatening.[14] As with acute dystonic crises of post-encephalitic parkinsonism, antipsychotic-induced acute dystonic reactions may be accompanied by catatonic symptoms and psychotic experiences with bizarre or dramatic presentation.[15]

2.1 Diagnosis

Although the diagnosis of antipsychotic-induced acute dystonic reactions is usually obvious, the differential diagnosis is extensive and includes: true cramps (related to heat, haemodialysis, electrolyte disturbances), idiopathic cramps (the most common type), contractures (occurring in metabolic myopathies and thyroid diseases), tetany (usually caused by hypocalcaemia), acute dystonic reactions to nonantipsychotic drugs, catatonia, occupational cramps, tetanus and restless legs syndrome.

Acute dystonic reactions are distinguished from tardive dyskinesia or tardive dystonia by their sudden onset, acute discomfort and stress to patients, and rapid resolution after the administration of anticholinergics. Symptoms preceding exposure to antipsychotics, progression of symptoms in the absence of change in medication, no response to anticholinergics or the presence of focal neurological signs suggest alternative diagnoses.

Acute dystonic reactions are sometimes misdiagnosed as 'psychogenic behaviour' or 'hysteria'.[16] Dystonia is uncommonly caused by primary psychological factors[17] and psychogenic movement disorder are uncommon among patients receiving antipsychotics.

2.2 Prevalence

The reported prevalence of acute dystonic reactions has varied from 2.3%[18] to 10%,[7] 16%,[19] 40%,[20] 60%[9] and 94%.[21] These discrepancies probably reflect differences in the examined population, type of antipsychotic drug, dosage and concurrent treatment with other drugs.

In the last decades, the reported incidence of antipsychotic-induced acute dystonic reactions has grown significantly. In 1961, Ayd[18] reported that 2.3% of 3775 patients treated with antipsychotics experienced acute dystonic reactions. In 1964, a US National Institute of Mental Health collaborative study[22] reported an incidence of 6.6%. Until the mid-1970s, reported rates were generally in the range of 6%[23] to 10%.[24] In the late 1970s, several studies reported antipsychotic-induced acute dystonic reaction rates of 37% to 46% in adult patients exclusively[25,26] or principally[20] treated with high-potency antipsychotics, and of 63% in a group of antipsychotic-treated adolescents.[27]

An analysis of pooled data from 9 studies[28] involving 1366 patients being treated with antipsychotics found that the incidence of antipsychotic-induced acute dystonic reactions in patients not receiving prophylactic anticholinergics was 14.8% in all 9 of the studies where patients were treated with any antipsychotic and was 51.2% in 6 studies (330 patients) where patients were only receiving high-potency antipsychotics.[28] The observed increase with time in the incidence of acute dystonic reactions may be attributed to the more frequent use of high-potency antipsychotics and the use of higher dosages than was seen initially.[29]

Antipsychotic-induced acute dystonic reactions are 15 times more common in patients under 35 years of age.[30] Among patients above 50 years of age, men are twice as likely as women to develop acute dystonic reactions. In contrast, the rate of acute dystonic reactions in patients older than 50

years is similar in men and women.[24] The highest incidence rate was found in a population of high risk young male patients.[21]

Antipsychotics from distinct chemical classes cause a diverse incidence of acute dystonic reactions, depending on the degree of their affinity for dopamine D_2, muscarinic and possibly σ-receptors.[10] High-potency compounds carry a higher risk of acute dystonic reactions than low-potency agents. Benzamide derivatives rarely induce acute dystonic reactions.

2.3 Pathophysiology

How antipsychotics induce acute dystonic reactions remains a mystery. Since these reactions tend to occur when plasma antipsychotic concentrations are decreasing after the administration of a single antipsychotic dose,[31] acute dystonic reactions have been attributed to the transient prevailing effect of increased dopamine output, caused by acute antipsychotic treatment, over D_2 receptor blockade.[32,33] This hypothesis is consistent with the finding that acute dystonic reactions are less frequent in the elderly. Since striatal D_2 receptors decrease with age,[34] older patients could have a striatal hypodopaminergic status protecting them from acute dystonic reactions.

However, there is evidence[20,35] suggesting an opposite mechanism, namely a decreased dopamine output: (i) there is a positive correlation between D_2 receptor blockade, antipsychotic potency and the frequency of acute dystonic reactions; (ii) presynaptic dopamine depletors (e.g. reserpine) can cause acute dystonic reactions; and (iii) dopamine agonists show an antidystonic effect. Abnormalities in the reciprocal balance between dopamine and acetylcholine receptor blockade in the basal ganglia could cause acute dystonic reactions.[36] The σ-receptor, which plays a role in the control of movement, might be also involved in the pathophysiology of the acute dystonic reaction.[12]

2.4 Therapy

Anticholinergic drugs (such as biperiden, benzatropine, trihexyphenidyl, orphenadrine) or antihistaminic drugs (such as diphenhydramine) effectively prevent[7,28,37] or reverse acute dystonic reactions.[38] These agents are diagnostic and curative. A prompt therapeutic response to either intramuscular or intravenous diphenhydramine 25 to 50mg or benzatropine 2mg or biperiden 2mg, is virtually diagnostic of acute dystonic reactions. The dose can be administered again if necessary. Intravenous diazepam can be an alternative therapy,[39,40] but the risk of respiratory depression is high. The dystonia is likely to recur unless a maintenance dose of an antiparkinsonian drug is prescribed for several days, even if the antipsychotic is discontinued.

Patients starting antipsychotic treatment should be warned about the possible manifestation of acute dystonic reactions, to avoid panic reactions and should receive instructions on how to manage the acute dystonic reactions adequately. However, acute dystonic reactions may induce problems and anxiety even in informed patients. In these circumstances, patients sometimes show poor compliance to treatment.

Acute dystonic reactions occur in a significant percentage of patients receiving antipsychotics, even when the agents are being administered at low dosages[7] and there is no way to predict which patients are going to experience this adverse effect. Therefore, many clinicians prefer to prescribe anticholinergics from the beginning of antipsychotic treatment. The most recent American Psychiatric Association guidelines[7] suggest that prophylactic anticholinergics may be considered particularly for patients being treated with high potency agents who have a prior history of experiencing acute extrapyramidal adverse effects, for those who prefer preventive treatment to avoid discomfort or distress, or those for whom the occurrence of adverse effects would lead to poor compliance. A WHO consensus statement[41] recommended prophylactic use of these agents in the first weeks of treatment to prevent acute dystonic reactions. Thereafter, anticholinergic treatment should be withdrawn and the need for their continued use should be re-evaluated. The need for anticholiner-

gic treatment should be also be re-evaluated when the antipsychotic dosage is decreased.

Decisions regarding the use of anticholinergics depend on the severity and degree of distress associated with extrapyramidal adverse effects and on consideration of alternative strategies, including lowering antipsychotic dosage or switching to an antipsychotic from a different class. The benefit of using prophylactic anticholinergics should be weighted against the potential for adverse effects. First, anticholinergics can mask some extrapyramidal adverse effects, the occurrence of which can provide useful information (e.g. as indicators for the future development of tardive dyskinesia) or can be a guide to adjusting antipsychotic dosage. For most patients, a dose of antipsychotic drug at which pharmacological activity is first apparent in the form of minimally increased rigidity ('antipsychotic threshold') seems to provide all the therapeutic benefit available to antipsychotic-responsive patients, at least at the beginning of the treatment.[42] Second, these drugs are associated with adverse effects, (e.g. tachycardia, mydriasis, urinary retention, constipation) which are potentially dangerous for patients with heart disease, glaucoma, prostatic disease or ileus, and impair cognitive function, especially in the elderly. Anticholinergics worsen the severity of tardive dyskinesia and may even exacerbate existing psychosis.[43,44] Furthermore, these drugs do have the potential to be abused. Caution is warranted in prescribing anticholinergics to patients with serious risk of suicide because of the toxicity of anticholinergics in overdose.

2.5 Atypical Antipsychotics

The atypical antipsychotics clozapine, risperidone, olanzapine, sertindole and quetiapine cause fewer extrapyramidal adverse effects than typical antipsychotics at clinically effective dosages. Atypical antipsychotics carry a minimal risk, or no risk in the case of clozapine, of acute dystonic reactions. Acute dystonic reactions induced by risperidone have been described, however, their frequency seems to be lower in comparison with typical antipsychotics.[45] In a Canadian multicentre study,[46] risperidone 2, 6, and 10 mg/day resulted in anticholinergic treatment of extrapyramidal adverse effects in 25, 32 and 46% of patients, respectively. In contrast, the extrapyramidal adverse effects rates for haloperidol and placebo were 74 and 23%, respectively.

In a US multicentre, double-blind study,[47] there was no significant difference in the number of patients requiring adjunctive anticholinergic treatment between patients treated with placebo and patients treated with ≤10 mg/day of risperidone. The extrapyramidal adverse effects rate was 38% with risperidone 16 mg/day and 46% with haloperidol 20 mg/day. At our hospital, we have seen only 1 patient presenting with acute dystonic reactions from among 75 patients treated with risperidone at a daily dosage of ≤8mg, slowly titrated (unpublished observations). At McLean Hospital and the Massachusetts Mental Health Center, Schatzberg et al.[48] reported that acute dystonic reactions were somewhat less common with risperidone relative to standard antipsychotics. Undoubtedly, the growing use of these compounds as first-line treatment of psychotic disorders will cause a dramatic decrease in the rate of acute dystonic reactions and will make the prophylactic use of anticholinergics unnecessary. Even in the infrequent cases of acute dystonic reactions induced by atypical antipsychotics, anticholinergic use is probably avoidable since the phenomenon is short-lived and rarely recurs.

However, since the novel antipsychotics are expensive and currently not available in injectable form, many patients with acute psychosis will continue to take conventional antipsychotics and to experience acute dystonic reactions.

3. Tardive Dystonia

Tardive dystonia is a late, potentially irreversible dystonic disorder induced by long term exposure to antidopaminergic drugs.[49] Although tardive dystonia has been often considered a subtype of tardive dyskinesia, some authors suggest that it is a distinct disorder since its epidemiology,

risk factors, pathophysiology, course, outcome and response to treatment appear to be different (table I). Among the tardive syndromes, tardive dystonia can be the most severe and the most difficult to treat.[50,62,63] Rib fractures have been reported as an unusual complication of severe tardive dystonia.[100]

3.1 Risk Factors

Since most studies have not distinguished between tardive dyskinesia and tardive dystonia, much information which would be potentially useful for understanding tardive dystonia is provided by studies on tardive dyskinesia (the last term often referring to the entire spectrum of tardive disorders). Older age is the most firmly established risk factor for tardive dyskinesia.[101-107] Other likely risk factors include female gender,[105,107] mood disorders,[32,108] brain dysfunction or damage, diabetes mellitus,[109-111] alcohol abuse,[112,113] presence of extrapyramidal adverse effects early in treatment,[105,114-120] use of high dosages of antipsychotics and edentulousness.[121] It remains uncertain whether a past history of acute dystonic reactions is a risk factor for tardive dystonia.[65,122,123]

3.2 Prevalence

Tardive dystonia has been considered a rare movement disorder.[62,65,124] Epidemiological studies have reported different values of tardive dystonia prevalence, ranging from 1 to 2%[51,125-127] to 13.4%[128] and 21.6%.[129] In 2 studies among inpatients with acute psychiatric disorders, we examined an overall sample of 354 patients and found 15 cases of tardive dystonia, giving a point prevalence of 4.2%.[50,52] Many factors could account for the variation in reports on the tardive dystonia prevalence, beginning with differences in studied populations and examination procedure. The examination of an unselected antipsychotic-treated population suggests that the prevalence of tardive dystonia, including its milder forms, may be more common than currently believed.

Table I. Reported differences between tardive dystonia and tardive dyskinesia

Variable	Tardive dystonia	Tardive dyskinesia
Age	Younger[50-57]	Older[58,59]
Duration of antipsychotic exposure	Shorter[50,53,54,60]	Longer
Gender susceptibility	Male[50,52-55,58]	Female[61]
Severity	More severe[50,52,62-64]	Less severe
Past history of acute drug-induced dystonia or postural tremor	More frequent[65]	Less frequent
Drug-free periods	Less common[66]	More common
Most frequently involved body area	Trunk and extremities[67]	Oral region[67]
Spontaneous remission	Rare[55,60]	Frequent[68,69]
Muscular rigidity	Stronger[52]	Weaker
Antipsychotic withdrawal form	Rare[60]	Frequent
Response to anticholinergics	Improvement[53,70-75]	Worsening[54,57]
Response to electroconvulsive therapy	Reported[76-79]	Not reported
Response to bromocriptine	Moderate improvement[80,81]	Slight improvement[80]
Response to clozapine	More evident[82-91]	Less evident[87,92-95]
Botulinum toxin efficacy	Excellent[96-98]	Good[99]

3.3 Semiology

The spectrum of semiological features of tardive dystonia is wide and includes: spasmodic torticollis, blepharospasm and blepharoclonus, the Pisa syndrome (characterised by twisting and bending the neck and the head to one side of the upper thorax), tardive oculogyric crises, tortipelvis, dromedary gait, propulsive gait, spasmodic dysphonia, lingual dystonia, oromandibular dystonia and diurnal bruxism.[130] Tardive myoclonus has been considered a variant of tardive dystonia. Sometimes, a chronic pain syndrome develops in patients with tardive dyskinesia, or tardive dystonia. It can be successfully treated with drugs effective in treating tardive disorders, such as tetrabenazine.[131]

3.4 Diagnosis

Burke et al.[53] established 4 criteria for the diagnosis of tardive dystonia: (i) presence of dysto-

nic movements or postures; (ii) their development during treatment with D_2 receptor blocking agents or within 2 months of discontinuation of such agents; (iii) exclusion of other causes of secondary dystonia; and (iv) no family history of dystonia. Tardive dystonia sometimes coexists with tardive dyskinesia or tardive akathisia. In these cases, the diagnosis should be made on the basis of the most prominent disturbance.

The differential diagnosis of tardive dystonia includes acute dystonic reactions, conversion disorder, Wilson's disease, primary dystonia and dystonia triggered by other drugs. The progressive course and possibly the family history differentiate primary dystonias from tardive dystonia. Secondary dystonias resulting from infections, metabolic disorders, or structural lesions of the brain should be distinguished on clinical grounds. Tardive dystonia, like the other dystonias, is involuntary and cannot be inhibited and thereby differs from stereotypes, mannerisms, habit spasms or tics.

No specific lesion has been consistently associated with tardive dystonia. The findings of neuroimaging studies on tardive dyskinesia have been conflicting. Various nonspecific abnormalities have been described, such as increased width of the third ventricle, cortical atrophy and increased ventricle-brain ratio. A meta-analysis of the reports of ventricular brain ratio found a trend for patients with tardive dyskinesia to have larger lateral ventricles than unaffected patients. The magnitude of the difference is small, however, and several studies have reported negative results.[132]

3.5 Management

The treatment of tardive dystonia should be a highly individualised process. The first step is to make a correct assessment. Tardive dystonia movements vary from week to week and throughout the day. In some patients with schizophrenia, tardive dyskinesia can be manifest only during psychotic relapses and will disappear when the disease is in remission.[133] In patients with bipolar disorder, tardive dystonia can worsen during periods of depression and improve or disappear during periods of mania.[134-136] A diurnal variation in tardive dyskinesia[137] and tardive dystonia[138] (worsening in the afternoon) has been reported, emphasising the importance of rating patients at the same time of day. As dyskinetic movements can be modified by anxiety and voluntarily inhibited, part of the neurological assessment should be performed unknown to patients (e.g. while they are attempting to memorise a picture). Voluntary movements involving the dyskinetic part tend to inhibit some forms of dystonia and to unmask or worsen other forms (action dystonia), while those involving other muscles tend to increase tardive dystonia. Patients should be examined on several occasions, a few hours apart, during spontaneous and requested movements.

Tardive disorders should be diagnosed according to standardised criteria,[139] while their severity should be measured using a rating scale.[140] Regarding the problem of measuring severity, the use of patients' worst score is the most logical approach since tardive dystonia is a fluctuating disorder. Some authors use the total score of a scale as a criterion of severity of tardive dyskinesia; others use the level of distress and degree of impairment; however, the first undervalues the severity of disorders localised in only one body area, and the second seems inadequate since patients with tardive disorders may rarely complain of their abnormal movements. Probably, rating the severity in one body area is the most appropriate criterion.[54]

3.6 Prevention

There is no established therapy for tardive dystonia. The disorder has been considered even more difficult to treat than tardive dyskinesia. Tardive dystonia spontaneously remits more rarely[55,60] than tardive dyskinesia.[68,69] Drugs can improve dystonic movements in some cases, yet most patients fail to obtain satisfactory relief. Therefore, preventive measures are indispensable.

Treatment starts with revaluation of the need for ongoing antipsychotic treatment. Antipsychotics should be prescribed only when definitely indi-

cated, at the lowest effective dosage. Remarkably, patients with mood disorders, who are at high risk of tardive syndromes, can benefit from more specific drugs.

Although not all studies have found an association between cumulative antipsychotic exposure and risk of tardive dyskinesia, few authors, if any, would doubt that the main preventive strategy for tardive dyskinesia is adjustment of antipsychotic dosage to the lowest effective dosage that controls psychosis and minimises extrapyramidal adverse effects. To reduce the risk of tardive dyskinesia, 2 strategies have been attempted: continuous low dosage antipsychotic treatment and intermittent or targeted medication. Both methods reduce cumulative antipsychotic exposure but require close monitoring of patients. Most of studies indicate that these strategies are feasible for some patients, but are associated with a higher risk of relapse than maintaining an established moderate dose. A low dosage regimen leads to fewer adverse effects (possibly including tardive dyskinesia) and improved subjective well being. However, relapse rates are high if the dosage is very low or if patients are not stable, and these rates become higher as treatment continues. Targeted treatment permits fewer cumulative antipsychotic exposure and fewer adverse effects but no clear benefit in terms of tardive dyskinesia or social functioning. Unfortunately, it is not possible to identify those patients in whom these strategies could be undertaken without an increased risk of relapse.[141]

Tardive dystonia may be severe to the point of being disabling, yet patients may require antipsychotics for an even more disabling mental illness. Difficult therapeutic choices become unavoidable in those patients with severe tardive dystonia who clearly benefit from antipsychotic treatment.

3.7 Therapy

An algorithm of possible therapeutic choices for management of tardive dystonia is shown in figure 1.

3.7.1 Clozapine

Clozapine has a strong antipsychotic activity and is more effective than conventional antipsychotics in treatment-resistant schizophrenia.[142,143] To date, clozapine is the only antipsychotic agent that has been established as having minimal, if any, risk of tardive dyskinesia.[144]

In humans, clozapine can produce mild bradykinesia and mild akathisia, but no acute dystonic reactions or rigidity have been reported and tremor has only rarely been reported. In patients with tardive dyskinesia, a switch to clozapine produces remission of dyskinesia in about half the cases, particularly those with dystonic features.[70,145] Successful clozapine treatment of both tardive dyskinesia[92-95,146] and tardive dystonia has been repeatedly reported.[82-86] It is not clear whether clozapine: (i) simply masks tardive dystonia; (ii) does not influence tardive dystonia directly, allowing the passage of time (without the presence of the offending drug) to result in a decrease of symptoms; or (iii) has a direct therapeutic effect. The last possibility is consistent with some studies reporting a dose dependent and time dependent therapeutic response to clozapine.[87]

Clozapine is probably the best therapeutic alternative for patients with dystonia and psychosis who need both neurological and psychiatric therapy.

3.7.2 Risperidone

Risperidone is at least as efficacious as haloperidol in treating psychotic symptoms, but produces significantly fewer extrapyramidal adverse effects, at low or moderate dosages (2 to 8 mg/day).[47,147,148] At higher dosages, risperidone causes extrapyramidal adverse effects similar both in character and incidence to those of haloperidol.[47] At present, there have been not enough patients treated on a long term basis with risperidone to assess its tardive dyskinesia risk correctly. Preliminary evidence from over 1100 patients, 503 of whom were treated with risperidone for at least one year, suggests that the annual incidence of tardive dyskinesia in patients treated with risperidone 7.6 to 9.4 mg/day is 0.3%, lower than the mean annual incidence of tardive dyskinesia (5 to 10%) in patients treated with typical antipsychotics.[48] Anecdotal cases have been reported of tardive dys-

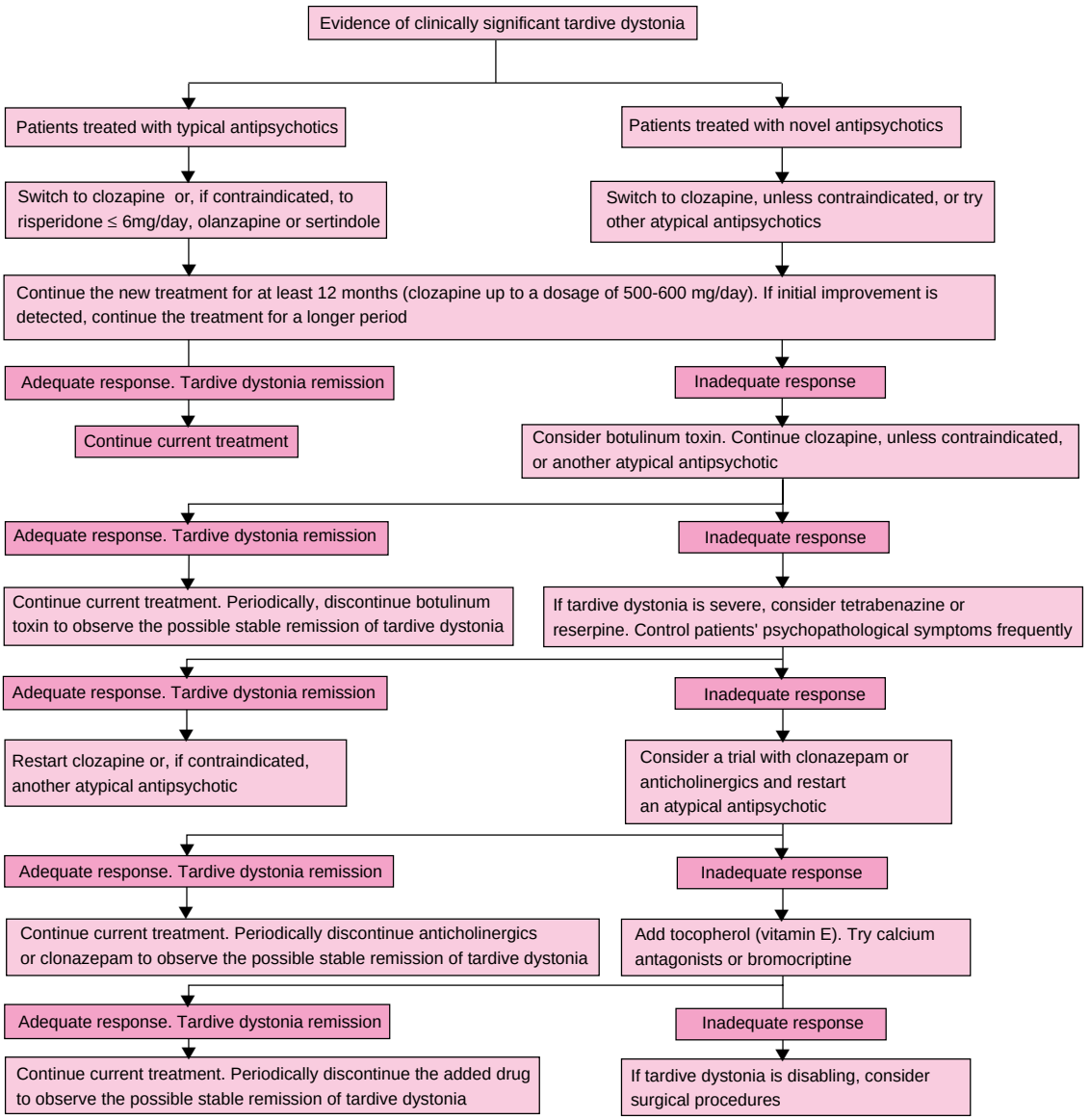

Fig. 1. Algorithm for the treatment of antipsychotic-induced tardive dystonia. In addition to the recommendations outlined in the algorithm, the following issues should be noted: (i) antipsychotics should only be prescribed for psychotic disorders, when definitely indicated, at the lowest effective dosage and following current guidelines for the treatment of psychotic disorders;[7] (ii) if possible, first psychotic episode or drug-naive patients should be treated with a novel antipsychotic agent, such as risperidone, olanzapine, sertindole or quetiapine; (iii) careful neurological examination of patients treated with antipsychotics should be arranged at least every 3 months; (iv) if a patient has a specific contraindication to any drug, that drug should not be considered for use in the patient; and (v) a medication should be chosen on the basis of past response, adverse effects, availability, cost and patient preference.

kinesia either induced[149,150] or improved by risperidone.[151]

In a Canadian multicentre, double-blind clinical trial of risperidone, a *post hoc* analysis indicated that risperidone 6 mg/day had the most beneficial effect on tardive dyskinesia, especially on the bucco-linguo-masticatory syndrome.[152] Risperidone has been found efficacious also in the treatment of idiopathic segmental dystonia.[153] Risperidone could have an antidyskinetic effect,[154-157] simply allowing the withdrawal of more offending antipsychotics. Since there are no long term studies comparing risperidone with a typical antipsychotic showing gradual and persistent (even after antipsychotic withdrawal) reduction in tardive dyskinesia, it is still uncertain whether risperidone can actively improve tardive dyskinesia. Undoubtedly, risperidone is a potent D_2 antagonist and therefore, like typical antipsychotics, can mask tardive dyskinesia. One can never expect to obtain a cure of tardive dyskinesia by masking it, however. Furthermore, there is also the risk of worsening the disorder.

In summary, the clinical efficacy of risperidone in tardive dystonia is still uncertain. As with other novel antipsychotics, risperidone could be a first-line treatment for first psychotic episode or drug-naive patients and for patients experiencing severe acute extrapyramidal adverse effects. It could also be indicated for patients whose disease is non-responsive to typical antipsychotics or who are affected by severe tardive disorders who need antipsychotic treatment and cannot be exposed to clozapine because of adverse effects.

3.7.3 Olanzapine, Sertindole and Quetiapine

Considerable progress has been made with the advent of new antipsychotics, stimulated by the rediscovery of clozapine. Novel antipsychotics are characterised by decreased or absent capacity to induce extrapyramidal adverse effects and to increase prolactin levels, and by their possible higher efficacy. Although the long term effects of olanzapine, sertindole and quetiapine have not been adequately observed, it seems plausible to expect that these compounds will be as effective at treating the chronic period of the illness as they are when used to treat acute episodes.

The emergence of acute extrapyramidal adverse effects early in treatment has been considered a risk factor for the later development of tardive dyskinesia.[110-120,158] Probably, atypical antipsychotics, which have a low propensity to cause acute extrapyramidal adverse effects early in treatment, are less likely to cause tardive disorders over prolonged maintenance periods. Furthermore, patients taking these compounds show better compliance and are more likely to continue antipsychotic therapy without interruptions thus lowering the risk of a relapse. However, prospective studies are needed to confirm this hope. Only long term follow-up will make it possible to assess the unique extrapyramidal adverse effects profile and the true tardive dystonia risk of each new antipsychotic.

The advantages of the atypical antipsychotics should be weighed against their higher costs and their current availability only in short acting, oral forms. The less frequent adverse effects of these drugs could still be unknown, and consequently caution is mandatory in their use, and it is vital to monitor a patient's status and keep abreast of revised scientific recommendations.

3.7.4 Electroconvulsive Therapy

Several case-reports described improvement of tardive dystonia with electroconvulsive therapy (ECT).[76-78] However, worsening of tardive dystonia with ECT has also been described.[159] The efficacy of ECT in the treatment of tardive dystonia has not been studied adequately. It is still uncertain whether: (i) the antidyskinetic effects of ECT are long lasting; (ii) a history of ECT is a risk factor for developing tardive dystonia; or (iii) ECT does not worsen tardive dystonia. Nevertheless, ECT can be considered when tardive dystonia does not respond to clozapine or to the atypical antipsychotics and when continuation of antipsychotic treatment is necessary.

3.7.5 Anticholinergic Agents

This class of drugs (particularly trihexyphenidyl) are effective in some patients with tardive dystonia,[160,161] but high dosages of anticholin-

ergics may cause severe adverse effects, especially in the elderly.

3.7.6 Benzodiazepines

Benzodiazepines enhance γ-aminobutyric acid (GABA) transmission and have been employed in the treatment of tardive dyskinesia.[162] They can provide benefit, but cause sedation and the degree of improvement is often unsatisfactory. Clonazepam has shown moderate efficacy, especially in patients with tardive dystonia or tardive myoclonus.[162] Tolerance to its antidyskinetic effect can develop with long term administration, but short clonazepam-free periods can recapture its antidyskinetic effect.[162]

3.7.7 Tetrabenazine

In contrast to typical antipsychotics, tetrabenazine, a monoamine-depleting and a dopamine-receptor blocking drug, has not been demonstrated to cause tardive disorders. Tetrabenazine has been found useful in patients with tardive dystonia.[163] Recently, Jankovic and Beach[164] reported high efficacy of tetrabenazine in the treatment of 526 patients with severe hyperkinetic movement disorders, including tardive dystonia. The mean duration of tetrabenazine treatment was 28.9 (± 31.1 standard deviation) months. Marked improvement was observed in 80.5% of 82 patients with tardive dystonia. The most common adverse effects included drowsiness (36.5%), parkinsonism (28.5%), depression (15.0%), insomnia (11.0%), nervousness or anxiety (10.3%) and akathisia (9.5%).

3.7.8 Reserpine

If tetrabenazine is contraindicated or unavailable, reserpine can be an alternative. According to Fahn's suggestions,[71] the drug should be started at a dosage of 0.25 mg/day and increased weekly by a daily dose of 0.25mg until clinical improvement is achieved or intolerable adverse effects, such as apathy, depression, postural hypotension, nasal stuffiness, diarrhoea and nightmares, develop.

3.7.9 Botulinum Toxin

Local injections of botulinum toxin, which block acetylcholine release at neuromuscular junctions, have strong efficacy in the treatment of focal dystonias.[99] The therapeutic effects of botulinum toxin last on average for 2 to 6 months. Patients who are treated early respond to botulinum toxin better than patients with long-standing dystonia, probably because prolonged dystonia causes secondary contractures. The therapeutic dosages of botulinum toxin used are roughly proportional to the mass of the muscle being injected. Excessive weakness of injected muscles, which is the main adverse effect of botulinum toxin, is usually mild and transitory. Proper selection of the involved muscles and dosage are the key factors of a favourable response to botulinum treatment. Up to 15% of patients may develop neutralising antibodies in response to botulinum treatment and become non-responders. Some patients who are immunoresistant to botulinum toxin A may benefit from treatments with other botulinum serotypes. In patients with dystonia who need antipsychotic treatment, botulinum is indicated when atypical compounds are unavailable or ineffective for the tardive dystonia.

3.7.10 Tocopherol (Vitamin E)

Free radicals are generated during normal metabolic processes, and, in excess, can initiate disruptive peroxidation reactions with various substrates damaging lipids, proteins and DNA. It has been hypothesised that tardive dyskinesia is mediated through free radical damage to the neurons, and treatment with antioxidant drugs has been suggested. The efficacy of an antioxidant treatment of tardive dyskinesia with tocopherol (vitamin E) has been tested in several studies.[165] Most,[166-172] but not all,[173] of them have shown a significant improvement of tardive dyskinesia. These studies have not differentiated between tardive dyskinesia and tardive dystonia. Thus, the specific relevance of these results for tardive dystonia remains uncertain.

3.7.11 Other Therapeutic Alternatives

Baclofen, a pre-synaptic acting GABA agonist, has been reported to induce dramatic improvement in children and adolescents with idiopathic dystonia. Occasionally, it has been reported to also improve tardive dystonia.[174]

Dose dependent, moderate, but not statistically significant, improvement has been reported in patients with tardive dystonia treated with the dopamine agonist bromocriptine.[80]

Studies examining the use of calcium antagonists in the treatment of tardive dyskinesia have yielded mixed results.[175] Positive findings have been reported for nifedipine, verapamil and diltiazem. Higher doses of calcium antagonists, advanced age and severe forms of tardive dyskinesia have been associated with a better response to calcium antagonist treatment. To validate the antidyskinetic efficacy of these drugs, additional data are needed from double-blind, placebo controlled studies with larger sample sizes and longer duration of treatment. Anecdotal cases of dramatic improvement of tardive dystonia with verapamil have been reported.[176] Calcium antagonists might be indicated as treatment for patients with tardive disorders and mood disorders or cardiovascular diseases.

Surgical treatments, such as local denervation, myectomy, thalamotomy, pallidotomy and deep brain stimulation can be considered only for patients with disabling dystonia and in cases where medical therapies have failed to provide meaningful improvement.

4. Conclusions

Since there is no established therapy for tardive dystonia, preventative measures are crucial. Antipsychotic agents should be prescribed only when clearly indicated, at the lowest efficacious dose. Second generation antipsychotics cause fewer acute extrapyramidal adverse effects than typical antipsychotics and will certainly reduce the incidence of acute dystonic reactions. The increased use of these agents also brings the hope of reducing the incidence of tardive disorders. If tardive dystonia has occurred, clozapine (and perhaps other atypical antipsychotics) is clearly indicated in patients who need antipsychotic treatment. Otherwise, tetrabenazine, reserpine or botulinum are possible therapeutic options. In the future, understanding the molecular basis of genetic dystonias could improve our comprehension of the pathophysiology of dystonic movements and could also suggest effective means of treatment of secondary dystonias.

References

1. Van Putten T, Marder SR. Behavioral toxicity of antipsychotic drugs. J Clin Psychiatry 1974; 48: 13-9
2. Rifkin A. Extrapyramidal side-effects: a historical perspective. J Clin Psychiatry 1987; 48 (9 Suppl.): 3-6
3. Van Putten T. Why do schizophrenic patients refuse to take their drugs? Arch Gen Psychiatry 1975; 31: 62-76
4. Gasser T. Idiopathic, myoclonic and Dopa-responsive dystonia. Curr Opin Neurol 1997; 10: 357-62
5. Gasser T. Advances in the genetics of movement disorders: implications for molecular diagnosis. J Neurol 1997; 244: 341-8
6. Mazurek MF, Rosebush PI. Circadian pattern of acute, neuroleptic-induced dystonic reactions. Am J Psychiatry 1996: 153: 708-10
7. American Psychiatric Association. Practice guideline for the treatment of patients with schizophrenia. Am J Psychiatry 1997; 154 (4 Suppl.): 1-63
8. Chakos MH, Mayerhoff DI, Loebel AD, et al. Incidence and correlates of acute extrapyramidal symptoms in first-episode of schizophrenia. Psychopharmacol Bull 1992; 28: 81-6
9. Aguilar EJ, Keshavan MS, Martinez-Quiles MD, et al. Predictors of acute dystonia in first-episode psychotic patients. Am J Psychiatry 1994; 151: 1819-21
10. Nasrallah HA, Churchill CM, Hamdan-Allan GA. Higher frequency of neuroleptic-induced dystonia in mania than in schizophrenia. Am J Psychiatry 1988; 145: 1455-6
11. Remington GJ, Voineskos G, Pollock B, et al. Prevalence of neuroleptic-induced dystonia in mania and schizophrenia. Am J Psychiatry 1990; 147: 1231-3
12. Jeanjean AP, Laterre EC, Maloteaux JM. Neuroleptic binding to sigma receptors: possible involvement in neuroleptic-induced acute dystonia. Biol Psychiatry 1997; 41: 1010-9
13. Ibrahim ZY, Brooks EF. Neuroleptic-induced bilateral temporomandibular joint dislocation. Am J Psychiatry 1996; 153: 293-4
14. Hyman SE. Manual of psychiatric emergencies. Boston: Little, Brown and Company, 1984: 171-3
15. Thornton A, McKenna PJ. Acute dystonic reactions complicated by psychotic phenomena. Br J Psychiatry 1994; 164: 115-8
16. Magnusson A, Opjordsmoen S, Dietrichs E. Medikamentinduserte dystonier mistolket som hysteri. Tidsskr Nor Laegeforen 1996; 116: 844-5
17. Lang AE. Psychogenic dystonia: a review of 18 cases. Can J Neurol Sci 1995; 22: 136-43
18. Ayd FJ. A survey of drug-induced extrapyramidal reactions. JAMA 1961; 175: 1054-60

19. Sweet Jr C. Drug-induced dystonia. Am J Psychiatry 1975; 132: 532-4
20. Keepers GA, Clappison VJ, Casey DE. Initial anticholinergic prophylaxis for neuroleptic-induced extrapyramidal syndromes. Arch Gen Psychiatry 1983; 40: 1113-7
21. Boyer WF, Bakalar NH, Lake CR. Anticholinergic prophylaxis of acute haloperidol-induced acute dystonic reactions. J Clin Psychopharmacol 1987; 7: 164-6
22. National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group. Phenothiazine treatment in acute schizophrenia. Arch Gen Psychiatry 1964; 10: 246-61
23. DiMascio A, Demirgian E. Antiparkinson drug overuse. Psychosomatics 1970; 11: 596-601
24. Swett Jr C. Drug-induced dystonia. Am J Psychiatry 1975; 132: 532-4
25. Binder RL, Levy R. Extrapyramidal reactions in Asians. Am J Psychiatry 1981; 138: 1243-4
26. Stern TA, Anderson WH. Benztropine prophylaxis of dystonic reactions. Psychopharmacology 1979; 61: 261-2
27. Chiles JA. Extrapyramidal reactions in adolescents treated with high-potency antipsychotics. Am J Psychiatry 1978; 135: 239-40
28. Arana GW, Goff DC, Baldessarini RJ, et al. Efficacy of anticholinergic prophylaxis for neuroleptic-induced acute dystonia. Am J Psychiatry 1988; 145: 993-6
29. Casey DE. Will the new antipsychotics bring hope of reducing the risk of developing extrapyramidal syndromes and tardive dyskinesia? Int J Psychopharmacol 1997; 12 (1 Suppl.): S19-S27
30. Addonizio G, Alexopoulos GS. Drug-induced dystonia in young and elderly patients. Am J Psychiatry 1988; 145: 869-71
31. Garver DL, Davis JM, Dekirmenjian H, et al. Dystonic reactions following neuroleptics: time course and proposed mechanisms. Psychopharmacology 1976; 47: 199-201
32. Casey DE. Neuroleptic drug-induced extrapyramidal syndromes and tardive dyskinesia. Schizophr Res 1991; 4: 109-20
33. Marsden CD, Jenner P. The pathophysiology of extrapyramidal side-effects of neuroleptic drugs. Psychol Med 1980; 10: 55-72
34. Wong DF, Wagner Jr HN, Dannals RF, et al. Effects of age on dopamine and serotonin receptors measured by positron emission tomography in the living human brain. Science 1984; 226: 1393-6
35. Casey DE. Neuroleptic-induced acute dystonia. In: Lang AE, Weiner WJ, editors. Drug-induced movement disorders. New York: Futura Press, 1991: 21-40
36. Chiu LPW. Transient recurrence of auditory hallucinations during acute dystonia. Br J Psychiatry 1989; 155: 110-3
37. Gelenberg AJ. Treating extrapyramidal reactions: some current issues. J Clin Psychiatry 1987; 48 Suppl.: S24-S27
38. Schatzberg AF, Cole JO, De Battista C. Manual of clinical psychopharmacology. 3rd ed. Washington, DC: American Psychiatric Press, Inc, 1997: 142-3
39. Korczyn AD, Goldberg GJ. Intravenous diazepam in drug-induced dystonic reactions. Br J Psychiatry 1972; 121: 75-7
40. Gagrat D, Hamilton J, Belmaker RH. Intravenous diazepam in the treatment of neuroleptic-induced acute dystonia and akathisia. Am J Psychiatry 1978; 135: 1232-3
41. World Health Organization Heads of Centres Collaborating in WHO co-ordinated studies on biological aspects of mental illness. Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment. Br J Psychiatry 1990; 156: 412
42. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. Arch Gen Psychiatry 1991; 49: 739-45
43. Singh MM, Kay SR. Therapeutical reversal with benztropine in schizophrenics. J Nerv Ment Dis 1973; 169: 258-66
44. Johnstone EC, Crow TJ, Ferrier JN, et al. Adverse effects of anticholinergic medications on positive schizophrenic symptoms. Psychol Med 1983; 13: 513-27
45. Faulk RS, Gilmore JH, Jensen EW, et al. Risperidone-induced dystonic reaction [letter]. Am J Psychiatry 1996; 153: 577
46. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993; 13: 25-40
47. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994; 151: 825-35
48. Schatzberg AF, Cole JO, De Battista C. Manual of clinical psychopharmacology. 3rd ed. Washington, DC: American Psychiatric Press, Inc., 1997: 162
49. Keegan DL, Rajput AH. Drug-induced dystonia tarda-treatment with L-dopa. Dis Nerv Systs 1973; 38: 167-9
50. 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: 145-51
51. Yassa R, Nair V, Dimitry R. Prevalence of tardive dystonia. Acta Psychiatr Scand 1986; 73: 629-33
52. Raja M, Azzoni A. Tardive dystonia. Prevalence, risk factors and clinical features. It J Neurol Sci 1996; 17: 409-18
53. Burke RE, Fahn S, Jankovic J, et al. Tardive dystonia: late onset and persistent dystonia caused by antipsychotic drugs. Neurology 1982; 32: 1335-46
54. Yassa R, Nair NPV, Iskandar H, et al. Factors in the development of severe forms of tardive dyskinesia. Am J Psychiatry 1990; 147: 1156-63
55. Wojcik JD, Falk WE, Fink JS, et al. A review of 32 cases of tardive dystonia. Am J Psychiatry 1991; 148: 1055-9
56. Gimenez-Roldan S, Mateo D, Bartolome P. Tardive dystonia and severe tardive dyskinesia. Acta Psychiatr Scand 1985; 71: 488-94
57. Gardos G, Cole JO, Salomaon M, et al. Clinical forms of severe tardive dyskinesia. Am J Psychiatry 1987; 144: 895-902
58. Kane JM, Woerner M, Borenstein M, et al. Integrating incidence and prevalence of tardive dyskinesia. Psychopharm Bull 1986; 152: 254-8
59. Glazer WM, Morgenstern H, Niedzwiecki D, et al. Heterogeneity of tardive dyskinesia. Br J Psychiatry 1988; 152: 253-9
60. Roller WC. Tardive dystonia: diagnosis and treatment. In: Wolf ME, Mosnaim AD, editors. Tardive dyskinesia: biological mechanisms and clinical aspects. Washington, DC: American Psychiatric Press, 1988
61. Yassa R, Jeste DV. Gender differences in tardive dyskinesia: a critical review of the literature. Schizophr Bull 1992; 18: 701-15
62. Yadalam KG, Korn ML, Simpson GM. Tardive dystonia: four case histories. J Clin Psychiatry 1990; 51: 17-20
63. Chiu HF, Lee S. Tardive dystonia. Aust N Z J Psychiatry 1989; 23: 566-70
64. Owens DGC. Dystonia: a potential pyschiatric pitfall. Br J Psychiatry 1990; 156: 620-34

65. Sachdev P. Risk factors for tardive dystonia: a case-control comparison with tardive dyskinesia. Act Psychiatr Scand 1993; 88: 98-103
66. Yassa R, Nair V, Iskander H. A comparison of severe tardive dystonia and severe tardive dyskinesia. Acta Psychiatr Scand 1989; 80: 155-9
67. Inada T. Yagi G, Kamijima K, et al. A statistical trial of subclassification for tardive dyskinesia. Acta Psychiatr Scand 1990; 82: 404-7
68. Casey DE, Hansen TE. Spontaneous dyskinesia. In: Jeste DV, Wyatt RJ, editors. Neuropsychiatric movement disorders. Washington, DC: American Psychiatric Press, 1984: 68-95
69. Casey DE, Toenniessen LM. Neuroleptic treatment in tardive dyskinesia: Can it be developed into a clinical strategy for long-term treatment? In: Bannet J, Belmaker RH, editors. New directions in tardive dyskinesia research. Basel: Karqer, 1983: 65-79
70. Lieberman JA, Johns C, Cooper T, et al. Clozapine pharmacology and tardive dyskinesia. Psychopharmacology 1989; 99: 54-9
71. Fahn S. Drug treatment of hyperkinetic movement disorders. Semin Neurol 1987; 7: 192-208
72. Kang UJ, Burke RE, Fahn S. Natural history and treatment of tardive dystonia. Mov Disord 1986; 1: 193-208
73. Burke RE, Kang UJ. Tardive dystonia: clinical aspects and treatment. Adv Neurol 1988; 49: 199-210
74. Lieberman JA, Lesser M, Johns C, et al. Pharmacologic studies of tardive dyskinesia. J Clin Psychopharmacol 1988; 8 (4 Suppl.): 575-635
75. Marsden CD, Quinn NP. The dystonias. BMJ 1990; 300: 139-44
76. Adityanjee, Jayaswal SK, Chan TM, et al. Temporary remission of tardive dystonia following electroconvulsive therapy. Br J Psychiatry 1990; 156: 433-5
77. Faber R, Trimble MR. Electroconvulsive therapy in Parkinson's disease and other movement disorders. Mov Disord 1991; 6: 293-303
78. Postolache TT, Londono JH, Halem RG, et al. Electroconvulsive therapy in tardive dystonia. Convuls Ther 1995; 11: 275-9
79. Kaplan Z, Benjamin J, Zohar J. Remission of tardive dystonia with ECT. Convuls Ther 1991; 7: 280-3
80. Lieberman JA, Alvir J, Mukherjee S, et al. Treatment of tardive dyskinesia with bromocriptine: a test of the receptor modification strategy. Arch Gen Psychiatry 1989; 46: 908-13
81. Luchins D, Goldman M. High dose bromocriptine in a case of tardive dystonia. Biol Psychiatry 1985; 20: 179-81
82. Adityanjee, Estrera AB. Successful treatment of tardive dystonia with clozapine. Biol Psychiatry 1996; 39: 1064-5
83. Friedman JH. Clozapine treatment of psychosis in patients with tardive dystonia: report of three cases. Mov Disord 1994; 9: 321-4
84. Shapleske J, Mickay AP, McKenna PJ. Successful treatment of tardive dystonia with clozapine a clonazepam. Br J Psychiatry 1996; 168: 516-8
85. Trugman JM, Leadbetter R, Zalis ME, et al. Treatment of severe axial tardive dystonia with clozapine: case report and hypothesis. Mov Disord 1994; 9: 441-6
86. van Harten PN, Campus DJ, Matroos GE. Use of clozapine in tardive dystonia. Prog Neuropsychopharmacol Biol Psychiatry 1996; 20: 263-74
87. Lieberman JA, Saltz BL, Johns CA, et al. The effects of clozapine on tardive dyskinesia. Br J Psychiatry 1991; 158: 503-10
88. Van Putten T, Wirshing W, Marder S. Tardive Miege syndrome responsive to clozapine. J Clin Psychopharmacol 1990; 10: 381-2
89. Blake LM, Marks RC, Nierman P, et al. Clozapine and clonazepam in tardive dystonia. J Clin Psychopharmacol 1991; 11: 268-9
90. Lamberti JS, Bellnier T. Clozapine and tardive dystonia. J Nerv Ment Dis 1993; 181: 137-8
91. Raja M, Altavista MC, Maisto G, et al. Tardive lingual dystonia treated with clozapine. Mov Disord 1996; 11 : 585-6
92. Tamminga CA, Thaker GK, Moran M, et al. Clozapine in tardive dyskinesia: observations from human and animal model studies. J Clin Psychiatry 1994; 55: 102-6
93. Chengappa KN, Shelton MD, Baker RW, et al. The prevalence of akathisia in patients receiving stable doses of clozapine. J Clin Psychiatry 1994; 55: 142-5
94. Johnson CG, Littrell KH, Magill AM. Starting patients on clozapine in a partial hospitalization program. Hosp Community Psychiatry 1994; 45: 264-8
95. Levkovitch Y, Kronenberg J, Kayser N, et al. Clozapine for tardive dyskinesia in adolescents. Brain Dev 1995; 17: 213-5
96. Kaufman DM. Use of botulinum toxin injections for spasmodic torticollis of tardive dystonia. J Neuropsychiatry Clin Neurosci 1994; 6: 50-3
97. Shulman LM, Singer C, Weiner WJ. Improvement of both tardive dystonia and akathisia after botulinum toxin infection. Neurology 1996; 46: 844-5
98. Kiriakakis V, Bhatia K, Quinn N, et al. Botulinum toxin treatment of tardive syndromes [letter]. Mov Disord 1997: 12: 26
99. Jancovic J, Brin MF. Therapeutic uses of botulinum toxin. N Engl J Med 1991; 324: 1186-94
100. Szymanski S, Lieberman JA, Safferman A, et al. Rib fractures as an unusual complication of severe tardive dystonia [letter]. J Clin Psychiatry 1993; 54: 160
101. Woerner M, Kane JM, Lieberman JA, et al. The prevalence of tardive dyskinesia. J Clin Psychopharmacol 1991; 11: 34-42
102. Glazer WM, Morgenstern H, Doucette JT. The prediction of chronic persistent versus intermittent tardive dyskinesia: a retrospective follow-up study. Br J Psychiatry 1991; 158: 822-8
103. Yassa R, Nastase C, Dupont D, et al. Tardive dyskinesia in elderly psychiatric patients: a 5-year study. Am J Psychiatry 1992; 149: 1206-11
104. Chiu H, Shum P, Lau J, et al. Prevalence of tardive dyskinesia, tardive dystonia, and respiratory dyskinesia among Chinese psychiatric patients in Hong Kong. Am J Psychiatry 1992; 149: 1081-5
105. McCreadie RG, Robertson LJ, Wiles DH. The Nithsdale schizophrenia surveys. IX: Akathisia, parkinsonism, tardive dyskinesia and plasma neuroleptic levels. Br J Psychiatry 1992; 160: 793-9
106. Jeste DV, Caligiuri MP. Tardive dyskinesia. Schizophr Bull 1993; 19: 303-15
107. Muscettola G, Pampallona S, Barbato G, et al. Persistent tardive dyskinesia: demographic and pharmacological risk factors. Acta Psychiatr Scand 1993; 87: 29-36
108. Casey DE. Affective disorders and tardive dyskinesia. Encephale 1988; 14: 221-6
109. Ganzini L, Heintz RT, Hoffman WF, et al. The prevalence of tardive dyskinesia in neuroleptic-treated diabetics: a controlled study. Arch Gen Psychiatry 1991; 48: 259-63
110. Ganzini L, Casey DE, Hoffman WF, et al. Tardive dyskinesia and diabetes mellitus. Psychopharmacol Bull 1992; 28: 281-6

111. Woerner MG, Saltz BL, Kane JM, et al. Diabetes and development of tardive dyskinesia. Am J Psychiatry 1993; 150: 966-8
112. Dixon L, Weiden PJ, Haas G, et al. Increased tardive dyskinesia in alcohol-abusing schizophrenic patients. Compr Psychiatry 1992; 33: 121-2
113. Duke PJ, Pantelis C, Barnes TR. South Westminster schizophrenia survey. Alcohol use and its relationship to symptoms, tardive dyskinesia and illness onset. Br J Psychiatry 1994; 164: 630-6
114. Barnes TRE, Braude WM. Akathisia variants and tardive dyskinesia. Arch Gen Psychiatry 1985; 42: 874-8
115. Barnes TRE. The present status of tardive dyskinesia and akathisia in the treatment of schizophrenia. Psychiatr Dev 1987; 4: 301-19
116. Chouinard G, Annable L, Ross-Chouinard A, et al. A 5-year prospective longitudinal study of tardive dyskinesia: factors predicting appearance of new cases. J Clin Psychopharmacol 1988; 8: 21-6
117. Annable L, Chouinard G, Ross-Chouinard A, et al. The relationship between neuroleptic-induced parkinsonism and tardive dyskinesia. Biol Psychiatry 1991; 29: 210-329S
118. Saltz BL, Woerner MG, Kane JM, et al. Prospective study of tardive dyskinesia: incidence in the elderly. JAMA 1991; 266: 2402-6
119. Kane JM, Woerner M, Lieberman J. Tardive dyskinesia: prevalence, incidence and risk-factors. J Clin Psychopharmacol 1988; 8: 525-65
120. Keepers GA, Casey DE. Use of neuroleptic induced extrapyramidal symptoms to predict future vulnerability to side-effects. Am J Psychiatry 1991; 148: 85-9
121. Sandyk R, Kay SR. Edentulousness and neuroleptic-induced neck and trunk dyskinesia. Funct Neurol 1990; 5: 361-3
122. Chiu HF, Leung JY, Lee S. Tardive dystonia in Chinese. Singapore Med J 1989; 30: 441-3
123. Sachdev P. Clinical characteristics of 15 patients with tardive dystonia. Am J Psychiatry 1993; 150: 498-500
124. Cooper SJ, Doherty MM, King DJ. Tardive dystonia: the benefits of time. Br J Psychiatry 1989; 155: 113-5
125. Crane GE, Naranjo ER. Motor disorders induced by neuroleptics. Arch Gen Psychiatry 1971; 24: 179-84
126. Friedman JH, Kuraski LT, Wagner RI. Tardive dystonia in a psychiatric hospital. J Neurol Neurosur Psychiatry 1987; 50: 801-3
127. Sachdev P. The prevalence of tardive dystonia in patients with chronic schizophrenia. Aust N Z J Psychiatry 1991; 25: 446-8
128. van Harten PN, Matroos GE, Hoek HW, et al. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia. The Caracas Extrapyramidal Syndromes Study: I. Schizophr Res 1996; 19: 195-203
129. Sethi KD, Hess DC, Harp RJ. Prevalence of dystonia in veterans on chronic antipsychotic therapy. Mov Disord 1990: 5: 319-21
130. Micheli F, Fernandez Pardal M, Gatto M, et al. Bruxism secondary to chronic antidopaminergic drug exposure. Clin Neuropharmacol 1993; 16: 315-23
131. Ford B, Greene P, Fahn S. Oral and genital tardive pain syndromes. Neurology 1994; 44: 2115-9
132. Hoffman WF, Casey DE. Computed tomographic evaluation of patients with tardive dyskinesia. Schizophr Res 1991; 5: 1-12
133. Jawed SH, Singh I. Tardive dyskinesia with schizophrenic relapse. J Ment Defic Res 1989; 33: 331-4
134. Sachdev P. Depression-dependent exacerbation of tardive dyskinesia. Br J Psychiatry 1989; 155: 253-5
135. Sandyk R, Pardeshi R. Mood-dependent fluctuations in the severity of tardive dyskinesia and psoriasis vulgaris in a patient with schizoaffective disorder: possible role of melatonin. Int J Neurosci 1990: 50: 215-21
136. Yazici O, Kantemir E, Tastaban Y, et al. Spontaneous improvement of tardive dystonia during mania. Br J Psychiatry 1991; 158: 847-50
137. Hide TM, Egan MF, Brown RJ, et al. Diurnal variation in tardive dyskinesia. Psychiatry Res 1995; 56: 53-7
138. Tan CH, Chiang PC, Ng LL, et al. Oculogyric spasm in Asian psychiatric in-patients on maintenance medication. Br J Psychiatry 1994; 165: 381-3
139. Schooler N, Kane JM. Research diagnoses for tardive dyskinesia. Acta Psychiatr Scand 1982; 39: 486-7
140. Guy W, editor. ECDEU assessment manual for psychopharmacology. Rockville (MD): NIMH Psychopharmacology Research Branch, 1976
141. Schooler NR. Maintenance medication for schizophrenia: strategies for dose reduction. Schizophr Bull 1991: 17: 31-24
142. Kane JM, Honigfeld G, Singer J, et al. Clozapine for the treatment resistant schizophrenic. Arch Gen Psychiatry 1988; 45: 789-96
143. Baldessarini RJ, Frankeburg FR. Clozapine. A novel antipsychotic agent. N Engl J Med 1991; 324: 746-54
144. Kane JM, Woerner MG, Pollack S, et al. Does clozapine cause tardive dyskinesia? J Clin Psychiatry 1993; 54: 327-30
145. Gerlach J, Peacock L. Motor and mental side-effects of clozapine. J Clin Psychiatry 1994; 55: 107-9
146. Peacock L, Solgaard T, Lublin H, et al. Clozapine versus typical antipsychotics. A retro- and prospective study of extrapyramidal side-effects. Psychopharmacology 1996; 124: 188-96
147. Claus A, Bollen J, De Cuyper H, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients: a multicentre double-blind comparative study. Acta Psychiatr Scand 1992; 85: 295-305
148. Muller-Spahn F. Risperidone in the treatment of chronic schizophrenic patients: an international double-blind parallel-group study versus haloperidol [abstract]. Clin Neuropharmacol 1992; 15 (1 Suppl.): 90A
149. Woerner MG, Sheitman BB, Lieberman JA, et al. Tardive dyskinesia induced by risperidone [letter]? Am J Psychiatry 1996; 153: 843
150. Gwinn KA, Caviness JN. Risperidone-induced tardive dyskinesia and parkinsonism. Mov Disorders 1997; 12: 119-21
151. Rangwani SR, Gupta S, Burke WJ, et al. Improvement of debilitating tardive dyskinesia with risperidone. Ann Clin Psychiatry 1996; 8: 27-9
152. Chouinard G. Effects of risperidone in tardive dyskinesia: an analysis of the Canadian multicenter risperidone study. J Clin Psychopharmacol 1995; 15 (1 Suppl.): S36-44
153. Zuddas A, Cianchetti C. Efficacy of risperidone in idiopathic segmental dystonia. Lancet 1996; 347: 127-8
154. Borison RL, Pathiraja AP, Diamond BI, et al. Risperidone: clinical safety and efficacy in schizophrenia. Psychopharmacol Bull 1992; 28: 213-8
155. Keltner NL. Risperidone: the search for a better antipsychotic. Perspect Psychiatr Care 1995; 31: 30-3
156. Kopala LC, Honer WG. The use of risperidone in severely demented patients with persistent vocalizations. MDE Ed J 1997; 12: 73-7
157. Madhusoodanan S, Brenner R, Araujo L, et al. Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder,

or senile dementia in 11 geriatric patients. J Clin Psychiatry 1995; 56: 514-8
158. Adler A, Angrist B, Reiter S, et al. Neuroleptic-induced akathisia: a review. Psychopharmacology 1989; 42: 872-4
159. Hanin B, Lerner Y, Srour N. An unusual effect of ECT on drug-induced parkinsonism and tardive dystonia. Convuls Ther 1995; 11: 271-4
160. Burke RE, Fahn S, Marsden CD. Torsion dystonia: a double blind, prospective trial of high dosage trihexyphenidyl. Neurology 1986; 36: 160-4
161. Greene P, Shale H, Fahn S. Analysis of open-label trials in torsion dystonia using high dosages of anticholinergics and other drugs. Mov Disord 1988; 3: 46-60
162. Thaker GK, Nguyen JA, Strauss ME, et al. Clonazepam treatment of tardive dyskinesia: a practical GABA mimetic strategy. Am J Psychiatry 1990; 147: 445-51
163. Jancovic J, Orman J. Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. Neurology 1988; 38: 391-4
164. Jankovic J, Beach J. Long term effects of tetrabenazine in hyperkinetic movement disorders. Neurology 1997; 48: 358-62
165. Dorevitch A, Kalian M, Shlafman M, et al. Treatment of long-term tardive dyskinesia with vitamin E. Biol Psychiatry 1997; 41: 114-6
166. Elkashef AM, Ruskin PE, Bacher N, et al. Vitamin E in the treatment of tardive dyskinesia. Am J Psychiatry 1990; 147: 505-6
167. Egan MF, Hyde TM, Albers GW, et al. Treatment of tardive dyskinesia with vitamin E. Am J Psychiatry 1992; 149: 773-7
168. Peet M, Laugharne J, Rangarajan N, et al. Tardive dyskinesia, lipid peroxidation, and sustained amelioration with vitamin E treatment. Int Clin Psychopharmacol 1993; 8: 151-3
169. Akhtar S, Jajor TR, Kumar S. Vitamin E in the treatment of tardive dyskinesia. J Postgrad Med 1993; 39: 124-6
170. Adler LA, Peselow E, Rotrosen J, et al. Vitamin E treatment of tardive dyskinesia. Am J Psychiatry 1993; 150: 1405-7
171. Dabiri LM, Pasta D, Darby JK, et al. Effectiveness of vitamin E for treatment of long-term tardive dyskinesia. Am J Psychiatry 1994; 151: 925-6
172. Lohr JB, Caligiuri MP. A double-blind placebo-controlled study of vitamin E treatment of tardive dyskinesia. J Clin Psychiatry 1996; 57: 167-73
173. Shriqui CL, Bradwejn J, Annable L, et al. Vitamin E in the treatment of tardive dyskinesia: a double-blind placebo-controlled study. Am J Psychiatry 1992; 149: 391-3
174. Greene P. Baclofen in the treatment of dystonia. Clin Neuropharmacol 1992; 15: 276-88
175. Cates M, Lusk K, Wells BG. Are calcium-channel blockers effective in the treatment of tardive dyskinesia? Ann Pharmacother 1993; 27: 191-6
176. Abad V, Osview F. Treatment of persistent myoclonic tardive dystonia with verapamil. Br J Pyschiatry 1993; 162: 554-6

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