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Managing Antipsychotic-Induced Tardive Dyskinesia

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Abstract

Antipsychotic-induced tardive dyskinesia is a common and clinically significant hazard of long term antipsychotic therapy. The arrival of atypical antipsychotics has markedly improved the outlook: atypical antipsychotics are emerging as effective treatments and may also reduce the prevalence and incidence of tardive dyskinesia.

In mild cases, careful monitoring of tardive dyskinesia by serial Abnormal Involuntary Movements Scale (AIMS) assessments may be the appropriate course. More severe tardive dyskinesia calls for intervention in order to treat the dyskinesia. Atypical antipsychotics and tocopherol (vitamin E) are effective and generally well tolerated treatment options for tardive dyskinesia. Tardive dyskinesia variants such as tardive dystonia and tardive akathisia tend to be more severe and difficult to treat compared with typical tardive dyskinesia.

Prevention of tardive dyskinesia is possible through careful selection of patients for antipsychotic therapy, use of the lowest effective antipsychotic dosages, use of atypical rather than traditional antipsychotics and concurrent tocopherol administration.

The clinician can now undertake the management of tardive dyskinesia with growing confidence.

1. Tardive Dyskinesia in Focus

The phenothiazine, thioxanthene and butyrophenone antipsychotics gained widespread use in the 1960s and 1970s and revolutionised the treatment of psychotic disorders. The initial euphoria of this breakthrough was tempered by the realisation that there was a price to pay in terms of frequent and troublesome adverse effects. Foremost among them were the extrapyramidal adverse effects: drug-induced parkinsonism, akathisia, dystonia and dyskinesia. Tardive dyskinesia has received the most attention and is the subject of this review article.

There are several factors which account for the voluminous literature on tardive dyskinesia and the dubious distinction of it being considered the foremost risk of long term antipsychotic drug therapy. Tardive dyskinesia is common, tends to be persistent and it is difficult to treat. Furthermore, tardive dyskinesia usually develops in the presence of a psychiatric disorder requiring active treatment which in turn may aggravate tardive dyskinesia. The management of a patient with tardive dyskinesia, therefore, requires a comprehensive treatment plan which simultaneously addresses the movement disorder and the underlying psychiatric disorder.[1]

The scope of the problem of tardive dyskinesia is underscored by its high prevalence: approximately 20% of patients receiving long term antipsychotic treatment may show tardive dyskinesia at any one time. In probably the largest epidemiological study of tardive dyskinesia, Woerner et al.[2] found an overall prevalence of 23.4% in 1441 antipsychotic recipients against a base rate of 2.6% for 'spontaneous dyskinesia'. Risk factors which increased the prevalence of tardive dyskinesia were: being in a state hospital, older age, greater lifetime antipsychotic exposure, and dentures.[2] The incidence of new tardive dyskinesia has been estimated at 5% per year of antipsychotic therapy.[3] Elderly patients are much more sensitive to antipsychotic-induced tardive dyskinesia. Jeste et al.[4] found an annual incidence of 26.1% with a low antipsychotic dosage in a cohort of patients with an average age of 65 years.

Not only is tardive dyskinesia common, it may become severe and incapacitating with complications such as impaired swallowing, choking, muffled speech, and shortness of breath due to jerky irregular respiration. Patients with severe dyskinesia may avoid social contacts or may become despondent and suicidal as a result of their movement disorder.[5]

The outlook for patients with tardive dyskinesia is no longer as dismal as it was first thought. The clinical management of patients with a psychiatric disorder who have tardive dyskinesia can be both feasible and effective. Moreover, the recent introduction of atypical antipsychotics has improved the treatment prospects and may lead to a significant reduction in the incidence and prevalence of tardive dyskinesia as well.

2. Assessment and Course of Tardive Dyskinesia

A careful clinical assessment of dyskinesia is the basis of effective management. Dyskinetic movements are classified according to type (e.g. choreiform, athetoid or dystonic), topographical distribution (e.g. oro-facial or axial) and severity, which may be further characterised by frequency and amplitude of movements. Global clinical judgements such as mild, moderate, or severe tardive dyskinesia convey helpful information to the clinician but their reliability and accuracy may be open to question.

The quantitative assessment of tardive dyskinesia is a valuable tool in the accurate monitoring of treatment studies and for the evaluation of course and outcome. Of the numerous published rating scales, the Abnormal Involuntary Movements Scale (AIMS) has been used most widely and is the gold standard of tardive dyskinesia assessment in the literature.[6] The arbitrary definition of 'a case of tardive dyskinesia' is usually based on 2 'mild' or 1 'moderate' item scores on the AIMS.[7]

The course of tardive dyskinesia without specific intervention to reduce movement severity has

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been assessed by longitudinal studies. Follow-up studies of tardive dyskinesia lasting over 5 years tend to show stability of tardive dyskinesia even with continued antipsychotic treatment.[8] In our group's recently completed study, entitled the 'Course of Early Dyskinesia',[9] in which approximately 200 patients with recently developed dyskinesia were followed for several years in naturalistic treatment settings, there was statistically and clinically significant improvement in tardive dyskinesia. Younger patients and those with more recent dyskinesia tend to improve more[8,9] while older patients with chronic disease may show increases in tardive dyskinesia ratings over time.[10]

In studies where typical antipsychotics were withdrawn for the purpose of treating tardive dyskinesia, remission of tardive dyskinesia, defined as a ≥50% decrease in rating scale scores, approached 50%.[11] However, withdrawal of antipsychotics is often a risky option because of the likelihood of psychotic decompensation. The arrival of atypical antipsychotics seems to provide a satisfactory alternative for patients with tardive dyskinesia who need to be maintained on antipsychotic drugs clinically.

3. Management of Tardive Dyskinesia

An algorithm for the management of tardive dyskinesia is presented in figure 1.

3.1 Mild Tardive Dyskinesia

Analysis of the risks versus benefits of the various treatment options is the cornerstone of the rational management of tardive dyskinesia which is mild and causes little or no functional impairment.

In a typical clinical situation a patient with chronic psychosis develops mild oro-facial dyskinesia during long term antipsychotic treatment. History shows that withdrawal of treatment results in psychotic decompensation. In the absence of significant medical problems or substance abuse, and provided the patient is well compensated on the current antipsychotic, the prudent course is to make no significant medication changes but simply monitor the level of tardive dyskinesia by serial AIMS examinations.

As long as the mental status remains satisfactory and the tardive dyskinesia ratings are stable and in the mild severity range, there is no clear need for specific intervention either for tardive dyskinesia or for the underlying psychosis. However, should the serial ratings suggest any exacerbation of tardive dyskinesia, or if there is less than optimal response to antipsychotic therapy, a change in treatment would appear indicated. For exacerbation of tardive dyskinesia, one of the antidyskinetic treatments [e.g. clozapine, tocopherol (vitamin E)] discussed in section 4 may be considered.

If the patient's unstable mental status suggests a relapse or unsatisfactory drug response, addition of a mood stabiliser and/or change of the antipsychotic to a different atypical or traditional antipsychotic may lead to clinical restabilisation. If patients can be withdrawn from treatment with traditional antipsychotics their tardive dyskinesia should improve in the long run, although temporary exacerbation of tardive dyskinesia may be seen when traditional antipsychotics are withdrawn or their dosage is reduced.[12]

In summary, patients with mild tardive dyskinesia need to be carefully monitored for any significant change in the movement disorder. At the same time the concurrent psychiatric disorder needs optimal pharmacotherapy on lowest effective antipsychotic dosages. Specific intervention is rarely needed for the dyskinesia which is typically mild and causes little or no functional impairment.

3.2 Moderate to Severe Tardive Dyskinesia

Patients who exhibit at least moderately severe tardive dyskinesia or those who are distressed by the movements or develop complications are candidates for specific antidyskinetic therapy.

Until recently no consistently effective treatments were available for tardive dyskinesia. The best statement that could be made was that each treatment appeared to benefit a minority of patients and that a series of empirical trials of different

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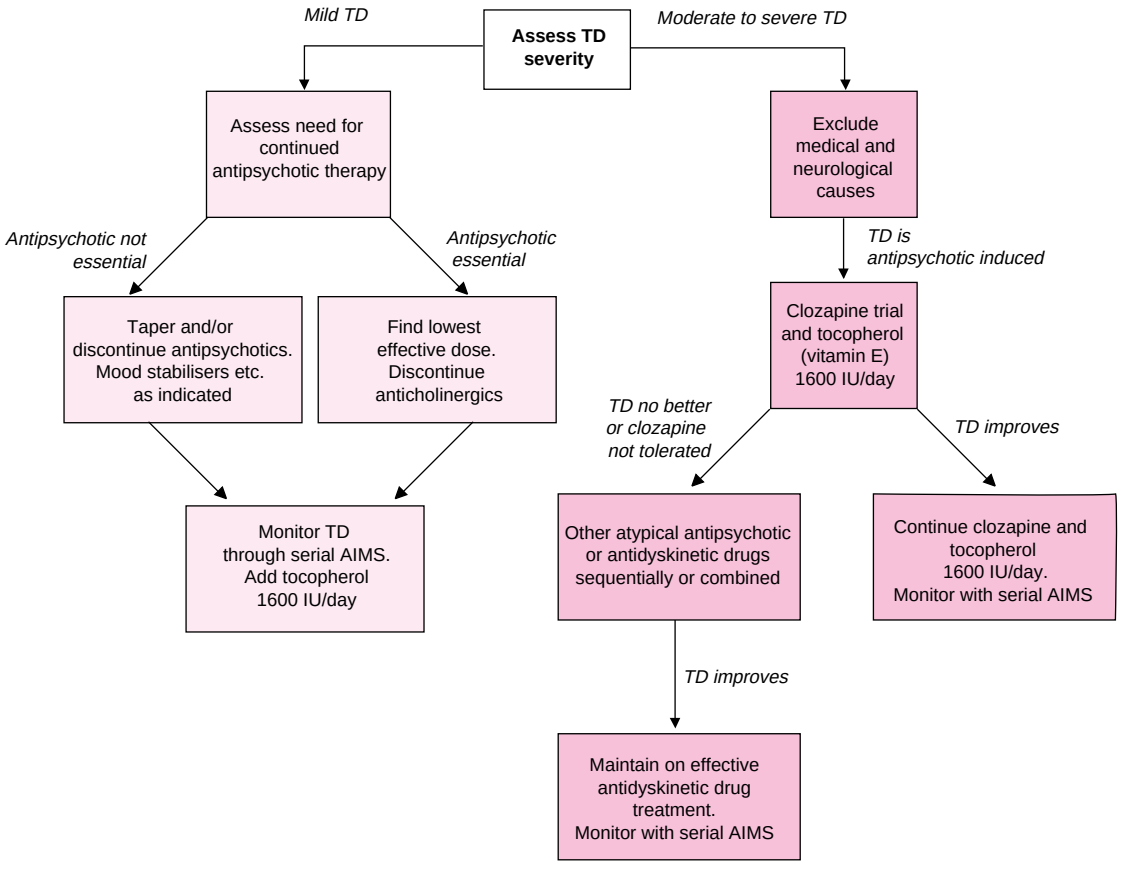

Fig. 1. Algorithm for the clinical management of tardive dyskinesia (TD). **AIMS** = Abnormal Involuntary Movements Scale; **IU** = international units.

compounds might eventually yield one with therapeutic efficacy in individual patients. Adverse effects are a significant clinical problem with many of these drugs and in some instances their positive effects on dyskinesia may be negated by adverse effects on psychiatric syndromes. The therapeutic approaches to tardive dyskinesia and the list of antidyskinetic drugs have been comprehensively reviewed.[11-13]

Traditional approaches to treating tardive dyskinesia were based on the assumption that tardive dyskinesia was associated with functional overactivity of dopamine in the basal ganglia. Therefore, compounds which reduce dopamine activity were prime candidates for antidyskinetic effects. Typical antipsychotics such as phenothiazines, thioxanthenes and butyrophenones, and drugs such as reserpine and tetrabenazine were evaluated in clinical trials and were found to be generally effective in reducing the severity of tardive dyskinesia.[11-13]

The problem with using typical antipsychotics for treating tardive dyskinesia is that parkinsonian symptoms of tremor, bradykinesia and rigidity are often produced and may nullify the benefits of the antidyskinetic effects. In addition, the reduction in tardive dyskinesia may be regarded as suppression rather than true movement amelioration: once the antipsychotic is withdrawn, there is often a rebound aggravation of tardive dyskinesia which is

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proportional to the degree of tardive dyskinesia suppression.[14] The limitations of reserpine and tetrabenazine are their significant adverse effects although these drugs are employed frequently by neurologists for the more severe dyskinesias and dystonias.[13]

The old hypothesis that tardive dyskinesia is linked to an imbalance between dopaminergic and cholinergic influences in the striatum stimulated interest in cholinergic treatments for tardive dyskinesia. Deanol aceglumate, choline chloride and lecithin were at one time popular treatments for tardive dyskinesia[15] but have been mostly abandoned because of only modest therapeutic benefits along with very unpleasant adverse effects. Anticholinergic drugs, which often aggravate tardive dyskinesia, may actually have beneficial effects in some instances.[16] γ-Aminobutyric acid (GABA)-ergic compounds and calcium antagonists sometimes improve tardive dyskinesia as does electroconvulsive therapy.[13] A variety of miscellaneous compounds have shown therapeutic effects in occasional tardive dyskinesia patients in non-comparative studies and case reports.[13]

4. Newer and More Effective Therapies

The arrival of atypical antipsychotics and of antioxidants has dramatically improved the outcome of tardive dyskinesia.

Clozapine has a very low propensity for drug-induced parkinsonism and practically never causes tardive dyskinesia.[17] In several controlled and nonblind studies, clozapine showed marked efficacy in tardive dyskinesia of all types and severity.[13] Lieberman et al.[18] proposed that clozapine exerted a specific antidyskinetic effect because of the absence of rebound after clozapine withdrawal and because of apparently greater efficacy in severe tardive dyskinesia. The optimal dose range of clozapine for tardive dyskinesia remains to be determined: European clinicians tend to favour dosages at or below 300 mg/day while in the US dosages of 500 mg/day or above are quite common.[19] Once begun, long term treatment with clozapine is recommended as tardive dyskinesia symptoms may be slow to remit.

There are several newer atypical antipsychotics: risperidone, olanzapine and quetiapine. These compounds were developed because of lower potential for drug-induced parkinsonism than traditional antipsychotics, and are therefore expected to be less likely to cause tardive dyskinesia. However, the liability of the newer atypical antipsychotics to induce tardive dyskinesia and their potential in the treatment of tardive dyskinesia need to be established by appropriate studies.

Tocopherol is a lipid-soluble antioxidant thought to counteract free radical formation. Free radicals may be a by-product of antipsychotic drug effect and may be neurotoxic. A review of double-blind controlled studies of tocopherol in the treatment of tardive dyskinesia revealed encouraging results.[20] Six studies showed drug efficacy as opposed to 1 negative study. The research suggests that dosages of 1600 IU/day may be required for at least 8 weeks for optimal drug efficacy. Tocopherol is well tolerated except for occasional diarrhoea. Patients who have had tardive dyskinesia for less than 5 years are more likely to respond than patients with long standing tardive dyskinesia. Tocopherol appears to be an effective treatment for tardive dyskinesia, and by virtue of being an antioxidant it may have neuroprotective effects and prevent the development of tardive dyskinesia. Prescribing tocopherol during antipsychotic treatment before tardive dyskinesia develops as well as after tardive dyskinesia onset may be beneficial. The definitive role of tocopherol will be better established once results from large on-going controlled studies are completed.

5. Tardive Dyskinesia Variants

Several types of involuntary movements may coexist with typical tardive dyskinesia. Although much less common than choreoathetoid tardive dyskinesia, these tardive dyskinesia variants may become severe and disabling.

Tardive dystonia consists of sustained muscle contractions and irregular postures, and patients

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may present with symptoms such as blepharospasm, torticollis, retrocollis, grimacing and the Pisa syndrome. Antipsychotic drug withdrawal rarely benefits patients with tardive dystonia but therapy with clozapine[18] may be effective. Some patients respond to anticholinergic drugs, reserpine, tetrabenazine or benzodiazepines.[13] Botulinum toxin A injections into affected muscles for cervical dystonia or blepharospasm have been markedly effective, but injections have to be repeated every few months.[21] Tardive akathisia consists of motor restlessness as well as subjective discomfort. Antipsychotic discontinuation is rarely effective but reserpine, tetrabenazine, β-blockers, benzodiazepines or clozapine may benefit certain patients.[22]

The algorithm (fig. 1) recommends that tardive dyskinesia be monitored on a regular basis preferably with a rating scale such as the AIMS.[6] A clozapine trial is at present the most likely treatment to succeed in treating moderate to severe tardive dyskinesia but other atypical antipsychotics may emerge as suitable alternatives. Tocopherol in adequate doses is suggested for all cases of tardive dyskinesia.

6. Prevention of Tardive Dyskinesia

When it comes to tardive dyskinesia the old saying, 'An ounce of prevention is better than a pound of cure', could not be truer. Prudent pharmacotherapy using lowest effective dosages and ascertaining the need for long term antipsychotic maintenance are important principles. Patients at high risk for developing tardive dyskinesia require particular scrutiny with respect to antipsychotic administration. Patients vulnerable to tardive dyskinesia include the elderly, those with affective disorder and patients who show sensitivity to acute extrapyramidal symptoms. In addition, recent research suggests that mutations in the dopamine D_2[23] and D_3[24] receptor genes may be associated with increased risk for tardive dyskinesia development. An unresolved issue is whether atypical antipsychotics should be first-line treatment for all patients needing antipsychotic drug treatment. Atypical antipsychotics are not without adverse effects and the choice of a traditional versus an atypical antipsychotic for a given patient rests with risk versus benefit considerations. For patients vulnerable to tardive dyskinesia, atypical antipsychotics are to be preferred in most instances. The routine use of tocopherol along with antipsychotics is also recommended.

7. Conclusion

Antipsychotic-induced tardive dyskinesia remains a common and potentially serious adverse effect. However, with the advent of the newer atypical antipsychotics there appears to be a significant decrease in the occurrence of tardive dyskinesia as well as improved treatment options. The management of mild cases of tardive dyskinesia hinges on careful monitoring with a rating scale such as AIMS, while severe cases tend to require direct intervention with clozapine or other atypical antipsychotics as well as with tocopherol. Future research needs to refine the characteristics of patients especially vulnerable to tardive dyskinesia so that use of traditional antipsychotics can be avoided. Definitive studies are desirable to confirm the effectiveness of tocopherol and of atypical antipsychotics in the treatment of tardive dyskinesia.

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