Our experience in this study shows that some treatment-refractory schizophrenic and schizoaffective patients who have not responded to olanzapine at a dose of 20 mg/day may respond when their dose is increased to 25 or 30 mg/day, and that these larger doses are generally well-tolerated. This increased effect may be a result of increased D_2 receptor occupancy at higher doses. It has been shown that olanzapine doses of 5 to 15 mg/day are associated with approximately 90% saturation of 5-HT_2 receptors.[6] However, saturation of D_2 receptors increases with dose and plasma level and goes beyond 80% at 30 mg/day.[6]

Although our results are limited by a small sample size and the lack of dissociability of the effects of increased dose and duration of treatment, there was an attempt to reduce the effect of treatment duration by requiring a minimum length of 3 weeks at each new dosage. A further limitation was the observation that patients were concomitantly receiving other psychotropic medications. However, all of these were instituted months before the onset of treatment with olanzapine and had been determined to have little therapeutic effect. Our results suggest that it would be worthwhile to undertake larger-scale controlled studies of higher-dose olanzapine in patients considered to be treatment-refractory.

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Risperidone-Induced Tardive Dyskinesia in First-Episode Psychotic Patients

Editors:

This is a report of four cases of tardive dyskinesia/dystonia that developed in patients being treated with risperidone at an early intervention facility for young people with psychosis.

Mr. L. is a 19-year-old Taiwanese man with undifferentiated schizophrenia, tic disorder not otherwise specified (grunting), and questionable prior closed head injury. He was treated for psychosis intermittently with pimozide (up to 4 mg daily), thiothixene (up to 6 mg daily for approximately 1 month), and fluoxetine 20 mg for 4 months. He was lost to follow-up for 6 months and was then started on risperidone after referral to the early intervention program. His dose was slowly increased to 5 mg daily with resolution of grunting and mild improvement of positive symptoms, but with marked persistence of negative symptoms. An electroencephalogram and head computed tomographic scan were normal. After 7 months he developed lip smacking and multiple lingual movements. Risperidone was tapered to 2 mg, and vitamin E was added. (He was reluctant to try clozapine, and olanzapine was not yet available.) Over the following month, he developed increasing agitation and dystonias of the face, mouth, and neck. Clonazepam and benztropine improved his symptoms somewhat. He went to Taiwan, where his medications were changed to diazepam, bromazepam, biperiden, orphenadrine, fluoxetine, and sulpiride (600 mg). His dystonia and dyskinesias rapidly resolved, as well as most of his positive and some of his negative symptoms. Upon returning to New Zealand 5 months later, he exhibited only mild lingual dyskinesias.

Mr. J. is a 21-year-old white man with schizoaffective disorder and past closed head injuries. His first episode of psychosis was briefly treated with low-dose haloperidol which was then was changed to risperidone (ultimately 3 mg). Lithium was added 3 months later, with improved mood stability at 1,200 mg. He exhibited only mild residual positive and negative symptoms, but he developed inferior tongue thrusting, evident with his mouth open and closed, after 12 months of treatment. His risperidone is being slowly reduced, and olanzapine will be started if his psychotic symptoms worsen.

Mr. P. is a 22-year-old white man with social phobia and paranoid schizophrenia. He was treated with an average of 5 mg of haloperidol during his initial presentation. Risperidone was started after 5 months because of sedation and poor concentration. He had mild residual positive symptoms and moderate negative symptoms at 1.5 mg, but he developed akathisia and truncal dyskinesias despite the addition of 30 mg of propranolol. Sixteen months after his first presentation, he developed lip pursing that worsened despite the addition of 800 IU of vitamin E. Olanzapine 5 mg was started and resulted in a reduction (possibly as a result of suppression) of lip pursing after 2 weeks, and risperidone is being tapered.

Mr. C. is a 20-year-old white man with undifferentiated schizophrenia and a history of alcohol abuse, reading disorder, and closed head injury. His first psychosis was briefly treated with haloperidol, and then the treatment was changed to risperidone. Most of his positive symptoms resolved at 6 mg, but his negative symptoms remained severe. Eight months after initial treatment, he developed progressive, intermittent, rapid tapping of his tongue on the posterior aspect of his upper teeth, with no other abnormal movements.

Risperidone is currently being replaced with olanzapine, with no change in dyskinesias thus far.

The incidence of neuroleptic-induced tardive dyskinesia in patients with chronic schizophrenia who are treated with risperidone is approximately 0.34% per year—much lower than that of typical antipsychotics.[1] Current studies suggest that the risk of dyskinesia is also quite low in patients with first-episode psychosis (Emsley RA, McCreadie R, Livingston M, De Smedt G, Lemmens P. Risperidone in the treatment of first episode patients with schizophreniform disorder. Unpublished report obtained from Janssen Cilag, New Zealand, 1995). The ability of olanzapine to ameliorate risperidone-induced dyskinesia in this group is as yet unknown, but most patients early in their illness are reluctant to consider clozapine. Leiberman[2] has suggested that patients with their first episode of psychosis are more sensitive to both the beneficial and the deleterious effects of all antipsychotics. The number of complications at this facility highlights this sensitivity and is far greater than anticipated for the 84 patients accepted thus far for care, of whom 46 have been treated primarily with risperidone. Explaining this increased incidence of dyskinesia is difficult, given the small number of patients, their diverse presentations and comorbid illnesses, and their initial treatment with typical antipsychotics. Hopefully this report will stimulate further studies that attend to these side effects and their possible correlates in first-episode patients treated with atypical antipsychotic medication.

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Effectiveness of Anticholinergics and Neuroleptic Dose Reduction on Neuroleptic-Induced Pleurothotonus (the Pisa Syndrome)

Editors:

In 1972, Ekbom and associates[1] described a persistent dystonia of the trunk during prolonged exposure to neuroleptics, which became termed the Pisa syndrome (neuroleptic-induced pleurothotonus[2]). This condition exhibits abnormally sustained posturing with a flexion of the body and head to one side with slight axial rotation of the trunk. Thus, it has also been described as a spasm of the lower back muscles. It has been suggested[1,3,4] that certain functional or organic changes in the brain are involved in the development of pleurothotonus. Clinical evidence[5–13] suggests that drug-induced pleurothotonus is similar to tardive dystonia and benefits little from anticholinergic therapy. However, no treatment has been consistently effective, and the pathophysiologic mechanisms underlying tardive dystonia remain unknown. In this study, we report the therapeutic effect of anticholinergics in the treatment of 21 patients with drug-induced pleurothotonus during long-term administration of antipsychotics.

Methods

Subjects included 21 patients, consisting of 20 inpatients and 1 outpatient, at the University of Tsukuba Hospital and an affiliated psychiatric hospital of the University of Tsukuba. They were recruited between April 1986 and March 1996. Upon admission, 20 patients were taking two or more of the following antipsychotic drugs orally: phenothiazines (chlorpromazine, levomepromazine, etc.), butyrophenones (haloperidol, pipamperone, etc.), and zotepine. One patient was taking a combination of tricyclic antidepressants (amitriptyline, imipramine, nortriptyline). All patients receiving antipsychotics were also concurrently taking an anticholinergic, trihexyphenidyl 6 mg/day, to prevent the appearance of extrapyramidal symptoms. Patients developed postural disturbances corresponding to pleurothotonus after an exposure to an additional antipsychotic or without additional drugs. The severity or change of pleurothotonus was estimated by two psychiatrists. The primary psychiatric disorders were schizophrenia in 13 patients, affective disorder in 2 patients, mental retardation in 5 patients, and multi-infarct dementia in 1 patient, according to DSM-IV criteria. All patients were free of major medical illnesses. Possible neurologic diseases were excluded by family histories and neurologic examinations. For the treatment of the pleurothotonus, all patients initially received additional anticholinergic medications: trihexyphenidyl orally (4 mg three times a day) or biperiden hydrochloride intramuscularly (5 mg per dose). Differences in gender, age, psychiatric diagnosis, direction of trunk, accompanying extrapyramidal symptoms, and brain organic changes between responders and nonresponders to anticholinergics on the Pisa syndrome were statistically tested using the Fisher exact probability test.

Results

A summary of the clinical characteristics of the patients with drug-induced pleurothotonus is given in Table 1. The ages (mean ± SE) of the 7 men and 14 women were 40.3 ± 7.2 years and 40.4 ± 3.9 years, respectively. Their age at onset of drug-induced pleurothotonus ranged from 18 to 71 years. The trunk in men and in women was tilted to the right in 9 patients (2 men and 7 women) and to the left in 12 patients (5 men and