Tardive dyskinesia was associated with poor treatment response and higher antipsychotic drug dose after the first episode of schizophrenia


Objective
To determine whether tardive dyskinesia (TD) is associated with underlying pathophysiologic factors as well as antipsychotic drug treatment in adults who had a first episode of schizophrenia.

Design
Inception cohort followed for up to 8.5 years (median 2.5 y).

Setting
A teaching hospital in New York City, USA.

Patients
118 adults (mean age 25 y, 52% men, 41% white) who were hospitalized with a first episode of schizophrenia. Inclusion criteria were a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder using Research Diagnostic Criteria; age 16 to 40 years; < 12 weeks of previous antipsychotic drug exposure; no current substance abuse; and no neuromedical illness.

Main outcome measures
TD was defined using the modified Simpson Dyskinesia Scale (SDS). Patients with presumptive TD had a score of ≥ 2 on the SDS; patients with persistent TD had symptoms for ≥ 3 months.

Main results
Cumulative incidence at 1, 2, and 4 years was 6.3%, 11.5%, and 17.5%, respectively, for presumptive TD and 4.8%, 7.2%, and 15.6%, respectively, for persistent TD. TD was not associated with sex, age, race, diagnosis, baseline symptoms, adolescent PAS scores, or extrapyramidal signs. Presumptive TD was associated with greater impairment on childhood PAS scores (hazards ratio [HR] 1.67; 95% CI 1.09 to 2.58), but this association disappeared after adjusting for dose, clozapine exposure, and treatment response status. After adjustment for clozapine dose and use, presumptive and persistent TD were positively associated with dose (HR for presumptive TD 1.06, CI 1.01 to 1.12 per 100 mg increase in mean daily dose, and HR for persistent TD 1.12, CI 1.03 to 1.22 per 100 mg increase in mean daily dose). With adjustment for antipsychotic drug dose and clozapine status, treatment responders had a lower risk for presumptive TD (HR 0.06, CI 0.01 to 0.38) and for persistent TD (HR 0.09, CI 0.01 to 0.98).

Conclusion
Tardive dyskinesia was associated with poor response to treatment and antipsychotic drug dose in adults who had a first episode of schizophrenia.

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Assessment of prognostic factors
Psychopathological conditions and extrapyramidal abnormalities were assessed using standardised research measures. The Premorbid Adjustment Scale (PAS) was used to evaluate achievement of developmental goals in childhood, adolescence, and adulthood. Medications were prescribed using a standard algorithm with stepped increases based on lack of improvement and remission status. Scores and drug use were recorded at each visit.

Commentary
When faced with a new patient who has a probable diagnosis of schizophrenia, clinicians have the unenviable tasks of both predicting illness prognosis and assessing the risks and benefits of (usually long-term) antipsychotic medication for the patient (and the effects of the patient's response to the medication on the relatives). This study is particularly valuable because patients had essentially no previous exposure to antipsychotic drugs. Treatment was based on a standardised algorithm, and despite the protective effect of the medication regimen, the cumulative incidence of persistent TD was 15.6% after 4 years. This finding lends support to similar results from more heterogeneous groups of patients.

118 patients with a first episode of schizophrenia were recruited, but the study had insufficient power to convincingly unravel some of the authors' main questions. Although higher antipsychotic drug dose and poor initial treatment response are inevitably confounded, they both appear to contribute to the onset of TD. Developmental difficulties in childhood may also be associated with TD, but more research is required to confirm this.

If treatment response and childhood developmental problems contribute to TD independently of antipsychotic drug dose, then this would be further evidence for underlying pathophysiological vulnerability to TD. This association will inform future basic and clinical research. In clinical practice, it is unlikely that a history of childhood developmental delays will influence treatment plans. The study, however, underlines the dilemma for psychiatrists who are tempted to increase the dose of antipsychotic medication in patients who have failed to respond to initial treatment.

Clozapine is the only antipsychotic drug that has currently been shown not to have a high risk for causing TD. Does this investigation by Chakos and colleagues put additional pressure on clinicians to use this expensive medicine more often? If so, perhaps the time has come for governmental prescribing authorities to force down the cost of clozapine, if necessary by “unbundling” its prescription from the monitoring of potential haematological side effects.

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