Drug-Induced Extrapyramidal Syndromes

Implications for Contemporary Practice

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KEYWORDS

• Antipsychotic drugs • Schizophrenia • Tardive dyskinesia • Catatonia
• Neuroleptic malignant syndrome • Akathisia • Parkinsonism • Dystonia

KEY POINTS

- Awareness of acute drug-induced extrapyramidal syndromes (EPS) remains important for patient safety in clinical practice.
- Investigations of new treatments offer promise for managing patients with tardive dyskinesia.
- Advances in understanding the genetics and pathophysiology of EPS may illuminate the mechanisms of action of antipsychotic drugs and the biological bases of psychotic disorders.

INTRODUCTION

Although the origins of antipsychotic pharmacology began with the search for compounds to improve anesthesia, clinicians reported unusual "psychic indifference" as the defining effect of these drugs.[1] Nevertheless, early antipsychotics were thought to be useful primarily for sedation rather than specific antipsychotic effects, whereas drug-induced extrapyramidal syndromes (EPS) were considered necessary indicators that therapeutic doses had been achieved. Thus, the neurologic properties received pride of place in the original designation, "neuroleptics."

However, it soon became apparent that EPS can be mistaken for or worsen psychotic symptoms, are sometimes irreversible or lethal, necessitate additional burdensome adverse effects from antiparkinsonian agents, can be disfiguring and

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Abbreviations	
ECT	Electroconvulsive therapy
EPS	Extrapyramidal syndromes
FGA	First-generation antipsychotic
NMS	Neuroleptic malignant syndrome
SGA	Second-generation antipsychotic
TD	Tardive dyskinesia
VMAT2	Vesicular monoamine transporter type 2

stigmatizing, and may influence compliance, relapse, and rehospitalization.[2–4] As a result, EPS dominated concerns about tolerability of antipsychotics and drove new drug development.

In 1988, Kane and colleagues[5] reported that clozapine had broader efficacy in schizophrenia with negligible EPS, stimulating the search for new antipsychotics. Industry-sponsored trials heralded subsequent "second-generation antipsychotics" (SGAs) as superior to "first-generation antipsychotics" (FGAs) in causing fewer EPS.[6–13] Cumulative evidence, including the general consensus of clinicians, confirmed reduced liability for EPS with SGAs, contributing to their market dominance and the concept of "atypicality" in their mechanism of action.[14–21]

However, subsequent postmarketing studies challenged the advantages of SGAs in reducing EPS. The discrepancy between effectiveness and marketing trials stems from the choice of comparator drugs and dosages. Although haloperidol was a reasonable choice as a comparator in industry-sponsored trials as the first-line antipsychotic drug at the time, subsequent studies suggested that the advantages of SGAs in reducing EPS were diminished when lower doses or lower potency FGAs are used, or if prophylactic antiparkinsonian drugs are administered.[19,22–30] This implies that haloperidol is not paradigmatic of all FGAs; therefore, the dichotomy between first- and second generation drugs and the concept of SGA "atypicality" based on EPS liability was overstated. Antipsychotic drugs should be considered a single drug class with a spectrum of risk for EPS depending on dopamine D2 receptor binding affinity combined with affinity for other receptors.

Even though there is some reduction in risk of EPS with the SGAs, it remains important for clinicians to be familiar with EPS for several reasons. First, because dopamine D2 receptor blockade is preserved in all currently marketed antipsychotics and is necessary for antipsychotic efficacy, EPS remains a potential liability for all drugs in this class. Second, FGAs are still used in psychiatry, in medical settings, and in developing nations. Third, EPS must be balanced with risk for other significant adverse effects, for example, the metabolic syndrome. Fourth, the higher costs of newer drugs may be a consideration. Fifth, although the proportion of patients who develop EPS may be reduced, aggressive marketing and off-label prescribing contribute to an ever-widening population at risk. This development is especially concerning related to high-risk groups such as children, the elderly, and medically compromised patients. Familiarity with tardive dyskinesia (TD) is important because new drug treatments are likely to become available. In the future, genetic testing may uncover genetic susceptibilities to drug-induced EPS. Finally, research into EPS may provide insights into the mechanism of action of antipsychotic drugs. We, therefore, provide an updated review of the literature on diagnosis and management of the classic EPS syndromes including emerging evidence on treatment of TD.[1,30–32]