The Epidemiology of Drug-Induced Akathisia: Part I. Acute Akathisia

by Perminder Sachdev

Abstract

This article reviews the epidemiological data on drug-induced acute akathisia, examining studies in which akathisia was the primary focus as well as those in which it was one of a number of drug side effects studied. The studies are diverse in methodology and suffer from many limitations. Incidence rates for acute akathisia with conventional neuroleptics vary from 8 to 76 percent, with 20 to 30 percent being a conservative estimate; preliminary evidence suggests that the newer atypical antipsychotic drugs are less likely to produce acute akathisia. A number of nonneuroleptic drugs—in particular the serotonin-specific reuptake inhibitors—have been implicated in the development of akathisia, but the epidemiological data are limited. Risk factors for neuroleptic-induced akathisia are not completely understood. Drug dose, rate of increment of dose, and drug potency seem to be important, but the role of sociodemographic factors and other treatment-related variables is modest. Drug-induced parkinsonism is significantly correlated with akathisia. Evidence for iron deficiency as a risk factor is conflicting, and its contribution is likely to be minor.


Epidemiology, with its description of the population affected by an illness and the identification of possible risk factors, often lies at the heart of treatment and prevention programs. Drug-induced akathisia is considered a poorly understood side effect of psychotropic drugs and is often referred to as the “Cinderella” of psychiatry (Stahl 1985). Since a number of studies have now been published that examine its incidence, prevalence, and risk factors, it is appropriate to review these studies and, thus, the current status of the epidemiology of akathisia. For this purpose, we have classified akathisia into acute, tardive, and withdrawal subtypes (Sachdev 1994b). Part I of this review deals with acute akathisia, examined in relation to both neuroleptic and nonneuroleptic drugs; the accompanying article, Part II, deals with chronic akathisia, tardive akathisia, and withdrawal akathisia, as well as with akathisia in special populations. Acute akathisia refers to the onset of akathisia within hours or days of drug initiation, increase in dose, or change in type of drug. For neuroleptics, the onset is almost always within the first 6 weeks (Ayd 1961), and our proposed criteria consider onset after 3 months as a tardive onset (Sachdev 1994b).

A review of akathisia studies encounters the following limitations. First, most early investigations lumped akathisia together with other extrapyramidal reactions. Some early authors (e.g., Freyhan 1958; Ayd 1961) did attempt to describe akathisia separately, but it was not until the mid-1970s that akathisia received serious attention in its own right, and it was in the 1980s that incidence and prevalence estimates became available from well-conducted studies. Second, until recently, no definite diagnostic criteria for akathisia had

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been proposed. In many studies (e.g., Ayd 1961; Hunter et al. 1964; Kennedy et al. 1971), a clinical diagnosis was made but the process of diagnosing was not specified. Even when rating scales were used (e.g., Levinson et al. 1990; Rifkin et al. 1991), it was often not specified whether both subjective and objective features were considered necessary for the diagnosis. The reliability and validity of many of the scales have not been adequately examined. One group of investigators (Van Putten et al. 1974) used a positive response to parenteral biperiden, an acetylcholine antagonist, as the diagnostic criterion for akathisia, but this has not been independently replicated. Only somewhat recently have operational diagnostic criteria been proposed (Burke et al. 1987; Lang 1994; Sachdev 1994b), and it is hoped that future epidemiological studies will give due regard to these criteria in arriving at incidence and prevalence estimates. Third, the majority of the published epidemiological studies have not taken into consideration the various subtypes of akathisia. Since the pathophysiology, pharmacological characteristics, longitudinal course, and prognosis of the subtypes may be distinct (Sachdev 1994b), it is necessary to consider the epidemiological characteristics separately. In this review, we have attempted to subtype the akathisia described in each study according to the descriptions provided by the investigators and using the definitions described elsewhere (Sachdev 1994b) as applicable. Where the descriptions were inadequate, we applied a best guess and stated this in the descriptions so that firm conclusions are not drawn from such studies. In some cases, while it can be confidently stated that most subjects belonged to a particular subtype, this cannot be assumed for the entire population; such studies are included in the section appropriate for the majority. Fourth, a distinction has not always been made between the incidence and the prevalence of akathisia. One difficulty in comparing and contrasting incidence and prevalence rates stems from the fact that the natural history of akathisia is poorly understood. It is not certain at what point acute akathisia becomes chronic, and whether this is different from chronic akathisia of tardive or withdrawal onset. Barnes and Braude (1985) attempted to distinguish acute akathisia that tended to persist and yet retain its pharmacological characteristics from tardive akathisia, and they called it “acute persistent akathisia.” While this may be a reasonable distinction to make in a longitudinal study, its validity in retrospective analyses is questionable because of the difficulty in establishing that akathisia had been continuously present since its acute onset. The published literature therefore presents a mix of incidence and prevalence data.

Types of Studies

The above limitations notwithstanding, the following types of studies that deal with the epidemiology of akathisia can be identified.

Studies in Which Akathisia Was the Primary Focus of an Epidemiological Investigation. Examples of this are studies by Van Putten (1975), Braude et al. (1983), Van Putten et al. (1984b), and Sachdev and Kruk (1994). The ideal design of a study to examine the incidence of akathisia is a prospective longitudinal study of patients treated with a particular neuroleptic or with other psychotropic drugs, and of control subjects not treated with any such drugs. Since neuroleptics are used to treat serious mental illness, an untreated psychiatric control group is usually not possible. Further, since akathisia is by definition a drug-induced state, a control group may indeed not be necessary, provided a baseline examination has excluded subjects with akathisia-like syndromes. Because neuroleptic dose and the rate of its increment are potentially important for the development of akathisia, only those studies that use “clinical” doses and the usual routes of administration are clinically relevant. Single-dose challenge studies (e.g., Magliozzi et al. 1985) may serve the important function of identifying risk factors for akathisia, but the incidence rates obtained from such studies have limited clinical relevance. Reviewing patient charts and interviewing patients for past history of akathisia, as is done in retrospective studies, are likely to be poor epidemiological methods for this disorder because akathisia is often unrecognized clinically and patients have difficulty distinguishing it from restlessness due to other causes. Thus, a prospective design is essential if predisposing factors to akathisia have to be studied.

Studies That Focused on “Side Effects of Drugs,” With Akathisia One of Many Side Effects Studied. The classic article by Ayd (1961) is an example of such a study. The advantage of this kind of investigation is that it can
place akathisia in relation to other side effects and thus examine the relative vulnerability factors as well as the burden. However, the lack of focus leads to a compromise on diagnostic rigor, and predisposing factors often cannot be adequately assessed.

Studies Primarily to Investigate Clinical Aspects of a Drug, With Akathisia, to Some Extent an Incidental Observation. Examples are studies designed to compare different doses of neuroleptics (e.g., Levinson et al. 1990; Van Putten et al. 1990; Rifkin et al. 1991) or to examine the clinical profile of a new drug in comparison with that of an earlier established one (e.g., Claghorn et al. 1987 and Cohen et al. 1991) for clozapine or of a nonneuroleptic drug not generally known to produce akathisia (e.g., Goff et al. 1991 for buspirone).

Incidence and Prevalence of Acute Akathisia

Freyhan (1957) examined for extrapyramidal side effects (EPSE) all patients who were treated with either chlorpromazine or reserpine over 2 years in his hospital. While he did not use the term "akathisia," he described patients who complained of inner restlessness and have at times an irresistible urge to be in motion ... reminiscent of the hyperkinetic behaviour of encephalitic patients" (p. 466). This reaction was seen in 6 to 8 percent of the reserpine patients but in none of the chlorpromazine patients. In another study, Freyhan (1959) made explicit the term "akathisia" and also said he believed that "the various references to 'paradoxical reactions' or 'turbulent phases' are descriptions of the syndromes of akathisia" (p. 582). He reported slightly different prevalence rates for akathisia resulting from different phenothiazines: trifluopromazine (sample \( n = 25 \)) 12 percent; prochlorperazine (\( n = 68 \)) 19.1 percent; trifluoperazine (\( n = 65 \)) 12.3 percent; and perphenazine (\( n = 22 \)) 9.1 percent. However, equivalent doses, as we now recognize them, for the different drugs were not used.

The largest survey of drug-induced EPSE was that of Frank Ayd, Jr. (1961), who examined 3,775 subjects (1,833 men and 1,942 women) between the ages of 4 and 88 years who had been treated with one of seven phenothiazines for periods ranging from 3 months to 6 years. Akathisia, which was described as "motor restlessness," was diagnosed in 21.2 percent of the subjects (compared with parkinsonism in 15.4% and dyskinesia—largely acute dystonia—in 2.3%). The diagnosis was clinical, and no rating scale was used. Akathisia developed slightly before the EPSE, and 90 percent of the cases occurred in the first 72 days after initiation of drugs. The onset was earlier and at smaller doses as the potency of the offending drug increased. No demographic or other drug-related vulnerability factors were identified.

Van Putten and his colleagues have reported a number of studies in which they diagnosed akathisia if subjective restlessness was present and the subject responded to challenges with an anticholinergic drug. Van Putten et al. (1974) examined 80 consecutive hospital admissions to study phenothiazine-induced exacerbations of psychosis. Nine patients (11%) had sudden decompensations, and all of them had akathisia, sometimes subtle and evanescent, which could be reversed by an intramuscular injection of biperiden—an observation that needs independent replication. Twenty-three other patients (29%) had EPSE (akathisia, parkinsonism, or dystonia). All nine patients being treated with fluphenazine enanthate had akathisia. In another study by the same author (Van Putten 1975), 110 inpatients on neuroleptics were examined. The subtype of akathisia was not specified but presumably was largely acute. Akathisia was diagnosed in 49 inpatients (45%), with the manifestations being very variable.

The study by Van Putten et al. (1984a) is of interest because of its methodological rigor. Subjects were acutely challenged with either 5 mg haloperidol (\( n = 44 \)) or 0.22 mg/kg thiothixene (\( n = 67 \)) and were examined over the next 6 hours for the development of akathisia. The haloperidol group was then maintained on 10 mg/day and the thiothixene group on 0.44 mg/kg/day of the same drug and followed up over the next 4 weeks. In the haloperidol group, 17 (39%) developed akathisia after the acute challenge (5 mild, 5 moderate, 3 severe, 4 very severe), and by the seventh day of maintenance therapy, 31 (70%) had developed it. In the thiothixene group, 13 (20%) developed akathisia acutely, but if the 7 who received an anticholinergic drug for dystonia are excluded from analysis, the figure becomes 22 percent. Over the next 4 weeks, the cumulative percentage of those with akathisia rose to 63 percent.

A few studies have been published that examined the development of akathisia in response to neuroleptic administration in non-psychiatric populations. Murray et
al. (1977) performed a double-blind crossover study of haloperidol in stuttering and found that 8 out of 26 patients had poor concentration, akathisia, or dystonia. When Magliozzi et al. (1985) administered intravenous or oral haloperidol to normal subjects, 8 of the 12 subjects in the intravenous group and 3 of the 9 subjects in the oral group developed akathisia. No other risk factors were identified.

A number of studies whose primary focus was the comparison of different doses of neuroleptic drugs have also reported on rates of akathisia. Only a few such studies that make a clear statement on akathisia will be mentioned. McClelland et al. (1976) conducted a double-blind trial of 6 months’ duration to compare very high dose (250 mg weekly) with standard dose (12.5 mg weekly) of fluphenazine decanoate in 50 patients ages 18 to 60. By the 24th week, 22 percent in the high-dose and 9 percent in the standard-dose groups had developed akathisia. No specific akathisia rating scale was used. The side effect was mild, however, and only one patient in the high-dose group needed treatment. Van Putten et al. (1990) compared three doses of haloperidol (5, 10, or 20 mg per day) over 4 weeks in acute or relapsing schizophrenia and measured akathisia on a 7-point scale (May et al., unpublished manuscript 1983). Although the incidence of akathisia was not stated, there was a significant difference between the 5- and 20-mg groups, with the latter tending to have more akathisia. Levinson et al. (1990) conducted a randomized, fixed-dose, double-blind trial of oral fluphenazine, and they used a modified version of the Simpson and Angus (1970) rating scale to include a rating for akathisia. Of the 51 patients who did not receive any antiparkinsonian drugs, 22 (43%) developed akathisia, typically after 2 to 3 weeks of treatment. Patients with akathisia tended to have a worse outcome for their psychosis. Rifkin et al. (1991) conducted a randomized trial to compare three doses of haloperidol (10, 30, and 80 mg; n = 29 in each group), again using the modified Simpson and Angus (1970) rating scale. Akathisia showed a nonsignificant trend toward worsening over time in the 10- and 80-mg groups, but the three doses did not differ overall in the relative risks for akathisia. Any akathisia present was mild.

An important “naturalistic” study that examined the epidemiology and clinical features of acute akathisia was that by Braude and colleagues (1983). The authors systematically examined at baseline and at least at weekly intervals 104 patients (30 men, 74 women) who were consecutively admitted to a psychiatric ward and who required antipsychotic medication. The detailed symptoms of akathisia were rated, and a diagnosis of akathisia was made in 25 percent of the subjects. The study had some limitations, however. First, many patients were not drug free at the time of admission (although the authors do not provide figures on this). However, only one patient was assessed to be “restless” at admission and was excluded from the final figures. Second, antiparkinsonian medication was not controlled, and the authors do not state how many patients received anticholinergic or beta-adrenergic antagonist drugs. This would certainly affect the incidence figures. But despite these limitations, this study remains one of the more influential studies in this field.

Sachdev and Kruk (1994) examined 100 consecutive inpatients who had nonorganic psychotic disorders, were not currently on neuroleptic or other drugs, and were free of akathisia and related disorders at admission. They assessed these patients for psychiatric status and movement disorders at baseline and daily for 2 weeks after the initiation of a neuroleptic. The authors used different sets of diagnostic criteria to demonstrate that the incidence varied with the particular criteria used. When they used a global rating, 40 percent of the subjects developed at least mild akathisia and 21 percent developed moderate to severe akathisia. When the proposed research criterion of a rating of 2 or more on the sums of both the subjective and the objective items of the akathisia rating scale (Sachdev 1994a) were used, 31 percent were diagnosed with akathisia. This study addresses some of the deficiencies of previous studies, with its limitation being that systematic examination was restricted to 2 weeks after drug initiation. Since 85 percent of subjects in the Braude et al. (1983) study and the majority of subjects in the Van Putten et al. (1984a) study developed akathisia in the first week after initiation of medication, the Sachdev and Kruk (1994) figures are unlikely to be a gross underestimate. The latter authors also examined a number of predisposing factors to acute akathisia. The factors that most significantly predicted the development of akathisia were the severity of extrapyramidal symptoms such as rigidity and tremor, the current neuroleptic dose and its rate of increment, with lesser contributions being...
The incidence rates of acute akathisia vary from 8 percent (McClelland et al. 1976) to as high as 76 percent (Van Putten et al. 1984a). The incidence rates for the conventional neuroleptics vary from 8 percent (McClelland et al. 1976) to as high as 40 percent with different criteria (Van Putten et al. 1984a). To have clinical relevance, the incidence rates should pertain to commonly used neuroleptic drugs at dosages and rates of increment that are applied in clinical practice. The incidence rates of 25 percent (McLeod et al. 1983) and of 31 percent (21% to 42% with different criteria) reported by Braude et al. (1983) and of 31 percent (21% to 42% with different criteria) reported by Sachdev and Kruk (1994) are relevant in this context. The diversity of the studies does not permit a confident statement of akathisia in an individual patient made by the drug potency (more potent drugs) and a low serum iron level. Predictability of akathisia is 20 to 30 percent, but as is discussed later, this rate is significantly affected by treatment-related variables. For example, the highest rates are supported in parenteral administration, potency of the drug, initial dose used, etc., while all other variables. For example, the highest rates are supported in parenteral administration, potency of the drug, initial dose used, etc., and other variables. For example, the highest rates are supported in parenteral administration, potency of the drug, initial dose used, etc., and other variables. For example, the highest rates are supported in parenteral administration, potency of the drug, initial dose used, etc., and other variables.

Table 1. Epidemiological studies of acute neuroleptic-induced akathisia: Summary results

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Definition of akathisia</th>
<th>Drug(s)/route</th>
<th>n</th>
<th>Results (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary investigations of akathisia</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Van Putten 1975</td>
<td>Psychiatric patients</td>
<td>Subjective, response to bilateral i.v.</td>
<td>Multiple/oral</td>
<td>110</td>
<td>45</td>
<td>Subtype not specified; largely acute</td>
</tr>
<tr>
<td>Van Putten, et al. 1984a</td>
<td>Healthy subjects</td>
<td>Subjective, response to bilateral i.v.</td>
<td>Haloperidol, thiothixene i.v., oral phases</td>
<td>44</td>
<td>76</td>
<td>In two phases; initial i.v. challenge, then used for 4 weeks</td>
</tr>
<tr>
<td>Maglioizzi et al. 1985</td>
<td>Healthy subjects</td>
<td>Not specified</td>
<td>Haloperidol i.v., oral</td>
<td>12 (i.v.), 9 (oral)</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Braude et al. 1983</td>
<td>Psychiatric patients</td>
<td>Subjective and objective</td>
<td>Multiple/oral</td>
<td>104</td>
<td>25</td>
<td>Systematic &quot;naturalistic&quot; study</td>
</tr>
<tr>
<td>Sachdev and Kruk 1994</td>
<td>Psychiatric patients</td>
<td>Subjective and objective (various criteria)</td>
<td>Classical neuroleptics</td>
<td>100</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

Studies of neuroleptic-induced side effects (in general) that included akathisia

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Definition of akathisia</th>
<th>Drug(s)/route</th>
<th>n</th>
<th>Results (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>McClelland et al. 1976</td>
<td>Psychiatric patients</td>
<td>Clinical diagnosis</td>
<td>Fluphenazine decanoate</td>
<td>50</td>
<td>22</td>
<td>Mild akathisia: only one patient needed treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250 mg weekly vs. 12.5 mg weekly/i.m.</td>
<td></td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Population</td>
<td>Definition of akathisia</td>
<td>Drug(s)/route</td>
<td>$n$</td>
<td>Results (%)</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------</td>
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</tr>
<tr>
<td>Murray et al. 1977</td>
<td>Stutterers</td>
<td>Clinical</td>
<td>Haloperidol/oral</td>
<td>26</td>
<td>&lt; 30</td>
<td>Poor concentration, akathisia, and dystonia included</td>
</tr>
<tr>
<td>Levinson et al. 1990</td>
<td>Psychiatric patients</td>
<td>Rating scale</td>
<td>Fluphenazine/oral</td>
<td>51</td>
<td>43</td>
<td>Typically after 2–3 weeks of treatment</td>
</tr>
<tr>
<td>McCreadie et al. 1988</td>
<td>Psychiatric patients</td>
<td>Not stated</td>
<td>Thioridazine vs. remoxipride/oral</td>
<td>?</td>
<td>8</td>
<td>More seen with remoxipride 4%</td>
</tr>
<tr>
<td>Lindström et al. 1990</td>
<td>Psychiatric patients</td>
<td>Not stated</td>
<td>Haloperidol vs. remoxipride/oral</td>
<td>48</td>
<td>57</td>
<td>—</td>
</tr>
<tr>
<td>Andersen et al. 1990</td>
<td>Psychiatric patients</td>
<td>Not stated</td>
<td>Haloperidol vs. remoxipride/oral</td>
<td>32</td>
<td>68</td>
<td>—</td>
</tr>
<tr>
<td>Van Putten et al. 1990</td>
<td>Schizophrenia patients</td>
<td>Rating scale</td>
<td>Haloperidol 5 vs. 10 vs. 20 mg/oral</td>
<td>22+38</td>
<td>—</td>
<td>More with 20 mg</td>
</tr>
<tr>
<td>Rifkin et al. 1991</td>
<td>Psychiatric patients</td>
<td>Rating scale</td>
<td>Haloperidol 10, 30, and 80 mg/each group</td>
<td>29</td>
<td>—</td>
<td>Usually mild; no difference among groups</td>
</tr>
</tbody>
</table>

**Studies of therapeutic drug effects, with akathisia also assessed (selected studies)**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Definition of akathisia</th>
<th>Drug(s)/route</th>
<th>$n$</th>
<th>Results (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freyhan 1959</td>
<td>Psychiatric patients</td>
<td>Clinical diagnosis</td>
<td>Trifluoperazine, prochlorperazine, trifluopromazine, perphenazine/oral</td>
<td>65</td>
<td>12.3</td>
<td>Open study; &quot;paradoxical reactions&quot; considered to be akathisia; drug doses not equivalent</td>
</tr>
<tr>
<td>Ayd 1961</td>
<td>Psychiatric patients</td>
<td>Clinical diagnosis</td>
<td>7 oral/phenothiazines</td>
<td>3,775</td>
<td>21.2</td>
<td>Largest open study</td>
</tr>
<tr>
<td>Van Putten et al. 1974</td>
<td>Psychiatric inpatients</td>
<td>Subjective, response to biperidin i.v.</td>
<td>Multiple drugs/oral</td>
<td>80</td>
<td>&gt; 11</td>
<td>Phenothiazine-induced exacerbations studied primarily</td>
</tr>
</tbody>
</table>
made in some studies, but since acute akathisia is of short duration in most of these studies, the distinction is not of great clinical importance. Most investigators will agree that acute akathisia, along with parkinsonism, is one of the most common side effects of neuroleptic drugs.

**Akathisia Induced by Specific Drugs**

A number of published studies have reported the prevalence of akathisia in patients treated with specific drugs other than conventional neuroleptics. A summary of these studies is presented in tables 2 and 3. Some notable examples are discussed here.

**Akathisia Related to Newer Antipsychotic Drugs.** Studies that have examined akathisia secondary to the newer antipsychotics are of particular interest because of the different pharmacological profiles of these drugs and the fact that, unlike the conventional neuroleptics, many of these drugs are not potent dopamine D₂ receptor antagonists.

Clozapine is one such drug with an atypical profile, being a relatively weak D₂ antagonist but a more potent serotonin 5HT₂ and adrenergic α₁ antagonist, as well as a D₄ antagonist (Peroutka and Snyder 1980; Lee and Tang 1984; Richelson and Nelson 1984). Clozapine is associated with a low incidence and severity of EPSE (Claghorn et al. 1987; Kane et al. 1988). The literature with regard to akathisia is somewhat inconsistent. Much of the earlier literature suggests that clozapine produces little akathisia (Gerlach 1991) except at the highest doses in vulnerable patients (Casey 1989). Claghorn et al. (1987), in a double-blind comparison of clozapine and chlorpromazine, reported that, contrary to expectation, clozapine produces akathisia as frequently as chlorpromazine does (6.7% vs. 5.3%, respectively). Cohen et al. (1991), in a naturalistic study, assessed 23 patients receiving clozapine for akathisia using the Chouinard et al. (1980) scale for assessment, and compared these patients with 29 control patients receiving a standard neuroleptic. Using a total score of 3 or more (maximum possible = 9) to diagnose akathisia, they found that 39 percent of the clozapine group and 45 percent of the control group had akathisia. The mean (standard deviation [SD]) ratings for the two groups were 2.17 (SD = 1.8) and 2.41 (SD = 2.6), respectively. However, those with severe akathisia (a score of 6 or more) tended to be more common in the control group (14%) than in the clozapine group (9%). In this study, patients were not randomly allocated to different treatments, and the dose equivalence of the treatments was not certain. The package insert for clozapine reports an akathisia rate of 3 percent in 842 patients (Sandoz Pharmaceutical Corporation 1991). Safferman et al. (1992)

<table>
<thead>
<tr>
<th>Drug and authors</th>
<th>Rate (%)</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Clozapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claghorn et al. 1987</td>
<td>6.7</td>
<td>Similar to chlorpromazine (5.3%)</td>
</tr>
<tr>
<td>Cohen et al. 1991</td>
<td>39</td>
<td>Usually mild</td>
</tr>
<tr>
<td>Sandoz Pharmaceutical Corporation 1991</td>
<td>3</td>
<td>Product insert (n = 842)</td>
</tr>
<tr>
<td>Safferman et al. 1992</td>
<td>0</td>
<td>Akathisic patients (n = 21)</td>
</tr>
<tr>
<td>Remoxipride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lund Laursen and Gerlach 1986</td>
<td>30</td>
<td>Median dose 600 mg/day</td>
</tr>
<tr>
<td>Farde et al. 1988</td>
<td>0</td>
<td>Over 4 days</td>
</tr>
<tr>
<td>McCreadie et al. 1988</td>
<td>4</td>
<td>Comparison with thioridazine</td>
</tr>
<tr>
<td>Lindström et al. 1990</td>
<td>32</td>
<td>Comparison with haloperidol</td>
</tr>
<tr>
<td>Andersen et al. 1990</td>
<td>36</td>
<td>Comparison with haloperidol</td>
</tr>
<tr>
<td>Sulpiride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robertson et al. 1990</td>
<td>7.9</td>
<td>Open study</td>
</tr>
<tr>
<td>Lepola et al. 1989</td>
<td>8.7</td>
<td>Comparison with perphenazine</td>
</tr>
<tr>
<td>Munk-Andersen et al. 1989</td>
<td>44</td>
<td>Comparison with haloperidol</td>
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<tr>
<td>Amisulpiride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mann et al. 1984</td>
<td>21.5</td>
<td>Open study</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jungmann and Schoffling 1982</td>
<td>25</td>
<td>Single dose (10 mg i.v.) study</td>
</tr>
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Table 3. Akathisia induced by nonneuroleptic drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Authors</th>
<th>Rate (%)</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Serotonin-reuptake inhibitors</td>
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<td></td>
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<tr>
<td>Fluoxetine</td>
<td>Lipinski et al. 1989</td>
<td>9.8–25</td>
<td>Open study (only 20/51 systematically examined)</td>
</tr>
<tr>
<td></td>
<td>Eli-Lilly Pty. Ltd. 1993</td>
<td>10–15</td>
<td>Anxiety, nervousness, and insomnia</td>
</tr>
<tr>
<td></td>
<td>Maany and Dhopesh 1990</td>
<td>0</td>
<td>23 patients in open study</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Klee and Kronig 1993</td>
<td>—</td>
<td>Single case report</td>
</tr>
<tr>
<td></td>
<td>Settle 1993</td>
<td>—</td>
<td>Single case report</td>
</tr>
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<td>Serotonin antagonists</td>
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<td>Cyproheptadine</td>
<td>Calmels et al. 1982</td>
<td>—</td>
<td>Single case report</td>
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<td>Bemick 1988</td>
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<td>Single case report</td>
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<td>Ritchie et al. 1988</td>
<td>—</td>
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<td></td>
<td>Patterson 1988</td>
<td>—</td>
<td>Single case report</td>
</tr>
<tr>
<td>Heterocyclic antidepressants</td>
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<td>Tricyclics + estrogen</td>
<td>Krishnan et al. 1984</td>
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<td>3 patients reported</td>
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<td>Zubenko et al. 1987</td>
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<td>Multiple case reports</td>
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<td>Barton 1982</td>
<td>—</td>
<td>4 cases of agitation</td>
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<tr>
<td></td>
<td>Shen 1983</td>
<td>—</td>
<td>3 cases</td>
</tr>
<tr>
<td></td>
<td>Hullett and Levy 1983</td>
<td>—</td>
<td>9 cases</td>
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<td>Anticonvulsants</td>
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<td>Carbamazepine</td>
<td>Schwarcz et al. 1986</td>
<td>—</td>
<td>Single case with left temporal lobe injury</td>
</tr>
<tr>
<td></td>
<td>Milne 1992</td>
<td>—</td>
<td>2 patients</td>
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<tr>
<td>Ethosuximide</td>
<td>Ehyai et al. 1978</td>
<td>—</td>
<td>2 cases with questionable akathisia</td>
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<td>Jacob 1983</td>
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<td>Kuzuhara et al. 1989</td>
<td>—</td>
<td>5 patients</td>
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<td>Chouza et al. 1986</td>
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<td>2 patients</td>
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<td></td>
<td>Meyboom et al. 1986</td>
<td>—</td>
<td>Single case</td>
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<tr>
<td></td>
<td>Micheli et al. 1987</td>
<td>—</td>
<td>Single case</td>
</tr>
<tr>
<td>Cinnarizine</td>
<td>Gimenez-Roldán and Mateo 1991</td>
<td>—</td>
<td>?</td>
</tr>
<tr>
<td>Mood stabilizing drugs</td>
<td></td>
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<tr>
<td>Lithium carbonate</td>
<td>Channabasavanna and</td>
<td>—</td>
<td>Single case</td>
</tr>
<tr>
<td></td>
<td>Goswami 1984</td>
<td>—</td>
<td></td>
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<td></td>
<td>Price and Zimmer 1987</td>
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recently examined the impact of clozapine on patients with (n = 21) and without (n = 49) akathisia at baseline after a 2-week washout period. Patients who did not have akathisia at baseline (acute or tardive) did not develop it during the 1 year of treatment with clozapine (mean dose = 565 mg/day). Those with akathisia, which was possibly a mixture of acute and tardive akathisia and/or agitation, improved considerably in the first 3 weeks and then continued to improve over 3 months, even though the dosage of clozapine was increasing. This finding is in contrast to findings in the
Claghorn et al. (1987) and Cohen et al. (1991) studies, which the authors argue, were deficient in not assessing akathisia adequately at baseline in that they may have included tardive akathisia, or the carryover effect of acute akathisia, as being caused by clozapine. Their own study, however, suffered from the limitation of a 50-percent dropout over the year (although no patients were withdrawn because of EPSE) and the use of a modified Simpson and Angus (1970) rating scale for the diagnosis of akathisia, which is less than optimal for such purposes.

It is, therefore, difficult to give a definite rate of akathisia secondary to clozapine. The rate for the large number of patients enrolled in the Sandoz Pharmaceutical Corporation (1991) trials, as well as the findings from the Saffermer et al. (1992) study, suggests that akathisia may be relatively uncommon. The latter study also suggests that clozapine may even permit recovery from chronic akathisia due to conventional neuroleptics. However, the conflicting evidence presented by Claghorn and associates (1987) and especially by Cohen and associates (1991) argues for further examination of the issue.

A number of recently introduced substituted benzamides are effective antipsychotics but have an atypical side effects profile (Lund Laursen and Gerlach 1986; Andersen et al. 1990). Remoxipride has been investigated with regard to akathisia. Lund Laursen and Gerlach (1986) treated 10 patients with a median dose of remoxipride of 600 mg/day (range: 300–1,200) and reported akathisia in 3 patients, with a mean rating of 1.6 on the St. Hans Hospital rating scale (rating 0–6). Farde et al. (1988) administered remoxipride at two dosage levels—70 and 140 mg t.i.d.—for 4 days. The drug was well tolerated at the lower dose, but the higher dose resulted in akathisia in 7 of 8 subjects.

McCreadie et al. (1988) compared remoxipride (75–375 mg) with thioridazine (150–759 mg) in a double-blind study of acute schizophrenia. Although the method of assessment was not stated, akathisia was diagnosed in 8 percent of thioridazine patients and in 4 percent of remoxipride patients, with the syndrome in the latter group being reportedly more severe. In a multicenter, double-blind comparison of the effects of remoxipride and haloperidol, akathisia was noted to be less common with the former. Lindström et al. (1990) reported that in their study (n = 48 in each group), akathisia occurred in 32 percent of the remoxipride patients and 57 percent of the haloperidol patients (p < 0.05). Andersen et al. (1990) reported a 36-percent incidence with remoxipride (n = 39) and a 68-percent incidence with haloperidol (n = 32). The method of diagnosis of akathisia was again not specified.

Another drug from this group that has received increasing attention is sulpiride. In an open study, Robertson et al. (1990) treated 63 patients suffering from Tourette's syndrome with sulpiride and reported that 5 patients (8%) developed akathisia (1 of the 26 who discontinued the drug and 4 of the 37 who continued it). They suggested that the drug was better tolerated on this count than the conventional neuroleptics. In a double-blind study, Lepola et al. (1989) compared sulpiride with perphenazine in schizophrenia. Two of 23 in the sulpiride group, and 6 of 23 in the perphenazine group developed akathisia. The criteria for diagnosis were again not specified. Munk-Andersen et al. (1989) compared sulpiride (median = 1,600 mg/day) with haloperidol (median = 12 mg/day) in a double-blind crossover study (n = 16) and reported akathisia in 8 haloperidol and 7 sulpiride patients.

Only preliminary data on raclopride are available (Farde et al. 1988; Cookson et al. 1989); they suggest that it often produces dystonia and akathisia. In an open clinical study of amisulpiride, 3 of 14 patients reportedly developed akathisia (Mann et al. 1984). Sufficient data on other substituted benzamides (e.g., emonapride) are not available.

A benzamide that is not generally used as an antipsychotic is metoclopramide. This drug is important because of its extensive nonpsychiatric usage to treat severe nausea, esophageal reflux, dyspepsia, neurogenic bladder, orthostatic hypotension, nonprolactinemic amenorrhea, hiccups; etc. Numerous reports of metoclopramide-induced akathisia have been published in the literature (e.g., Bui et al. 1982; Allen et al. 1985; Saller and Hellenbrecht 1985; Graham-Pole et al. 1986; Richards et al. 1986). The literature on metoclopramide-induced movement disorders was recently reviewed by Miller and Jankovic (1989), who recorded 1,031 reported cases, 10 percent (n = 106) of which had akathisia (acute or tardive). Good incidence data are unavailable. Borenstein and Bles (1965) administered high doses to psychiatric patients and reported EPSE in 25 percent, but they did not specify the rate of akathisia. Jungmann and Schoffling (1982) investigated the effect of an intravenous bolus
of 10-mg metoclopramide in healthy volunteers and found that 25 percent "complained of akathisia," usually within 15 to 30 minutes and lasting for 3 to 4 hours. That this distressing side effect is frequently unrecognized or ignored has been repeatedly highlighted (Miller and Jankovic 1989).

Risperidone is a novel benzisoxazole derivative that shows a different side-effects profile from that of the conventional antipsychotics. It is a potent D2, 5HT2, and α1 receptor antagonist (Janssen et al. 1988). A recent double-blind parallel group trial comparing different fixed dosages of risperidone with haloperidol suggests that the former produces less akathisia (Janssen Research Foundation 1992). This difference is currently being investigated in greater detail in a multicenter trial.

A number of drugs that, like risperidone, act on D2 as well as on other receptors are currently being investigated for their antipsychotic properties and side effects profiles (Gerlach 1991). ICI 204.636 is a dibenzothiazepine with a relatively weak D2 antagonism but a stronger blockade of the 5HT2 receptor. In a small clinical study, no EPSE were observed (Fabre et al. 1990). Sertindole has a biochemical profile like risperidone (Skarsfeldt and Perregaard 1990), but its clinical profile is still under investigation. Amperozide is a diphenylbutylpiperazine with an unusual biochemical profile of potent 5HT2 antagonism; a moderate affinity for α1 receptors; and minimal affinity for D1, D2, and 5HT1a receptors. In a small clinical study of amperozide, Axelsson et al. (1991) reported no akathisia. Savoxepine is a novel tetracyclic cyanodibenzoepinoacepine derivative with strong D2 antagonistic properties, which is 10 times greater for the hippocampal than for the striatal receptors (Bischoff et al. 1986). Additionally, it blocks D1, 5HT2, α1, and histamine H1 receptors. In three open studies, savoxepine was found to commonly produce EPSE, including akathisia (Butler and Bech 1987; Moller et al. 1989; Wetzel et al. 1991).

Partial D2 agonists have recently aroused interest as potential antipsychotics, and a few drugs—for example, SDZ HDC912, terguride, roxindole, and B-HT 920—have been tried mostly in open clinical trials. EPSE, including akathisia, have been low or absent in these trials, but the data are preliminary and more definitive studies are awaited (Gerlach 1991). Dopamine D1 antagonists have shown promise as potential antipsychotics in animal studies and may produce fewer or different side effects, but clinical trials have yet to be published.

In conclusion, the preliminary evidence from the use of the newer antipsychotic drugs in relation to acute akathisia is encouraging, and further systematic work is necessary. The dosages used should be kept in mind when rates for different drugs are being compared, as it is possible that newer drugs are being used at relatively lower doses.

Serotonin-Specific Reuptake Inhibitors (SSRIs) and Acute Akathisia. Akathisia has recently been reported to occur with SSRIs used in the treatment of depression and obsessive-compulsive disorder, and its form is quite indistinguishable from that caused by neuroleptics. Lipinski et al. (1989) reported five cases of fluoxetine-induced akathisia. The akathisia was rapid in onset, started within hours up to 5 days of drug initiation, was mild, manifested subjective and objective features, and responded to dose reduction or treatment with propranolol. In one patient, akathisia continued for more than 1 year while the patient was maintained on fluoxetine. Interestingly, four of the reported five patients were young women with obsessive-compulsive disorder, and the fifth was a man with a depressive illness. The incidence of akathisia with fluoxetine is uncertain. The Lipinski et al. (1989) cases were observed in a series of 51 patients so treated, but only 20 patients were systematically examined; this suggests that the incidence could be anywhere between 9.8 percent (5 of 51) and 25 percent (5 of 20). The product insert for fluoxetine (Eli-Lilly Pty. Ltd. 1993) describes "anxiety, nervousness, and insomnia" in 10 to 15 percent of treated patients, leading to drug discontinuation in 5 percent. It is likely that a proportion of these patients suffer from akathisia.

The issue of fluoxetine-induced akathisia, in spite of the above report, remains controversial. Maany and Dhapesh (1990) challenged the Lipinski et al. (1989) article, arguing that the observed side effect was in fact not akathisia and could be attributed to neuroleptics or trazodone. They cited their own experience of treating 23 patients with fluoxetine, noting anxiety and insomnia in 1 patient but no cases of akathisia. The criticism, however, was adequately rebutted by the authors (Lipinski et al. 1990), and it is likely that fluoxetine does not commonly produce akathisia at smaller doses, which were the ones used by Maany and Dhapesh (1990). The literature also suggests that fluoxetine-induced akathisia
may be misdiagnosed or missed altogether. Ioannou (1992) reported a patient who developed a “horrible feeling inside,” which was not recognized as akathisia; rather, the suicidal ideas this patient developed subsequently were highlighted. That suicidal ideation sometimes seen in patients treated with SSRIs (Teicher et al. 1990) may, at least in part, be due to akathisia has been suggested by Opler (1991), Hamilton and Opler (1992), and Wirshing et al. (1992).

Two cases (Klee and Kronig 1993; Settle 1993) of akathisia have recently been reported secondary to sertraline, a newer SSRI. We could not trace any reports of akathisia secondary to other SSRIs (e.g., paroxetine, fluvoxamine, indalpine, etc.). There is evidence, however, that these drugs worsen neuroleptic-induced parkinsonism or Parkinson’s disease, thus suggesting a propensity to produce EPSE and possibly akathisia (Lipinski et al. 1990).

Other Drugs Reportedly Associated With Acute Akathisia.

Table 3 summarizes the published reports of akathisia in association with other nonneuroleptic drugs. It must be emphasized that akathisia is not generally considered to be a complication of heterocyclic antidepressants, although a few reports have appeared to this effect (Krishnan et al. 1984; Zubenko et al. 1987). A number of investigators (Barton 1982; Hulett and Levy 1983; Ross et al. 1983; Shen 1983) have recognized that the dibenzoapine antidepressant amoxapine, which has intrinsic neuroleptic activity (Donlon 1981), produces akathisia. The phenomenon of jitteriness has been reported in some patients with panic disorder who were treated with tricyclic antidepressants (Zitrin et al. 1978; Pohl et al. 1988); this phenomenon entailed restlessness, trouble sitting still, “shakiness inside,” insomnia, increased energy, and increased anxiety. At this stage, however, too little is known about the jitteriness syndrome to group it with drug-induced akathisia.

While akathisia has been reported in association with a number of nonneuroleptic drugs, as listed in table 3, the evidence is preliminary and larger epidemiological studies are necessary. Further, the clinical characteristics should be examined in detail to determine if akathisia secondary to neuroleptic or nonneuroleptic drugs is similar.

Care should be taken when drugs are used in combination—for example, lithium and haloperidol in a patient with bipolar disorder, or a calcium antagonist and a neuroleptic drug in a hyperensive patient with psychosis—for a possible additive effect in the causation of akathisia.

Risk Factors for Acute Akathisia

In the various epidemiological studies, the following risk factors for acute akathisia have been examined.

Sociodemographic Variables.

Age. The relationship between age and acute akathisia has not been adequately examined. Ayd (1961) suggested that akathisia was most prevalent between the ages 12 and 64 years in his sample, which was in contrast to dystonia (more likely in the young) and parkinsonism (more likely in the elderly). The oldest person with akathisia in this series was 64, even though a significant proportion (not stated) of subjects were in their seventies and eighties. In the Braude et al. (1983) study, the age range of the sample was 19 to 72 years (mean = 40.6, SD = 15.0), and there was no significant difference in age between the akathisia (n = 24) and nonakathisia (n = 23) groups. In the Sachdev and Kruk (1994) study, the akathisics did not differ significantly from the nonakathisics in age; and on logistic regression analysis, age was significant only at the 0.15 level with an adjusted odds ratio of 1.034.

There are only a few studies of akathisia in children, and these give a lower incidence and prevalence than are found in the adult populations. The literature on akathisia in the elderly is even more scanty (see Part II Sachdev 1995, this issue).

Sex. The relationship between akathisia and sex has also been inadequately investigated. In his sample of 48.5 percent men and 51.5 percent women, Ayd (1961) found the male:female ratio for akathisia to be 35:65. Sarwer-Foner (1960), on the other hand, stated that “akathisia...tend[s] to prevail in men” (p. 316) but did not provide any figures to support this. Most epidemiological studies have not reported any sex differences in the vulnerability to akathisia (Braude et al. 1983; Van Putten et al. 1984a; Sachdev and Kruk 1994). An exception is the study by Sandyk and Kay (1990), in which a larger proportion of female (40.6%) than male (20%) residents in a long-term unit of a psychiatric hospital were found to have akathisia. The patients were elderly (mean age = 63.9 years, SD = 8.9 years), and no attempt was made to separate acute from tardive akathisia.
From the limited data available, one must conclude that sex does not seem to significantly determine the occurrence of acute akathisia. However, it may possibly interact with age as a vulnerability factor so that its importance may become apparent in the very young or the old. This needs to be empirically examined using well-diagnosed acute akathisia populations.

Race. Akathisia has been reported in many racial groups (Sandyk and Kay 1990; Inada et al. 1991), although comparative studies examining incidence have not been published. There is no suggestion that any particular racial group is more vulnerable to acute akathisia.

Psychiatric Diagnosis. Most of the epidemiological studies of acute akathisia have been performed in patients suffering from schizophrenia. Some studies, however, have included mixed psychiatric populations. The Braude et al. (1983) study included patients with affective disorder or personality disorder, and a few with "other neurotic conditions" or alcoholism. There was no suggestion that any diagnostic group was particularly vulnerable. The Sachdev and Kruk (1994) study included 25 patients with nonschizophrenic psychotic disorders; psychiatric diagnosis was again not a significant predictor. The data would, therefore, suggest that the nature of the psychiatric disorder is probably not important. It must be pointed out that neuroleptic drugs tend to be used at different doses in different disorders, and since akathisia is dose related, this aspect needs to be considered in the analysis. The report by Galdi and Bonato (1988) is of interest, although the implications of their finding are difficult to assess. While examining the relationship of adverse drug reactions and the length of stay in hospital, they found that akathisia was associated with an increased hospital stay in only the schizophrenia patients who had a family history of affective disorder. Gardos et al. (1992), who attempted to quantify psychomotor activity in akathisia using ambulatory activity monitoring, reported that the clinical ratings of akathisia tended to be higher in the depressed patients than in the manic and schizophrenia patients, even though the depressed patients were on smaller doses of neuroleptics. This therefore raises the possibility that depressed patients may be more vulnerable to akathisia, as has been suggested for tardive dyskinesia (TD) (Khot et al. 1992) and possibly for drug-induced parkinsonism (Friedman 1992). This suggestion should be examined more systematically in a larger sample. The Gardos et al. (1992) study also suggests that the motor manifestations of akathisia interact with those of the primary psychiatric disorder. The latter condition should therefore be taken into consideration, particularly if quantification of the movements is intended.

As already pointed out, akathisia often occurs in healthy individuals or in patients suffering from medical or surgical illnesses when challenged with neuroleptics or other drugs known to cause akathisia. There is no suggestion that the akathisia seen in normal individuals is phenomenologically different from that seen in psychiatric patients.

Drug-Related Variables.

Nature of drugs causing akathisia. This article has already alluded to the various drugs reported to cause akathisia. In summary, akathisia is typically associated with the classical neuroleptics, but many newer antipsychotics and a number of other drugs have also been reported to cause akathisia. These drugs share the property of directly or indirectly influencing the dopaminergic or the serotonergic system. Since serotonin has an inhibitory effect on the mesolimbic and mesocortical projections (Meltzer et al. 1979), the biochemical property that best links the various drugs is their ability to reduce dopamine function in the central nervous system. However, the relative role of the different dopamine receptors and the brain areas that may be particularly responsible for this function cannot be decided from this information. There are a few drugs—for example, anticonvulsants on a substrate of organic impairments, methysergide, etc.—that are occasionally reported to cause akathisia and that may ostensibly challenge this hypothesis, but the evidence in their favor is weak.

Neuroleptic drug potency and akathisia. There is a general clinical impression that akathisia is more likely to occur with higher potency drugs. Ayd (1961) commented that akathisia developed earlier and with smaller doses as the potency of the drug increased. Van Putten et al. (1984a) studied subjects treated with oral haloperidol (5 mg) or thiothixene (0.22 mg/kg); 70 percent of the former and 22 percent of the latter developed akathisia by the seventh day. In the Sachdev and Kruk (1994) study, the effect of medication type was significant but small, with higher potency again associated with an increased risk of akathisia.
Drug dose and rate of increment of dose. The positive association of akathisia with drug dose is generally accepted. In the McClelland et al. (1976) study, the rate of akathisia was 22 percent in the high-dose and 9 percent in the standard-dose groups. In the Van Putten et al. (1990) study, the 20-mg haloperidol group had a higher overall rate of akathisia than the 5- or 10-mg groups. In the Sachdev and Kruk (1994) study, drug dose made a significant contribution to overall akathisia rates. Only the study by Rifkin et al. (1991) was at variance as it did not find a significant difference between the 10-, 30-, and 80-mg haloperidol groups.

The rate of increment of dose is another variable of some significance. Braude et al. (1983) reported that in patients with a large dose increase in the first 10 days after admission (log ratio of increase > 3.0), akathisia rates increased considerably. This finding was supported by Sachdev and Kruk (1994).

Clinical experience would also suggest that parenteral administration of the neuroleptic is more likely to cause akathisia. This is not supported by any research evidence that we are aware of, and if true, it may be because of any of the following possibilities: (1) that neuroleptics administered parenterally are usually of high potency; (2) that parenteral drugs are often given during acute management, thus rapidly increasing the plasma levels from nil or low baseline levels; and (3) that bypassing the first-pass metabolism leads to a rapid increment of levels.

Plasma levels of drugs. Patients on the same dosage are known to be at enormous variance in their plasma levels, which may be up to a hundredfold in some cases (Dahl 1986). This observation raised the hope that aberrant plasma levels could explain the occurrence of side effects in some patients. Overall, this hope has not been fulfilled. Van Putten et al. (1991) studied the relationship between plasma haloperidol levels and drug effects in 61 patients; they found that patients with levels above 12 ng/mL tended not to do so well and felt that this was due to adverse effects. Objectively rated akathisia and akinesia did not show a significant relationship with plasma haloperidol levels. However, when side effects were rated on a Clinical Global Impression scale (Guy 1976), there was a powerful relationship between plasma levels and what the patient experienced as "disabling side effects" (Van Putten et al. 1991, p. 204). The same authors demonstrated a significant relationship (p = 0.0008) between disabling side effects and plasma levels of fluphenazine; the disabling side effects ratings were significantly correlated with the ratings of akathisia (r = 0.6) and akinesia (r = 0.44). There is, therefore, some evidence that increasing plasma levels are associated with more side effects—in particular, akathisia and akinesia—but more systematic examination of this relationship is necessary.

Past exposure to neuroleptic drugs and the duration of such exposure. It has been suggested that patients may be more likely to develop akathisia at the time of first exposure to the drug, a tendency that may decrease with repeated or chronic exposure. The Sachdev and Kruk (1994) study supports this contention but suggests that the effect is probably small.

EPSE. A number of studies have pointed to an association between parkinsonian EPSE (generally, rigidity and resting tremor) and akathisia (Freyhan 1959; Ayd 1961; Medinar et al. 1962; Braude et al. 1983; Levinson et al. 1990; Sachdev and Kruk 1994). In the Sachdev and Kruk (1994) study, the correlation between the EPSE and akathisia ratings was 0.40 (p < 0.01), and it was the most significant variable on a logistic regression analysis. These findings suggest that the two side effects often occur together. Whether EPSE can be used to predict akathisia depends on the time course of the two, and the evidence points to a similar or slightly delayed time course for the development of EPSE in comparison with akathisia following a challenge with neuroleptic medication. Therefore, EPSE may not be very useful in predicting acute akathisia, but the association probably reflects a common vulnerability and is important for our understanding of the pathophysiology of akathisia. It has also been suggested (Braude et al. 1983) that akathisia associated with EPSE, with a positive response to anticholinergic medication, may have a different pharmacological profile from the akathisia not so associated, but this needs to be investigated further (Sachdev and Loneragan 1993).

Other Variables.

Iron status. The role of iron deficiency in the pathogenesis of akathisia has been examined in a number of studies that have been reviewed elsewhere (Sachdev 1993). The evidence is conflicting, and the conclusion one can draw is that most patients who develop akathisia do not have iron deficiency and that the overall contri-
bution of iron to the development of akathisia, if indeed significant, is likely to be small. Further, hematological and serum biochemical measures are inadequate in assessing iron function in the brain in vivo. Magnetic resonance imaging shows promise in this area, but further delineation of appropriate measures to assess brain iron is necessary.

Organic brain disease. Akathisia has been described in relation to a number of neurological disorders, such as encephalitis lethargica (Jelliffe 1932), Parkinson's disease (Lang and Johnson 1987), traumatic brain lesions (Stewart 1989), and brain abscess involving the subthalamus and basal ganglia (Carrazana et al. 1989). A feature common to these disorders is the involvement of the basal ganglia. Since this article deals specifically with drug-induced akathisia, we will not discuss “akathisia due to general medical condition” in any detail except to emphasize that the presence of any such disorder is likely to increase the propensity for the drug-induced syndrome.

Alcohol. Case reports have appeared in which the ingestion of alcohol was temporally associated with the development of akathisia in patients being treated with neuroleptics (Lutz 1976) or amoxapine (Shen 1984). The exact mechanism is not known, but the finding is not inconsistent with the dopamine hypothesis of akathisia (Lai et al. 1978).

Smoking. Menza et al. (1991) reported that in their patients with chronic psychiatric illness, female smokers had more objective, but not subjective, akathisia. One possible interpretation of this finding is that their patients had tardive akathisia rather than acute akathisia, and one can predict that the finding for tardive akathisia would be similar to that for TD. Of course, the study is an isolated one and needs replication. Further, the smokers in this study had higher levels of neuroleptics, and this could account for the higher rates of akathisia quite independent of the status of smoking.

Diabetes mellitus. The reported association between glucose intolerance and TD (Mukherjee et al. 1985), as well as the effect of glucose on striatal dopaminergic activity (Saller and Chiodo 1980), prompted Sandyk et al. (1991) to examine 68 chronic schizophrenia patients referred to the movement disorder clinic of a large urban psychiatric hospital for an association between diabetes mellitus and akathisia. Sixteen of their patients (23.5%) had diabetes on retrospective chart review, and the akathisia ratings in the diabetics were more than twice those in the non-diabetics. This study had many methodological limitations, which we will not discuss in detail, but it does draw attention to a hitherto unexplored risk factor.

Conclusions
The factors that predispose an individual to the development of akathisia are incompletely understood. The high rates of akathisia reported in some studies (e.g., the 76-percent incidence reported by Van Putten and colleagues [1984a]) suggest that most individuals will develop akathisia under some circumstances. It is uncertain whether everyone is vulnerable to the development of akathisia if challenged with very high doses of neuroleptics. As our review suggests, we have limited information on the factors that increase vulnerability to acute akathisia, and even this information is restricted to neuroleptic-induced akathisia. Drug-related factors—in particular, drug dose, rate of increment of dose, and drug potency—are clearly important. Further, the development of parkinsonism also predicts the development of akathisia, although akathisia may occur first or concurrently in many cases. The role of sociodemographic factors and other treatment-related variables is modest. The evidence for iron deficiency as a risk factor is conflicting, but the contribution of iron deficiency is likely to be minor. As is apparent, a significant proportion of the susceptibility to akathisia is unexplained (Sachdev and Kruk 1994).

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