Drug-induced Parkinsonism in Older Adults

Joseph H. Friedman, MD, Professor, Clinical Neurosciences, Brown University School of Medicine; Chief, Neurology; Director, Parkinson’s Disease and Movement Disorders Center, Memorial Hospital of Rhode Island, Pawtucket, RI, USA.

Drug-induced parkinsonism, an often overlooked condition, is frequently an iatrogenic result of antipsychotic medications, particularly in older adults. Spontaneous features of parkinsonism are common in the community-dwelling older adult as well as in patients with the common dementing illnesses. Parkinsonism is associated with increased mortality and morbidity, and a greater need for support services. This article reviews current knowledge of parkinsonism and stresses the need for diligence. The newer antipsychotics, while reducing the incidence of tardive dyskinesia, are not at all completely free of inducing extrapyramidal side effects, with parkinsonism being the most common.

Key words: drug-induced parkinsonism, atypical antipsychotics, extrapyramidal syndromes.

Introduction

The development of the “atypical” antipsychotic drugs is mistakenly believed by many physicians to have put an end to drug-induced movement disorders. Unfortunately, not only is this not true, but the newer antipsychotics may have actually increased the risk of movement disorders by causing a decline in diligence. Those most at risk for some of these drug-induced movement disorders are older adults, particularly the frail and parkinsonian. Although no antipsychotic has been approved for use in the treatment of psychotic features of dementia, a significant number of patients in general nursing homes, and not just those within locked wards, are presently taking them.

Since the motor side effects of the antipsychotic drugs were discovered, the major long-term concern of psychiatrists treating psychoses has been tardive dyskinesia. However, with the growing use of antipsychotic drugs in older people and the highly effective marketing techniques that preach their “relative” freedom from extrapyramidal side effects, parkinsonism may actually be the most important side effect. It is probably the most common and yet the least recognized.

Definition

Parkinsonism is defined as an akinetic rigid syndrome and in general terms refers to something that looks like Parkinson’s disease. Parkinsonism is common in older adults, is considered a non-pathological concomitant of “normal” aging and is present in the majority of community-dwelling people over the age of 85. It is also a frequent feature of all the common dementing illnesses, including Alzheimer disease, Lewy body disease, vascular dementia and the dementia of Parkinson’s disease. In these illnesses the appearance of parkinsonism is a bad prognostic sign. Drug-induced parkinsonism (DIP) is associated with an increased risk of falls, diminished dexterity, diminished mobility, increased dependence, reduced quality of life and increased need for attention by caregivers.

Comparison with Idiopathic Parkinson’s Disease

The cardinal features of idiopathic Parkinson’s disease (IPD) are hypokinesia (akinesia and bradykinesia), rigidity, tremor at rest and the typical gait, posture and balance abnormalities. Although DIP has some clinical differences from IPD, the overlap in clinical signs is very large. DIP tends to be asymmetric, starting on one side which will usually remain the more severely affected, whereas DIP tends to be symmetric. About 80% of patients with IPD have resting tremor, whereas the drug-induced form has tremor in about 40% of cases. However, IPD may be symmetric and there remains 20% of these patients who do not have tremor. Thus, it is impossible to distinguish IPD from DIP in any individual patient. DIP is more likely to occur in older patients, particularly women, than in other groups, and IPD is slightly more common in men. Any patient, especially an older one who develops parkinsonism on antipsychotics, cannot be confidently diagnosed with DIP until followed for a long time. DIP is, presumably, fully reversible whereas IDP will worsen over time.

Detection of Parkinsonism

Parkinsonism is under-recognized, particularly in older adults and especially if tremor is absent, as is typically the case in DIP. In a community teaching hospital, charts in which a neurology consultation was obtained for any reason were reviewed in order to determine how often the consultant diagnosed parkinsonism, regardless of whether or not it was the reason for the consultation. Cases with previously diagnosed parkinsonism were excluded. It was found that 50% of Parkinsonism cases had not been recognized by any of the caring physicians, which included the emergency department doctors, the medical intern and residents and the attending physician, even though the study took place at a hospital that housed the university Parkinson’s disease centre. In another study, all patients at a nursing home were assessed for signs of parkinsonism. Such signs were found to be quite common but were virtually never noted by the attending physician, registered nurse or physical therapists. Of particular concern was the finding that 20–24 patients treated with atypical...
antipsychotics were parkinsonian, of whom only one was recognized by anyone who wrote notes in the chart.

**Physiology**

The drugs that block dopamine receptors cause several different movement disorders, all lumped together under the term extrapyramidal syndromes (EPS). EPS have different time frames and epidemiologies. Acute dystonic reactions usually occur first in the few days following drug initiation or dose increase. These tend to occur in the young and affect males more than females. Episodes of recurrent, painful or painless acute muscle contractions occur, lasting about 20–30 minutes and causing abnormal sustained postures, usually in the neck or above. Acute akathisia also occurs early and is a syndrome of profound motor restlessness in which people tend to be unable to sit still and fidget or stand to march in place. Parkinsonism tends to occur over weeks but may develop in people who have tolerated the drug at the same dose for many years. Tardive dyskinesia refers to a collection of syndromes that develop after long-term exposure, although the Diagnostic and Statistical Manual of Mental Disorders, version IV, definition requires only a one-month exposure in someone older than 60 years. The most common syndrome involves choreoathetoid movements of the oral, buccal and lingual regions. While the tardive syndromes are frequently permanent, the others are always considered reversible.

Of the extrapyramidal syndromes, only DIP is understood. In IPD there is a loss of neurons that synthesize and secrete dopamine. Any process that interferes with dopaminergic activity at the dopamine D2 receptor produces parkinsonism; while there are at least five dopamine receptor subtypes, only the D2 has been linked to parkinsonism. All of the previous generation of antipsychotic drugs block the D2 receptor, and therefore cause parkinsonism. However, all of the atypical antipsychotics also block the D2 receptor, but with a much reduced likelihood of inducing any EPS. Some of the atypicals, such as risperidone, block the
D2 receptor as powerfully as the traditional antipsychotic thioridazine. There are two hypotheses for why EPS are so much less of a problem with the newer antipsychotics. One theory holds that the freedom from EPS is due to the balance between blockade of the serotonin 5-HT2a receptors and the dopamine D2 receptors. Another equally influential group holds that the important facet of the newer drugs is that they only block the D2 receptor for short time intervals, referred to as the "fast off" theory (Figure).

DIP is not associated with histological brain changes, yet the effects of the parkinsonism can be very long lasting, particularly in older patients. One article reports parkinsonism persisting for 36 months after the offending drug was stopped. More troubling is a report of patients who became parkinsonian on one of two calcium channel blockers, flunarizine and cinnarizine, both popular in South America and which commonly cause parkinsonism. Some of these patients had stable parkinsonism seven years after the drug was stopped. In a report on older adults with parkinsonism, most commonly induced by prochlorperazine, the symptoms were severe enough to cause hospitalization in 50% of the cohort, 25% suffered from falls, while two-thirds had complete resolution on stopping the drug. The mean duration of resolution was seven weeks, with a range up to 36. Obviously the time an older person has for recovery is limited, but equally important is the reduced ability to recover from any disorder that interferes with walking for any protracted period of time. Older people whose gait is impaired from a disorder that is temporary may become unable to walk permanently.

**Medications That Cause Parkinsonism**

The most common culprits causing parkinsonism in older adults in North America are the antipsychotics. Other drugs also may have this side effect, including the antiemetics prochlorperazine and metoclopramide, which are basically "low potency" neuroleptics. That is, they are antipsychotics that block dopamine D2 receptors and cause all of the EPS that stronger antipsychotics, such as haloperidol, do, but less commonly. Unfortunately, the antiemetics are used mostly by internists and surgeons who do not appreciate these potential movement disorder side effects. Since the parkinsonism is most likely to occur in an older person who may be slightly parkinsonian to begin with, and since the parkinsonism does not begin to progress until after a few weeks of drug use, it may be mistakenly interpreted as the natural course of the underlying illness, or simply as aging, whereas in fact it represents an iatrogenic complication.

Valproic acid has been reported to cause parkinsonism that reverses with drug discontinuation. This appears to be an uncommon side effect but since it is a recommended treatment for the management of agitation in the demented, it must be considered when evaluating such patients. Flunarizine and cinnarizine are calcium channel blockers not available in North America, but with a growing influx of immigrants they should be remembered when assessing South American immigrants. Lithium usually produces only postural and action tremors, but may induce parkinsonism. Lithium is only used in patients with bipolar affective disorder, and will therefore not be commonly encountered.

**Atypical Antipsychotic Drugs**

There is no consensus definition of "atypicality." The term has been used to describe antipsychotic drugs that: have a pharmacological profile in which the blockade of 5-HT2a serotonin receptors outweighs the blockade of the dopamine D2 receptors; have few motor effects in animal models of psychosis even when given in high doses; cause "relatively" few EPS in humans and; have better effects on the "negative symptoms" (anhedonia, absent thought, apathy) in schizophrenia than the previous generation of antipsychotics. Clozapine, the first atypical, remains the paradigm, fulfilling all of the criteria that have been proposed. However, the drugs that have followed, while free of some of the non-motor side effects of clozapine, are all less effective and less free of motor side effects.

The accompanying Table lists the atypicals commercially available in 2003, with others soon to be released. Several have been the subject of published trials in older populations, all of which report similar results—good efficacy against psychotic symptoms and relative immunity from parkinsonism and other motor side effects. The conclusions on the motor side effects, however, may be suspect due to two major design flaws in every one of the published reports. First, the subjects often had been on antipsychotics prior to enrolment. Since the washout period was only one week, it may be more accurate to propose that the antipsychotic tested caused less parkinsonism than the previously used drug, rather than that it was free from causing EPS. The second problem was the scale used; the Simpson-Angus scale is difficult to use in this population and may not accurately reflect the clinical degree of parkinsonism actually present. There are data about the effects of many of the atypicals in Parkinson's disease itself, from which motor dysfunction may serve as a litmus test for the motor side effects of any drug. The IPD patients already have a severe dopaminergic impairment. Thus, if a patient with IPD suffers no motor decline, then it may be assumed that the drug will most likely be well tolerated, in terms of motor side effects, in someone less sensitive.

Clozapine has been the subject of two double-blind, placebo-controlled trials in drug-induced psychosis in
Drug-induced Parkinsonism

IPD, and both concluded that motor function was unaf- fected and that low doses of the drug were effective in controlling the psychosis. Risperidone has been the subject of a number of open label reports with mixed outcomes, with some showing motor decline while others did not. Other reports found little motor differences between risperidone and haloperidol in older patients or in young schizophrenics, when used at similar doses. Olanzapine was found in three double-blind, placebo-controlled trials and one double-blinded comparative trial (to low-dose clozapine) to cause significant worsening of motor function with no benefit in psychiatric function. Quetiapine has been the subject of several open label studies which all attest to its relative freedom from motor side effects and excellent efficacy against psychosis—less impressive than clozapine but far better than any of the other atypical medications. Although some mild motor decline has been reported, quetiapine is generally well tolerated and its motor effects are of little clinical significance. Aripiprazole is currently being evaluated in IPD, while there are no data for ziprasidone, likely due to an exaggerated concern over a QT interval prolongation.

Based on the published reports of the effects of the atypical antipsychotics in IPD, one can say that clozapine is free of parkinsonian side effects and that quetiapine is relatively free, whereas olanzapine and risperidone should be considered likely causes of parkinsonism and likely explanations for worsened parkinsonism in those patients already parkinsonian. These effects should be strongly considered when prescribing an antipsychotic, as parkinsonism is potentially devastating in reducing functionality, and is often long lasting.

Dr. Friedman has been a speaker for or paid consultant to AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, Pfizer and Acadia Pharmaceutical.

References