Fortnightly Review

Parkinsonism—recognition and differential diagnosis

Niall Quinn

At first sight the diagnosis of Parkinson's disease might seem a fairly simple and straightforward affair, and indeed often it is. How many other medical conditions can sometimes be instantaneously recognised from a distance across a crowded street? The diagnosis of Parkinson's disease remains entirely clinical, made with eyes, ears, and hands without recourse to the laboratory. However, in two large recent studies from parkinsonian brain banks, one quarter of cases still carrying, at death, a diagnosis of idiopathic Lewy body Parkinson's disease made by a specialist did not have the disease.^{1,2} The rate of misdiagnosis at early stages by non-specialists is probably higher still. These findings at necropsy (that most ultimate of audits, and the quality control of our diagnostic skills) indicate a need for better diagnostic accuracy. In this article I shall consider the diagnostic process, possible pitfalls, and clinical clues (box 1) that may be useful in parkinsonism and Parkinson's disease. The list of conditions that can masquerade as Parkinson's disease is extensive, so I shall concentrate in the text on those that most frequently cause problems (box 2).

Parkinsonism

The first step in diagnosis is to confirm that the patient indeed has true parkinsonism, since many mistaken diagnoses of Parkinson's disease fall at this first hurdle. Thus, for a diagnosis of established parkinsonism, upper body akinesia must be present. Akinesia—the core, disabling clinical feature of parkinsonism—is a symptom complex containing most or all of the following deficits: slowness of movement (bradykinesia), poverty of movement (for example, facial amimia, impaired arm swing), difficulty initiating movement, progressive fatiguing and diminishing amplitude of repetitive alternating movements, and inordinate difficulty in accomplishing some simultaneous or sequential motor acts. Rigidity (either lead pipe, or cogwheel, due to superimposed or underlying tremor) is usually, but not always, present. The increase in tone is fairly equal in flexors and extensors of all four limbs, but slightly more in flexors, resulting in a part flexed "simian" posture. Postural instability is usually seen late in Parkinson's disease, but may be an early feature in other parkinsonisms.

Tremor may be regarded as an optional extra: it is absent in about 30% of patients with Parkinson's disease at presentation, and throughout its course in some. The classic 3-5 Hz pill rolling, pronation-supination parkinsonian rest tremor of the upper limb is often intermittent but can usually be brought out by getting the subject to count backwards with eyes closed and hands dangling over the armrests of the seat. However, occasionally it is seen only when the subject

Summary points

- The cumulative lifetime risk of a person developing parkinsonism has been estimated at 1 in 40
- Idiopathic Parkinson's disease is the commonest cause, but about a third of patients with the syndrome of parkinsonism or a diagnosis of Parkinson's disease have some other disease instead
- The diagnosis of Parkinson's disease is entirely clinical, but the results of certain investigations may help in recognising alternative causes for parkinsonism
- For a diagnosis of established parkinsonism, upper body akinesia must be present; rigidity is usually, but not always, present; tremor is an optional extra
- The two conditions that are most commonly misdiagnosed as Parkinson's disease—essential tremor and arteriosclerotic pseudoparkinsonism—do not display true parkinsonism

is walking. This characteristic rest tremor disappears or lessens during movement of the limbs and is much more suggestive of idiopathic, or sometimes drug induced, parkinsonism than other parkinsonian syndromes. A faster, 6-10 Hz postural tremor may be seen as well as, or instead of, a classic rest tremor.

Pseudoparkinsonism

The two conditions that are most commonly misdiagnosed as Parkinson's disease by many non-specialists, and even by some specialists, do not even display true parkinsonism.

ESSENTIAL TREMOR

This monosymptomatic disorder is often dominantly inherited with incomplete penetrance; may be improved by alcohol, β blockers, or primidone; and is commoner than Parkinson's disease but shares with it a rising incidence with increasing age.³ The tremor is evident on posture but sometimes maximal at the termination of a movement, particularly when it is mechanically amplified—for example, when the fingers are held in front of the nose. This accounts for many entries in medical notes of apparent "cerebellar intention tremor" unaccompanied by any other cerebellar signs. It is important also to recognise that a severe postural tremor may also be present, but less

Institute of Neurology,
National Hospital for
Neurology and
Neurosurgery, London
WC1N 3BG
Niall Quinn, reader in clinical
neurology

BMJ 1995;310:447-52

Box 1—Clinical “red flags” suggesting non-idiopathic parkinsonism

Early instability or falls	Cold, dusky extremities
Rapid progression	Contractures
Poor or waning response to levodopa	Disproportionate antecollis
Absent or atypical levodopa dyskinesias	Severe dysphonia, dysarthria, or dysphagia
Lower body parkinsonism	Inspiratory sighs
Autonomic failure	Pseudobulbar crying
Pyramidal signs	Palilalia or palilogia
Cerebellar signs	Groaning
Dementia	Respiratory stridor
Downgaze palsy	Jerky tremor or myoclonus
Levator inhibition	“Wheelchair sign”
Blepharospasm	

Some of these can also be seen, uncommonly, in Parkinson’s disease.

evident, at apparent rest; however, it does not cause typical pill rolling. In essential tremor, there is often also secondary cogwheeling when tone is passively examined, but there is no lead pipe rigidity and no true akinesia. In addition, the presence of tremors elsewhere than in the hands may be a useful clue. Thus patients with essential tremor may, in addition to arm tremor, have a vocal tremor, or a tremor of the head on the neck (no-no or yes-yes), neither of which normally occurs in parkinsonism. Conversely, a slow vertical jaw tremor, or tremor of the leg at rest, is often seen in Parkinson’s disease, but rarely in essential tremor. To complicate the issue, many patients with dystonia also display a postural tremor of the neck or arms and sometimes lips, tongue, or jaw as part of their illness.⁴

ARTERIOSCLEROTIC PSEUDOPARKINSONISM

In the past vascular disease was considered a major cause of parkinsonism, and even as a cause of Parkinson’s disease. However, we now realise that cerebrovascular disease very rarely causes true parkinsonism; hence the introduction of the term arteriosclerotic (or vascular) pseudoparkinsonism.⁵ Other terms used to describe a broadly similar clinical picture are lower body (as opposed to Lewy body) parkinsonism and parkinsonian ataxia. These patients are generally elderly and often hypertensive. The most striking thing is that the top half of their body does not seem to “go” with the bottom half—rather like those split page children’s books that superimpose the top half of a dalmatian on the bottom half of a hippopotamus to give a “dalmatamus” (fig 1). The gait is short stepped (the term *marche à petits pas* was coined for these individuals) and often wide based (unlike in Parkinson’s disease), and postural stability may be impaired. Start hesitation and freezing may occur, as in Parkinson’s disease, but above the waist there is a striking absence of true parkinsonism. Thus, the voice and facial expression are lively and well modulated, the arms are used freely in spontaneous gesture, rest tremor is absent, there is no fatigue or decrement of

alternating movements, and the posture is usually upright.

Imaging often shows basal ganglia lacunae or white matter change, but sometimes hydrocephalus or, rarely, cerebral tumour can give rise to a broadly similar picture.

It is important to recognise that people with Parkinson’s disease can have additional cerebrovascular disease. This may sometimes be the cause of disproportionate and atypical walking and balance problems in someone who also has relatively mild classic upper body parkinsonism, or it may cause a relatively abrupt onset of gait difficulty with falls in an elderly subject with a long history of typical Parkinson’s disease.

Lower body parkinsonism illustrated by the “dalmatamus” (reproduced from *Animal Allsorts* by Helen Oxenbury, with permission from Walker Books Ltd)

Computed tomography or magnetic resonance imaging may be useful in this context. When in any doubt over whether the patient has arteriosclerotic pseudoparkinsonism, Parkinson’s disease, or arteriosclerotic pseudoparkinsonism plus Parkinson’s disease, an adequate trial of levodopa should be instituted.

Differential diagnosis of parkinsonism

The commonest cause of true parkinsonism is Parkinson’s disease. Apart from the two main causes of pseudoparkinsonism considered above, the conditions most frequently mistaken for Parkinson’s disease, at least by specialists, are drug induced parkinsonism, multiple system atrophy, and Steele-Richardson-Olszewski disease.

IDIOPATHIC PARKINSON’S DISEASE

Parkinson’s disease is a clinicopathological entity characterised by parkinsonism due to neuronal loss,

Box 2—Common causes of parkinsonism

<i>Pseudoparkinsonism</i>	<i>True parkinsonism</i>
Essential tremor	Idiopathic Parkinson’s disease
Arteriosclerotic (vascular) pseudoparkinsonism	Drug induced parkinsonism
	Multiple system atrophy
	Progressive supranuclear palsy

with Lewy bodies, in the substantia nigra.⁶ Other brain areas such as locus coeruleus, dorsal vagal nucleus, and the nucleus basalis of Meynert, but not the corpus striatum, are also involved, and in all cases at least some Lewy bodies are also present in the cerebral cortex. The disease usually presents asymmetrically (and remains asymmetrical throughout its course) with a combination of akinesia, rigidity, and usually additional tremor which is most commonly seen when the limbs are at rest but may be postural, or both. Clinical diagnostic criteria have been formulated by the United Kingdom Parkinson's Disease Society Brain Bank.⁶ The disease does not cause cerebellar or pyramidal signs, although the spontaneously extensor "striatal toe" and the tendency for tendon reflexes to be a little brisker on the more affected side may sometimes cause confusion. Autonomic failure may occur but, like impaired postural instability, freezing, and falls, tends to be a late feature of the isolated disease.⁷

Treatment with levodopa preparations (in adequate dosage, for an adequate period of time) for practical purposes always leads to major clinical improvement. If a patient does not respond to levodopa, uncomplicated Parkinson's disease is very unlikely. However, the converse is not true. Thus, although most patients with non-idiopathic parkinsonism do not respond, or respond poorly, to levodopa, some have a good or even excellent response, but this is usually transient. The "levodopa honeymoon" in Parkinson's disease is sooner or later followed in virtually all patients by fluctuations in motor response and dyskinesias, which usually predominate in the limbs as mobile choreo-dystonic movements and are more apparent on the presenting side. Depression may precede, coincide with, or follow diagnosis and treatment.⁸

Dementia occurs about three times as commonly as in elderly, age-matched controls,⁹ but still affects only a minority, and almost never those who are still young, despite longstanding severe motor disease. This suggests that often Parkinson's disease alone may not be sufficient to cause dementia, and that other age related factors may be necessary.¹⁰

Variants of Lewy body Parkinson's disease

Benign tremulous Parkinson's disease—A minority of patients with Parkinson's disease present with isolated tremor, usually of the resting type, and sometimes restricted to one or both legs; this can precede the other features of the disease by several years. The resting nature of the tremor may suggest the possibility of this variant, the diagnosis of which is confirmed by a good response to levodopa in adequate dosage.

Diffuse Lewy body disease—Many brains in dementia brain banks contain Lewy bodies in both the substantia nigra and corte, usually accompanied by plentiful senile plaques and variable numbers of Alzheimer neurofibrillary tangles. When cortical Lewy bodies are "plentiful" (universal criteria are lacking), such cases have been labelled diffuse Lewy body disease, and this "entity" has been claimed to be the second commonest cause of dementia in the elderly, after Alzheimer's disease.¹¹ The patients usually have parkinsonism that is responsive to levodopa but also develop dementia with prominent visual hallucinations and a fluctuating mental state.¹² However, the status of this condition is insecure. Lewy bodies are present in the cerebral cortex of all Parkinson's disease patients,² and in a series of 41 brains in the United Kingdom Parkinson's Disease Society Brain Bank cortical Lewy body density in anterior cingulate gyrus did not correlate with presence or degree of dementia (S E Daniel, personal communication). Moreover, in another recent dementia study, visual hallucinations and a fluctuating mental state were as common in patients with pure Alzheimer's disease as in those with

both Alzheimer's disease and Lewy body disease, although the load of Alzheimer pathology in the patients with Lewy bodies was less.¹³ This raises the possibility that the coincidental occurrence of the pathologies of these two common diseases in elderly patients may often summate to produce some, but by no means all, demented patients with parkinsonism and parkinsonian patients with dementia.¹⁰

DRUG INDUCED PARKINSONISM

This can be caused either by drugs that deplete presynaptic dopamine stores (reserpine or tetrabenazine, for example) or, more commonly, by neuroleptic drugs such as phenothiazines (chlorpromazine), butyrophenones (haloperidol), thioxanthines (flupenthixol), and substituted benzamides (sulpiride). These drugs have often been given as major tranquillisers in psychiatric illness; other settings include the use of prochlorperazine for sickness, vertigo, or unsteadiness; metoclopramide for gastrointestinal symptoms or migraine; the atypical calcium blocking drug cinnarizine for vestibular disorders or hypertension; and combined preparations of antidepressant and neuroleptic, perhaps the worst culprits of all because sometimes unknowingly prescribed.¹⁴ Thus, Motival and Motipress, which contain both fluphenazine and nortriptyline, are indexed in the *Monthly Index of Medical Specialities* under anxiolytics and antidepressants, and Parstelin (trifluoperazine plus tranlylcypromine) under antidepressants, but none of them appears under antipsychotics.

In psychiatric hospitals where uniforms are not worn by staff the patients can still be distinguished from afar because they do not move normally. Facial amimia and lack of arm swing are so common that psychiatrists often cease to notice them. Tremor is less common, but can be identical to the classic pill rolling tremor of Parkinson's disease. Moreover drug induced parkinsonism can be asymmetrical, like Parkinson's disease. Drug induced parkinsonism often resolves rapidly within weeks or sometimes even days of discontinuing the offending drug, but it can take months and occasionally up to a year to subside, especially after depot neuroleptic preparations. One important pointer to the possibility of previous neuroleptic intake is the presence of a mixed movement disorder incorporating akathisia (motor restlessness), stereotypies, and the paradox of untreated parkinsonism coexisting with an orofacial or respiratory dyskinesia.

"Parkinsonism plus" and multisystem degenerations

Both these terms are entirely non-specific. "Parkinsonism plus" implies the presence of additional features, over and above parkinsonism, that are incompatible with uncomplicated Parkinson's disease. The term "multisystem degenerations" covers a host of disorders with different pathologies involving different combinations of brain structures.

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy is the specific name given to a sporadically occurring condition of adult onset in which cell loss and gliosis (without Lewy bodies) occurs not only in substantia nigra but also in a multiplicity of other structures which may include striatum, olives, pons, cerebellum, and the intermediolateral cell columns and Onuf's nucleus in the spinal cord.¹⁵ The same condition has been labelled as striatonigral degeneration when parkinsonism predominates,¹⁶ as Shy-Drager syndrome when autonomic failure predominates,¹⁷ and as olivopontocerebellar atrophy when cerebellar features predominate.¹⁸ Recently a cytological hallmark (the oligodendroglial cytoplasmic inclusion)¹⁹ has been described that is present in multiple system atrophy (whatever the

Supranuclear downgaze palsy: (top) absent voluntary downgaze; (bottom) improved downgaze for reflex eye movements utilising doll's head manoeuvre (full neck extension was not possible because of neck rigidity)

clinical predominance) and is usually absent in cases of hereditary olivopontocerebellar atrophy and other multisystem degenerations.¹⁹

Multiple system atrophy most commonly begins in the early 50s, and, unlike Parkinson's disease, it shortens life considerably, with a median survival of 9.3 years. However, there is a wide range both for age at onset and for survival. Parkinsonism occurs in 90% of patients with multiple system atrophy and dominates the motor disorder in 80%. Cerebellar or pyramidal signs each occur in about half of patients.²⁰⁻²²

Some degree of autonomic failure occurs in virtually all patients but is usually more severe, and often occurs earlier, than in Parkinson's disease—indeed, it may precede the motor disturbance by months or even some years. In men, impotence is often the first symptom, and incontinence, more than retention, is common in both sexes (Parkinson's disease usually causes just frequency and urgency due to detrusor hyperreflexia, which is present in 75% of cases). Postural hypotension is common, but causes major problems only in a minority of patients (this can also occur in Parkinson's disease, but much less often). Respiratory stridor affects about 30% of patients at some stage, and when combined with parkinsonism is highly suggestive of multiple system atrophy. Patients often develop postural instability early in the disease, and their disability progresses more rapidly than Parkinson's disease. Malignant Parkinson's disease does not exist—if it is malignant, it is not Parkinson's disease.

The response of patients with multiple system atrophy to levodopa is most commonly absent or poor. However, it can be good or excellent in 25% of patients,²¹ but this is usually transient. Levodopa induced dyskinesias in multiple system atrophy may be absent or, when present, take the form of predominantly dystonic movements affecting the face and neck more than the limbs. Speech may differ qualitatively

from the hypophonic monotony of Parkinson's disease, incorporating quivering, strained, or slurring components. Many patients develop severe aphonia, anarthria, and dysphagia, which are rare in Parkinson's disease. Like Parkinson's disease, multiple system atrophy is asymmetrical in most cases, and most patients also have a tremor, although this is of a classic resting type in only 10%. An irregular postural and action tremor is more common. This may be wholly or partly due to the presence of small myoclonic jerks of the fingers, which are often stimulus sensitive. Some patients develop a disproportionate antecollis, in which the chin is flexed on the chest despite little flexion elsewhere, but this is not specific to multiple system atrophy. Dementia does not seem to be a feature of the disease.

Autonomic function tests can document disturbed control of blood pressure and heart rate, but taken in isolation they are not particularly helpful in determining whether this is due to multiple system atrophy or to Parkinson's disease, as similar results can be obtained in both diseases. In contrast, an abnormal external sphincter electromyogram reflecting loss of anterior horn cells in Onuf's nucleus in the sacral cord is highly suggestive of multiple system atrophy in the appropriate clinical setting²³; however, a normal result may be obtained, particularly early in the disease course. Structural imaging may show cerebellar atrophy, but often cerebellar signs are already evident clinically. The presence of putaminal hypointensity relative to globus pallidus on 1.5 tesla T2 weighted magnetic resonance imaging, or slit hyperintensity of the lateral putaminal margin, may suggest multiple system atrophy, but the sensitivity and specificity of these findings are not yet established. The diagnostic value of other techniques using positron emission tomography, single photon emission computed tomography, and magnetic resonance spectroscopy in separating different causes of parkinsonism is currently being investigated in a research setting. In fully developed disease, however, the diagnosis of multiple system atrophy is often evident clinically without recourse to investigations. This, the "full house" scenario of a non-demented patient who is impotent and incontinent with parkinsonism poorly responsive to levodopa and pyramidal and cerebellar signs can really have no alternative diagnosis. Proposed clinical diagnostic criteria for multiple system atrophy are given by Quinn.²²

STEELE-RICHARDSON-OLSZEWski DISEASE

Steele-Richardson-Olszewski disease is another sporadic multisystem degeneration; it is characterised by cell loss and neurofibrillary tangles principally in the brainstem, globus pallidus, and subthalamic and dentate nuclei.²⁴⁻²⁶ It classically causes the syndrome of progressive supranuclear palsy (PSP). By analogy with Parkinson's disease and parkinsonism, it probably accounts for 75% of progressive supranuclear palsy, the other quarter being due to still rarer diseases. It usually begins in the seventh decade and is fairly symmetrical, principally because the signs are predominantly axial. Median survival is six to seven years. Patients commonly present with early instability and backwards falls and then develop a rather growling and gruff dysarthria and sometimes involuntary groaning, followed by dysphagia. Sometimes their rigid neck is extended, but it may be flexed or in a normal position. Frontal lobe deficits are characteristic, but the degree of dementia is highly variable. Perseveration may be particularly obvious in speech, with repetition of syllables and words (palilalia) or even of whole phrases even of whole phrases (palilogia). Involuntary eye closure is often seen. Although true blepharospasm may occur, this is more commonly due to "levator

inhibition"—that is, difficulty opening the gently closed eyelids. The brow may be furrowed and the eyebrows raised from frontalis hyperactivity in attempting to keep the eyes open, resulting in a surprised expression.

The characteristic feature, from which the term progressive supranuclear palsy is derived, is a supranuclear (upper motor neurone) palsy (paresis, not paralysis) of voluntary down gaze (up gaze problems are common and non-specific in elderly patients with parkinsonism). Voluntary downgaze is slow and usually incomplete, but when the oculocephalic reflex is engaged (the patient fixating on the examiner's nose while the patient's neck is passively extended) full down gaze is obtained (fig 2). This example of voluntary-automatic dissociation, like the symmetrical laugh of the ticklish patient with an upper motor neurone facial paresis or the hemiplegic who extends his arm when yawning, shows that the nucleus and its nerve are intact, but can be activated from above only in certain ways. Patients may not volunteer any visual symptoms, but more commonly there is a vague and non-specific complaint, particularly concerning difficulty reading and feeding. The "sloppy tie sign" occurs when the patient cannot look down to keep food from his plate on his fork while conveying it up to his mouth and so drops it on his tie.

Although superficially masquerading as Parkinson's disease because of axial rigidity and gait problems, on close inspection Steele-Richardson-Olszewski disease does not usually cause prominent distal parkinsonism. Thus, only a minority of patients have distal limb akinesia or rigidity, and then it is usually mild; classic rest tremor is almost never seen, and levodopa is usually unhelpful. Autonomic failure is not part of the disease, and diagnosis is again largely clinical. Proposed diagnostic criteria are given by Lees.²⁶

RARER CAUSES OF PARKINSONISM

Many rarer conditions can occasionally give rise to true or pseudoparkinsonism (box 3). On examination there are usually clues that one is not dealing with Parkinson's disease, but poisoning with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) can produce an exact clinical mimic of the idiopathic disease,²⁷ except that onset is subacute and progression is absent or slow. Some patients with Alzheimer's disease have extrapyramidal features, usually restricted to rigidity.²⁸ Significant akinesia or the presence of rest tremor in someone with dementia should suggest concurrent Lewy body disease. Wilson's disease, though rare, should always be sought in a young (<45 years) individual with an unexplained movement disorder, since it is treatable and, without treatment, fatal. The akinetic-rigid (Westphal) variant of Huntington's disease usually affects juvenile cases of paternal inheritance, but can also be a presentation of later onset cases. Corticobasal degeneration is a rare degenerative condition that usually presents in one arm with rigidity, myoclonus, dystonia, and apraxia.²⁹ Its relation to Pick's disease (in the generalised form of which parkinsonism can also occur) remains controversial. In the early 20th century, very many survivors of the world pandemic of encephalitis lethargica, very few of whom are still alive, developed post-encephalitic parkinsonism. Since then, only a few cases have been reported. In Guam and some other parts of the Western Pacific there is a high, but falling, concentration of cases showing any combination of parkinsonism, dementia, and motor neurone disease. Unlike Parkinson's disease and motor neurone disease, the pathological hallmark in these cases is the presence of neurofibrillary tangles and, under the microscope, the brains can look indistinguishable from those of patients with Steele-Richardson-Olszewski disease and

Box 3—Rarer causes of parkinsonism

Alzheimer's disease
Wilson's disease
Huntington's disease
Corticobasal degeneration
Pick's disease
Postencephalitis lethargica
Parkinson-dementia-amyotrophic lateral sclerosis complex of Guam
Space-occupying lesions
Hydrocephalus
Pugilists' encephalopathy
MPTP toxicity
Carbon monoxide or manganese intoxication

post-encephalitic parkinsonism.³⁰ Other, still rarer, causes of parkinsonism are beyond the scope of this article.

Red flags

"Red flags" (see box 1) are clinical features that should cause doctors to think twice, or more, about diagnosing idiopathic Parkinson's disease. Most of them have been covered above; none of them are individually diagnostic; and some can also occasionally be seen in idiopathic disease. Nevertheless, particularly when multiple flags are present, they should raise suspicions that the patient does not have Parkinson's disease.

The "wheelchair sign" needs explanation. Many people with fairly advanced Parkinson's disease who are experiencing treatment related "on/off" motor fluctuations may acquire a wheelchair, but they usually use it only when "off" and walk about, sometimes pushing the chair, when "on" and mobile; they are rarely permanently wheelchair bound. In contrast, patients who never leave their wheelchair commonly do not have Parkinson's disease (fig 3).

This man with pathologically proved multiple system atrophy has ante-collis (with laterocollis) and hand contractures and displays the "wheelchair sign"

Useful addresses for patients, families, and health care professionals:

Parkinson's Disease Society, 22 Upper Woburn Place, London WC1H 0RA

International Tremor Foundation, c/o Mrs Karen Walsh, ALAC Centre, Harold Wood Hospital, Romford, Essex RM3 0BE

PSP (Europe) Association, c/o Mr Brian Fisher, 21 Church Street, Mears Ashby, Northampton.

- 1 Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism—a prospective study. *Can J Neurol Sci* 1991;18:275-8.
- 2 Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181-4.
- 3 Findley LJ, Koller WC. Essential tremor: a review. *Neurology* 1987;37:1194-7.
- 4 Fahn S. Torsion dystonia: clinical spectrum and treatment. *Neurology* 1983;2:316-23.
- 5 Critchley M. Arteriosclerotic pseudoparkinsonism. In: Rose FC, Capildeo R, eds. *Research progress in Parkinson's disease*. London: Pitman, 1981:40-2.
- 6 Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:745-52.
- 7 Bannister R, Oppenheimer DR. Degenerative diseases of the nervous system associated with autonomic failure. *Brain* 1972;95:457-74.
- 8 Dooneief G, Mirabello E, Bell K, Matder K, Stern Y, Mayeux R. An estimate of the incidence of depression in idiopathic Parkinson's disease. *Arch Neurol* 1992;49:305-7.
- 9 Biggins CA, Boyd JL, Harrop FM, Madeley P, Mindham RHS, Randall JJ, et al. A controlled longitudinal study of dementia in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1992;55:566-71.
- 10 Quinn N, Rossor MN, Marsden CD. Dementia and Parkinson's disease—pathological and neurochemical considerations. *Br Med Bull* 1986;42:86-90.
- 11 Byrne EJ, Lennox G, Lowe J, Godwin-Austen RB. Diffuse Lewy body disease: clinical features in 15 cases. *J Neurol Neurosurg Psychiatry* 1989;52:709-17.
- 12 McKeith IG, Fairbairn AF, Bothwell RA, Moore PB, Ferrier IN, Thompson P, et al. An evaluation of the predictive validity and inter-rater reliability of clinical diagnostic criteria for senile dementia of Lewy body type. *Neurology* 1994;44:872-7.
- 13 Förstl H, Burns A, Luthert P, Cairns N, Levy R. The Lewy-body variant of Alzheimer's disease. Clinical and pathological findings. *Br J Psychiatry* 1993;162:385-92.
- 14 Stephen PJ, Williamson J. Drug-induced parkinsonism in the elderly. *Lancet* 1984;iii:1082-3.
- 15 Graham JG, Oppenheimer DR. Orthostatic hypotension and nicotine sensitivity in a case of multiple system atrophy. *J Neurol Neurosurg Psychiatry* 1969;32:28-34.
- 16 van der Beeken H, Adams RD, van Bogaert L. Striopallidal-nigral degeneration. An hitherto undescribed lesion in paralysis agitans. *J Neuropathol Exp Neurol* 1960;19:159-61.
- 17 Shy GM, Drager GA. A neurological syndrome associated with orthostatic hypotension. *Arch Neurol* 1960;2:511-27.
- 18 Dejerine J, Thomas AA. L'atrophie olivo-ponto-cérébelleuse. *Nouvelle Iconographie de la Salpêtrière* 1990;13:330-70.
- 19 Lantos PL, Papp MI. Cellular pathology of multiple system atrophy: a review. *J Neurol Neurosurg Psychiatry* 1994;57:129-33.
- 20 Quinn N. Multiple system atrophy—the nature of the beast. *J Neurol Neurosurg Psychiatry* 1989(suppl):78-89.
- 21 Wenning GK, Ben Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. *Brain* 1994;117:835-45.
- 22 Quinn N. Multiple system atrophy. In: Marsden CD, Fahn S, eds. *Butterworth-Heinemann International Medical Reviews. Neurology 13, movement disorders 3*. London: Butterworth-Heinemann, 1994:262-81.
- 23 Beck RO, Betts CD, Fowler CJ. Genitourinary dysfunction in multiple system atrophy: clinical features and treatment in 62 cases. *J Urol* 1994;151:1336-41.
- 24 Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brainstem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Arch Neurol* 1964;10:333-59.
- 25 Lees AJ. The Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). In: Marsden CD, Fahn S, eds. *Butterworth International Medical Reviews. Neurology 7, movement disorders 2*. London: Butterworth, 1987:272-87.
- 26 Golbe LI, Davis PH, Schoenberg BS, Duvoisin RC. Prevalence and natural history of progressive supranuclear palsy. *Neurology* 1988;38:1031-4.
- 27 Ballard PA, Tetrad JW, Langston JW. Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): seven cases. *Neurology* 1985;35:949-56.
- 28 Tyrrell PJ, Rossor MN. Extrapyramidal signs in dementia of Alzheimer type. *Lancet* 1989;ii:920.
- 29 Rinne JO, Lee MS, Thompson PD, Marsden CD. Corticobasal degeneration: a clinical study of 36 cases. *Brain* 1994;117:1183-96.
- 30 Geddes JF, Hughes AJ, Lees AJ, Daniel SE. Pathological overlap in cases of parkinsonism associated with neurofibrillary tangles. A study of recent cases of postencephalitic parkinsonism and comparison with progressive supranuclear palsy and Guamanian parkinsonism-dementia complex. *Brain* 1993;116:281-302.

The number needed to treat: a clinically useful measure of treatment effect

Richard J Cook, David L Sackett

The relative benefit of an active treatment over a control is usually expressed as the relative risk, the relative risk reduction, or the odds ratio. These measures are used extensively in both clinical and epidemiological investigations. For clinical decision making, however, it is more meaningful to use the measure "number needed to treat." This measure is calculated on the inverse of the absolute risk reduction. It has the advantage that it conveys both statistical and clinical significance to the doctor. Furthermore, it can be used to extrapolate published findings to a patient at an arbitrary specified baseline risk when the relative risk reduction associated with treatment is constant for all levels of risk.

More emphasis is now being put on effective use of biomedical literature to guide clinical treatment. As a result accessing, critically appraising, and incorporating the results of clinical investigations into clinical practice are becoming higher priorities for doctors and medical students.¹

A pivotal step in translating clinical research into practice is the summarisation of data from randomised trials in terms of measures of effect that can be readily appreciated by doctors and other carers. Various measures of the effect of treatment are used in analysing results. Each measure has its own interpretation and statistical properties that make it suitable for some applications but perhaps not for others. We describe here a new measure referred to as number needed to treat² and a simple method of adopting this approach to individual patients at different levels of risk.

Measures of treatment effect

Consider a parallel group study in which patients are randomised to either an active treatment or a placebo control arm, are followed for a fixed amount of time, and are observed to experience a binary response to treatment (event/no event). We assume here that the events are adverse, and the objective is therefore to prevent them.

The effect of treatment is usually measured by comparing the probabilities of events in the two groups of patients. Point estimates of these measures are obtained by substituting the observed rate of events for the probabilities. For example, the absolute risk reduction is the difference in the probabilities of an event in the control and treatment groups and is estimated as the corresponding difference in the event rates. If the event rate in the treatment group is less than that in the control group this suggests a potential benefit from the active treatment. Similarly, if the event rate is greater in the treatment group than the control group (negative absolute risk reduction) the active treatment may be harmful. Before recommendations can be made regarding the treatment more formal analyses of the treatment effect are needed to quantify the strength of evidence: this is done by tests of significance or confidence intervals.

Another approach to summarising effects of treatment is based on the relative risk. Relative risk is defined as the probability of an event in the active treatment group divided by the probability of an event in the control group. The relative risk can be conveniently estimated as the ratio of the corresponding

Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, Canada N2L 3G1

Richard J Cook, assistant professor

Nuffield Department of Clinical Medicine (Level 5), John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU
David L Sackett, professor of clinical epidemiology

Correspondence to: Professor Cook.

BMJ 1995;310:452-4