Medical records documentation of constipation preceding Parkinson disease

A case-control study

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ABSTRACT

Objective: Parkinson disease (PD) may affect the autonomic nervous system and may cause constipation; however, few studies have explored constipation preceding the motor onset of PD. We investigated constipation preceding PD using a case-control study design in a population-based sample.

Methods: Using the medical records-linkage system of the Rochester Epidemiology Project, we identified 196 subjects who developed PD in Olmsted County, MN, from 1976 through 1995. Each incident case was matched by age (±1 year) and sex to a general population control. We reviewed the complete medical records of cases and controls in the medical records-linkage system to ascertain the occurrence of constipation preceding the onset of PD (or index year).

Results: Constipation preceding PD or the index year was more common in cases than in controls (odds ratio [OR] 2.48; 95% confidence interval [CI] 1.49 to 4.11; $p = 0.0005$). This association remained significant after adjusting for smoking and coffee consumption (ever vs never), and after excluding constipation possibly induced by drugs. In addition, the association remained significant in analyses restricted to constipation documented 20 or more years before the onset of motor symptoms of PD. Although the association was stronger in women than in men and in patients with PD with rest tremor compared with patients with PD without rest tremor, these differences were not significant.

Conclusions: Our findings suggest that constipation occurring as early as 20 or more years before the onset of motor symptoms is associated with an increased risk of Parkinson disease.
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GLOSSARY

CI = confidence interval; **OR** = odds ratio; **PD** = Parkinson disease.

Dysautonomia is a component of the pathogenetic process underlying Parkinson disease (PD), and Lewy bodies are consistently found in the autonomic nervous system of patients who died with PD.[1-3] Constipation is one of the most frequent clinical manifestations of this dysautonomia, and is commonly reported at the time of onset of motor symptoms of PD or during progression of the disease.[4-6]

In addition, it has been suggested that constipation may precede the appearance of motor symptoms of PD in some patients.[7-9] In the only cohort study that addressed this question, the Honolulu-Asia Aging Study, men who reported less frequent bowel movements had a significantly higher risk of PD over a 24-year follow-up period.[10,11] In subsequent publications from the same study, constipation was also associated with incidental Lewy body disease, which is thought to represent a preclinical phase of PD, and with a reduced neuronal density in the substantia nigra.[12,13] Consistent with these clinical and pathologic findings, the Braak staging of the neuropathologic involvement in PD predicts that the autonomic system is involved early in the disease process.[14]

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To further explore the hypothesis that constipation may be an early, premotor manifestation of PD, we conducted a population-based case-control study of incident PD cases. Because constipation was assessed through a medical records-linkage system, we were able to study the length of time between appearance of constipation and onset of motor symptoms without relying on the recall of historical events. In addition, we extended the scope of the Honolulu-Asia Aging Study by including both men and women in our study.

METHODS

Cases. Using the medical records-linkage system of the Rochester Epidemiology Project, we identified all subjects residing in Olmsted County, MN, who developed PD from 1976 through 1995. Details about the study population and the identification of incident cases were reported elsewhere.[15] Our diagnostic criteria included 2 steps: the definition of parkinsonism as a syndrome and the definition of PD within the syndrome. Parkinsonism was defined as the presence of at least 2 of 4 cardinal signs: rest tremor, bradykinesia, rigidity, and impaired postural reflexes. PD was defined as the presence of parkinsonism with all 3 of the following criteria. 1) No other cause (e.g., repeated stroke with stepwise progression; repeated head injury; history of encephalitis; neuroleptic treatment within 6 months before onset; hydrocephalus; brain tumor). 2) No documentation of unresponsiveness to levodopa at doses of at least 1 g/day in combination with carbidopa (applicable only to patients who were treated). 3) No prominent or early (within 1 year of onset) signs of more extensive nervous system involvement (e.g., dementia or dysautonomia) not explained otherwise.[15] Our clinical classification of patients with PD through medical records review by a movement disorders specialist (J.H.B.) was found to be valid compared with a direct neurologic examination by a movement disorders specialist, as reported elsewhere.[16] Onset of PD was defined as the year in which a cardinal sign of PD was first noted by the patient, by family members, or by a care provider (as recorded in the medical record).

Controls. Each case was individually matched by age (±1 year) and sex to a general population control residing in Olmsted County and free of PD, other parkinsonism, or tremor of any type in the index year (year of onset of PD in the matched case). The list of all county residents from which potential controls were randomly drawn was provided by the medical records-linkage system.[17] This list has been shown to be complete by comparison with a random-digit-dialing telephone sample and with the census.[17] Records of potential controls were reviewed by a neurologist (D.M.M.) to exclude the presence of PD, other types of parkinsonism, or tremor of any type before or during the index year. The presence of dementia or other neurologic diseases was not an exclusion criterion. Our exclusion of parkinsonism in controls through medical record review was found to be valid compared with a direct examination by a movement disorders specialist, as reported elsewhere.[16]

Ascertainment of constipation. The complete medical records of cases and controls, which are routinely linked and stored in the medical records-linkage system of the Rochester Epidemiology Project,[17] were reviewed and abstracted by a physician (R.S.) to ascertain the occurrence of constipation. Constipation was defined by the presence of at least 1 of 2 criteria: 1) a diagnosis of constipation in the medical records; or 2) the use of drugs to treat constipation (laxatives) even in the absence of a recorded diagnosis. We abstracted data for constipation in chronological order starting from the first available record through the onset of PD (or the index year).

To assess severity, we collected additional information on the referral of patients to a gastroenterologist (need for specialist care) and on the use of laxatives (need for treatment). In addition, we abstracted data on the concomitant use of constipation-inducing drugs (calcium-containing antacids, medications with anticholinergic effects, antidepressants, calcium channel blockers, cholestyramine, clonidine, diuretics, levodopa, narcotics, nonsteroidal antiinflammatory drugs, psychotropics, and sympathomimetics). Only occurrences of constipation documented in the medical record before the index year were accepted as exposure. To avoid a possible bias in the definition of constipation (exposure suspicion bias),[18] we included only subjects who were given a diagnosis of constipation by their caregiving physician (historically, at the time of medical evaluation) or were prescribed laxatives (in the absence of a diagnosis). We did not assign new diagnoses retrospectively and did not modify the historical diagnoses based on current criteria or practices.

To validate our abstracting procedure for constipation, a second physician (not a coauthor) who was kept unaware of the case or control classification of subjects reabstracted the complete medical records for a random sample of 20 study subjects (approximately 5% of all cases and controls). The interrater agreement on presence or absence of constipation was 90.0% (positive agreement for 5 pairs and negative agreement for 13 pairs) with a kappa value of 0.76 (95% confidence interval [CI] 0.46 to 1.00). This small study suggests that our abstracting procedure was reliable.

Data analysis. Consistent with our design, matched-pairs analyses were performed using conditional logistic regression, and the odds ratio (OR) was used to estimate the relative risk. For each variable, we calculated an OR, a 95% CI, and a p value (two-tailed test, alpha = 0.05). We conducted a set of primary analyses without adjustment and an additional set of secondary analyses adjusted by smoking and coffee consumption (ever vs never). Smoking and coffee consumption were considered potential confounding variables because they have been found to be associated with impaired gastrointestinal function,[19,20] and with a reduced risk of PD.[21,22] Because of incomplete data on smoking and coffee consumption, these adjusted analyses were conducted ignoring the matching and including age (age at index year in quartiles) and sex in the regression models to remove residual confounding.

In a sensitivity analysis, we restricted the definition of constipation to patients who were not using constipation-inducing drugs. In addition, to investigate severity of constipation, we performed analyses restricted to those subjects who ever used laxatives or who were ever referred to a gastroenterologist. We also conducted analyses stratified by sex, age at onset of PD (≤71 vs >71 years; median cutoff), and for PD with or without rest tremor.[23] To explore the effect of constipation experienced across life, we also conducted analyses stratified by lag time between onset of constipation (first diagnosis or first use of laxatives) and onset of PD (0 to 19 years vs 20 or more years before the onset of PD or index date) and analyses stratified by age at time of onset of constipation (0 to 49 years old vs 50 years or older). All analyses were performed using SAS® version 9 (SAS Institute, Cary, NC).

Standard protocol approvals, registrations, and patient consent. The study was approved by the institutional review boards of the Mayo Clinic and of Olmsted Medical Center. Written informed consent was not required for passive medical record review.

Table Association between Parkinson disease (PD) and preceding constipation (196 cases and 196 controls)

	Exposure frequency		Primary model*		Fully adjusted model†	
Definitions of constipation and strata	Cases, n (%)	Controls, n (%)	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value
Constipation, overall	71 (36.2)	40 (20.4)	2.48 (1.49, 4.11)	0.0005	2.18 (1.32, 3.61)	0.003
Constipation not caused by medication‡	58 (29.6)	36 (18.4)	2.00 (1.20, 3.34)	0.008	1.77 (1.04, 2.98)	0.03
Required laxatives	31 (15.8)	16 (8.2)	2.07 (1.09, 3.92)	0.03	2.17 (1.09, 4.32)	0.03
Required specialist	3 (1.5)	1 (0.5)	3.00 (0.31, 28.84)	0.34	2.40 (0.23, 24.87)	0.46
Stratified analyses§						
Men	34 (28.1)	22 (18.2)	1.92 (0.98, 3.76)	0.06	1.86 (0.94, 3.68)	0.07
Women	37 (49.3)	18 (24.0)	3.38 (1.53, 7.43)	0.003	3.18 (1.45, 6.98)	0.004
Onset of PD ≤71 y‖	24 (24.7)	12 (12.4)	2.20 (1.04, 4.64)	0.04	2.14 (0.93, 4.91)	0.07
Onset of PD >71 y‖	47 (47.5)	28 (28.3)	2.73 (1.37, 5.44)	0.004	2.17 (1.14, 4.13)	0.02
PD with rest tremor	55 (36.9)	31 (20.8)	2.50 (1.40, 4.46)	0.002	2.33 (1.31, 4.17)	0.004
PD without rest tremor	10 (27.0)	7 (18.9)	1.60 (0.52, 4.89)	0.41	1.43 (0.41, 4.98)	0.58
Time between onset of constipation and index year¶						
No constipation	125 (63.8)	156 (79.6)	1.00 (reference)	—	1.00 (reference)	—
0–19 years before index year	37 (18.9)	23 (11.7)	2.18 (1.20, 3.96)	0.01	1.96 (1.05, 3.65)	0.03
≥20 years before index year	34 (17.4)	17 (8.7)	2.98 (1.48, 6.03)	0.002	2.49 (1.24, 5.01)	0.01
Age at onset of constipation¶						
No constipation	125 (63.8)	156 (79.6)	1.00 (reference)	—	1.00 (reference)	—
Age 0–49 years	31 (15.8)	16 (8.2)	2.49 (1.28, 4.83)	0.007	2.26 (1.11, 4.59)	0.02
Age 50 years or older	40 (20.4)	24 (12.2)	2.46 (1.30, 4.67)	0.006	2.12 (1.15, 3.93)	0.02

*Analyses reflecting the case-control matching by age and sex. These analyses were considered primary because they were consistent with the fully adjusted models and did not have any missing values.
†Analyses adjusted for smoking (ever/never) and coffee consumption (ever/never). Because of missing information, the individual matching was ignored and the models included sex and age at index year (in quartiles). These analyses were considered secondary.
‡Analysis excluding constipation in subjects who were using constipation-inducing drugs (calcium-containing antacids, medications with anticholinergic effects, antidepressants, calcium channel blockers, cholestyramine, clonidine, diuretics, levodopa, narcotics, nonsteroidal antiinflammatory drugs, psychotropics, and sympathomimetics).
§None of the stratified primary analyses yielded a significant test for interaction ($p = 0.29$ for sex; $p = 0.68$ for age at time of onset of PD; $p = 0.49$ for rest tremor).
‖Analyses stratified using the median age at onset of PD in our sample as cutoff.
¶Onset of constipation was defined as the time of first diagnosis or of first use of laxatives.
CI = confidence interval.

RESULTS We identified 202 patients who developed PD from 1976 through 1995 (incident cases). These patients were matched by age and sex with 202 controls. However, 6 individuals (5 cases and 1 control) did not authorize the use of their medical records for research and the corresponding pairs could not be studied. Therefore, we included 196 case-control pairs for a total of 392 individuals. Among the cases, 121 (61.7%) were men and 75 (38.3%) were women; the median age at time of onset of PD was 71 years (range 41 to 97 years). The distribution by age and sex was similar in controls due to the matched design. The median duration of enrollment in the medical records-linkage system preceding the index year was 38 years (range 2 to 73 years) for cases and 38 years (range <1 to 73 years) for controls (Wilcoxon signed rank test, $p = 0.35$).

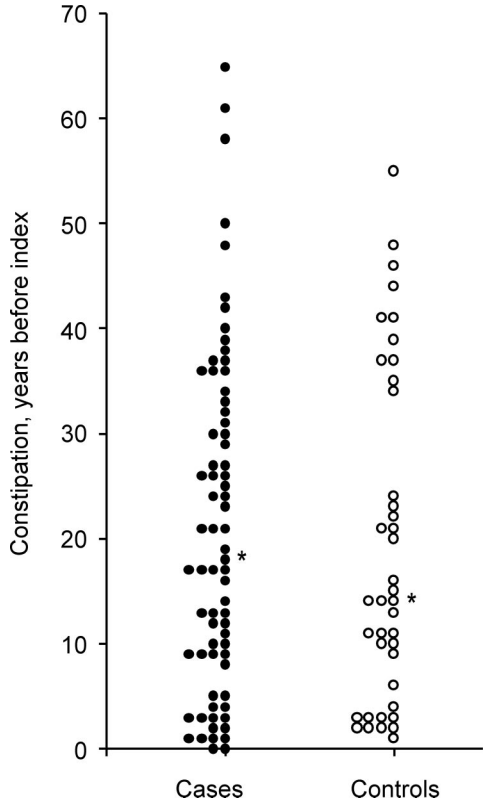
The table shows the results of our case-control analyses without adjustment (primary models) and with adjustment for smoking and coffee consumption (fully adjusted models). Seventy-one (36.2%) cases and 40 (20.4%) controls had constipation (OR 2.48; 95% CI 1.49 to 4.11; $p = 0.0005$). The association was confirmed after excluding constipation in subjects who were using constipation-inducing drugs (OR 2.00; 95% CI 1.20 to 3.34; $p = 0.008$). In addition, the association was confirmed after restricting the definition of constipation to subjects who used laxatives (OR 2.07; 95% CI 1.09 to 3.92; $p = 0.03$). Results were consistent in all adjusted analyses

including smoking and coffee consumption in the models (table, right columns). No significant differences were observed between strata by sex, age at onset of PD (≤71 vs >71 years), and for PD with or without rest tremor.

The association was stronger in women (OR 3.38; 95% CI 1.53 to 7.43; $p = 0.003$) than in men (OR 1.92; 95% CI 0.98 to 3.76; $p = 0.06$); however, the difference was not significant. In addition, the association did not differ significantly for early vs late onset of PD and for patients with or without rest tremor (see table, footnote §).

Our analyses showed similar associations between constipation and PD regardless of the time interval between the onset of constipation and the onset of PD (or index year). Indeed, we found an association both for constipation starting 20 or more years before PD onset (OR 2.98; 95% CI 1.48 to 6.03; $p = 0.002$) and for constipation starting within 20 years of PD onset or index year (OR 2.18; 95% CI 1.20 to 3.96; $p = 0.01$; p for interaction = 0.44). The figure shows that the distribution in cases was shifted toward longer lag times between onset of constipation and index year compared with controls; however, this difference was not significant. The association was also similar in 2 strata defined by age at the time of onset of constipation (table).

Figure **Distribution of the lag time between onset of constipation and onset of motor symptoms of Parkinson disease (or index year for controls)**



Each dot represents the lag time for a given case or control rounded to single years. The asterisk indicates the median. The distribution was shifted toward longer lag times in cases (median 17.9 years; range <1.0 to 65.2) compared with controls (median 14.0 years; range <1.0 to 54.9; Wilcoxon rank sum test, $p = 0.63$).

DISCUSSION Our findings may suggest that constipation is an early manifestation of the neurodegenerative process underlying PD, and that it frequently precedes the classic motor signs of PD by several decades in both men and women. This is consistent with the findings restricted to men from the Honolulu-Asia Aging Study. In that cohort study, men who reported less frequent bowel movements experienced an increased risk of PD,[10,11] of incidental Lewy body disease (presumed to reflect preclinical PD),[12] and of reduced neuronal density in the substantia nigra.[13]

The early occurrence of constipation is biologically plausible and consistent with the predictions of the Braak staging.[14] The earliest neuropathologic features of PD are found not only in the lower brainstem and olfactory bulbs, but also in the autonomic nervous system, including the gastrointestinal tract.[24,25] Indeed, Lewy bodies have frequently been reported in the autonomic nervous system of persons with incidental Lewy body disease, which is thought to reflect preclinical PD (Braak stages 1–2).[14,26-29] This contrasts with the later involvement of the substantia nigra, the substrate for the motor findings of PD, which becomes manifest only during more advanced Braak stages (Braak stages 3–4). In addition, the Honolulu-Asia Aging Study showed incidental Lewy bodies in the locus ceruleus and substantia nigra of subjects with constipation who died free of PD.[12] Finally, the Honolulu-Asia Aging Study showed that subjects with constipation who did not smoke had a reduced neuronal density in the substantia nigra, independent of the presence of Lewy bodies (after adjustment for PD and incidental Lewy bodies).[13]

The association between constipation and PD was evident several decades before the onset of PD. Indeed, the association remained significant when restricted to constipation documented more than 20 years before the onset of motor symptoms. This extends the findings from the Honolulu-Asia Aging Study where there was a mean of 12 years between the documentation of constipation and the subsequent development of PD.[10] This early link with constipation suggests that the neurodegenerative process underlying PD may begin more than 2 decades prior to the onset of motor symptoms of PD. A similar time frame has been reported for the associa-

tion of anxiety disorders preceding PD.[30] Similarly, REM sleep behavior disorder, another nonmotor manifestation of PD, was reported to precede PD by an average of nearly 13 years.[31]

These estimates of the duration of premotor PD are longer than the estimates derived from neuropathologic or imaging studies of the substantia nigra. In particular, neuropathologic extrapolation predicted a 4.6-year preclinical state,[32] and dopaminergic imaging estimated an approximate 6-year premotor interval.[33-36]

Despite the biologic plausibility of the hypothesis that constipation is an early nonmotor manifestation of PD, there are alternative explanations for this association. For example, both constipation and PD could be independent manifestations of a third unknown risk factor (e.g., a certain dietary preference or physical activity) or of a genetic susceptibility (e.g., one or several genetic variants). In addition, constipation may have an indirect causal role in PD by increasing the intestinal absorption of some unidentified substances that are toxic for the substantia nigra.[37] However, the evidence in support of these alternative interpretations remains limited.[10]

Our study has several strengths. First, it was based on a series of incident PD cases and on well-defined general population controls, thus reducing referral bias and incidence-prevalence bias.[18] Second, we were able to avoid recall bias by considering episodes of constipation or of use of laxatives that were historically documented in medical records before the onset of PD (or the index year).[18] Third, we carefully excluded from our case series patients affected by other types of parkinsonism with early autonomic failure, such as multiple system atrophy.[38] Fourth, our study included men and women, thus providing the opportunity to explore differences across sex, and also to extend the Honolulu-Asia Aging Study results, which were restricted to men.[10,11] Fifth, we conducted a set of secondary analyses to exclude 2 possible confounders, smoking and coffee consumption, which have been associated with PD and with constipation.[19-22] However, neither of these 2 potential confounders modified the association. Similarly, smoking and coffee consumption also failed to modify the association between bowel movement frequency and PD in the Honolulu-Asia Aging Study.[11] Finally, the use of historical medical records in the medical records-linkage system facilitated the study of episodes of constipation that occurred several decades before the motor onset of PD. This time frame was important to explore the possible lag time between onset of constipation and onset of motor symptoms of PD.

On the other hand, the study has several limitations. First, it is possible that some subjects did not bring constipation to the attention of medical personnel or were treated at a medical facility outside of the medical records-linkage system, and thus were not documented in the system. Second, we cannot exclude the possibility of underascertainment of constipation because the physicians did not use a systematic approach or a formal questionnaire to assess gastrointestinal symptoms. In particular, physicians may not have queried the patients about symptoms of defecatory dysfunction. By contrast, some subjects may have overreported constipation because constipation was not confirmed using, for example, a stool diary.[9] Because this overreporting or underreporting occurred historically before we designed our study, it should be symmetric between cases and controls (nondifferential over- or underascertainment). In addition, the frequency of constipation observed in our controls (20.4%) was similar to or higher than the frequency observed in the overall population of Olmsted County (8.0%) or in the United States (12% to 19%),[39,40] and our findings were consistent with a higher frequency of constipation in women than men, as reported by others.[39] Third, it is possible that patients with constipation were under more intensive medical care than subjects of the same age but without constipation (surveillance bias). However, the significant association for constipation experienced 20 or more years before the onset of motor symptoms of PD cannot be easily explained by a short-term surveillance bias. Fourth, information about physical activity or diet at the time of onset of constipation was not available from the medical records, and could not be considered in adjusted analyses. Finally, as part of this case-control study, we also investigated erectile dysfunction as another autonomic symptom that could precede the motor onset of PD in men. However, we did not find an association (results not shown).

AUTHOR CONTRIBUTIONS

Statistical analyses were conducted by J.M. Carlin and B.R. Grossardt.

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DISCLOSURE

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the prediction of Parkinson disease and the treatment of neurodegenerative disease; has received license fee payments and royalty payments from Alnylam Pharmaceuticals (Method to treat Parkinson's disease); and receives research support from the NIH [ES10751 (PI)]. Dr. Bharucha has served on scientific advisory boards for Novartis and Pfizer Inc.; serves on editorial advisory boards for the *American Journal of Gastroenterology*, the *International Foundation for Functional Gastrointestinal Disorders*, and *Neurogastroenterology and Motility*; has served as a consultant to Amylin Pharmaceuticals, American Medical Systems, Nordic Biotech, Helsinn Healthcare, and Merck Serono; and receives research support from Pfizer Inc., Novartis, Sucampo Pharmaceuticals, and the NIH/NIDDK [DK 78924 (PI), PO1 DK 68055 (PI of Project 3)]. Dr. Rocca receives research support from the NIH [AR030582 (PI), AG006786 (Co-I), and ES010751 (Co-I)].

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Editor's Note to Authors and Readers: Levels of Evidence coming to *Neurology*®

Effective January 15, 2009, authors submitting Articles or Clinical/Scientific Notes to *Neurology*® that report on clinical therapeutic studies must state the study type, the primary research question(s), and the classification of level of evidence assigned to each question based on the classification scheme requirements shown below (left). While the authors will initially assign a level of evidence, the final level will be adjudicated by an independent team prior to publication. Ultimately, these levels can be translated into classes of recommendations for clinical care, as shown below (right). For more information, please access the articles and the editorial on the use of classification of levels of evidence published in *Neurology*.[1-3]

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Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III. All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV. Studies not meeting Class I, II, or III criteria including consensus or expert opinion.

AAN classification of recommendations

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.