Appendix A. Major Parkinson's Disease Rating Scales

Numerous rating scales and diagnostic criteria are used to evaluate the severity of PD. While the most common scale in current use is the UPDRS, many of the studies in the database reported other scales. This section provides a brief description of the major scales and diagnostic criteria that are used to evaluate clinical severity of PD.

List of Scales Used:

1. Unified Parkinson Disease Rating Scale (UPDRS)
2. Abnormal Involuntary Movements Scale (AIMS Score)
3. Activities of Daily Living (ADL)
4. Barthel Index
5. Beck Depression Inventory
6. Brief Psychiatric Rating Scale (BPRS)
7. Columbia University Rating Scale (CURS)
8. Dyskinesia rating scale
9. Hamilton Depression Scale (HAM-D)
10. Hoehn and Yahr Clinical Staging Scale
11. Levodopa Equivalent Units (LEU)
12. Mini-Mental Status Exam (MMSE)
13. Northwestern University Disability Scale (NUDS or NWUDS)
14. Phenyl Ethyl Alcohol or Detection Threshold (PEA)
15. Parkinson Psychosis Rating Scale (PPRS)
16. Proposed Diagnostic Criteria for Parkinson Disease
17. Schwab & England Activities of Daily Living Scale (S&E) and (SEADL)
18. Sickness Impact Profile (SIP)
19. UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria
20. University of Pennsylvania Smell Identification Test (UPSIT)
21. Webster's Parkinson's Disease Rating Scale (WPDRS)

Unified Parkinson Disease Rating Scale (UPDRS)[1]

The UPDRS is a rating tool to follow the longitudinal course of Parkinson's Disease. A total of 199 points are possible. 199 represents the worst (total) disability, 0 indicates no disability.

UPDRS is made up of three distinct subscales:

I. Mentation, behavior, and mood
II. Activities of daily living (ADL) during "off" and "on" periods
III. Motor function during "on" periods

A fourth subscale is also sometimes used:

IV. Complications of therapy (In the past week)

Sections composing each subscale are usually 0-4 points.

These scores are calculated by interviewing the patient. Some sections require multiple grades assigned to each extremity.

I. MENTATION, BEHAVIOR, AND MOOD

1. Intellectual Impairment

0 = None.

1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.

2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.

3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.

4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.

4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression

0 = None

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.

2 = Sustained depression (1 week or more).

3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).

4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

0 = Normal.

1 = Less assertive than usual; more passive.

2 = Loss of initiative or disinterest in elective (nonroutine) activities.

3 = Loss of initiative or disinterest in day to day (routine) activities.

4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (ADL) for both "off" and "on"

5. Speech

0 = Normal.

1 = Mildly affected. No difficulty being understood.

2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

6. Salivation

0 = Normal.

1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal.

1 = Rare choking.

2 = Occasional choking.

3 = Requires soft food.

4 = Requires NG tube or gastrotomy feeding.

8. Handwriting

0 = Normal.

1 = Slightly slow or small.

2 = Moderately slow or small; all words are legible.

3 = Severely affected; not all words are legible.

4 = The majority of words are not legible.

9. Cutting food and handling utensils

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can cut most foods, although clumsy and slow; some help needed.

3 = Food must be cut by someone, but can still feed slowly.

4 = Needs to be fed.

10. Dressing

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Occasional assistance with buttoning, getting arms in sleeves.

3 = Considerable help required, but can do some things alone.

4 = Helpless.

11. Hygiene

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Needs help to shower or bathe; or very slow in hygienic care.

3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.

4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can turn alone or adjust sheets, but with great difficulty.

3 = Can initiate, but not turn or adjust sheets alone.

4 = Helpless.

13. Falling (unrelated to freezing)

0 = None.

1 = Rare falling.

2 = Occasionally falls, less than once per day.

3 = Falls an average of once daily.

4 = Falls more than once daily.

14. Freezing when walking

0 = None.

1 = Rare freezing when walking; may have start hesitation.

2 = Occasional freezing when walking.

3 = Frequent freezing. Occasionally falls from freezing.

4 = Frequent falls from freezing.

15. Walking

0 = Normal.

1 = Mild difficulty. May not swing arms or may tend to drag leg.

2 = Moderate difficulty, but requires little or no assistance.

3 = Severe disturbance of walking, requiring assistance.

4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)

0 = Absent.

1 = Slight and infrequently present.

2 = Moderate; bothersome to patient.

3 = Severe; interferes with many activities.

4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism

0 = None.

1 = Occasionally has numbness, tingling, or mild aching.

2 = Frequently has numbness, tingling, or aching; not distressing.

3 = Frequent painful sensations.

4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech

0 = Normal.

1 = Slight loss of expression, diction and/or volume.

2 = Monotone, slurred but understandable; moderately impaired.

3 = Marked impairment, difficult to understand.

4 = Unintelligible.

19. Facial Expression

0 = Normal.

1 = Minimal hypomimia, could be normal "Poker Face".

2 = Slight but definitely abnormal diminution of facial expression

3 = Moderate hypomimia; lips parted some of the time.

4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

0 = Absent.

1 = Slight and infrequently present.

2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present most of the time.

4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

0 = Absent.

1 = Slight; present with action.

2 = Moderate in amplitude, present with action.

3 = Moderate in amplitude with posture holding as well as action.

4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

0 = Absent.

1 = Slight or detectable only when activated by mirror or other movements.

2 = Mild to moderate.

3 = Marked, but full range of motion easily achieved.

4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)

0 = Normal.

1 = Slow; or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

28. Posture

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)

0 = Not disabling.

1 = Mildly disabling.

2 = Moderately disabling.

3 = Severely disabling.

4 = Completely disabling.

34. Painful Dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.

1 = Slight.

2 = Moderate.

3 = Severe.

4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)

0 = No

1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?

0 = No

1 = Yes

37. Are "off" periods unpredictable?

0 = No

1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?

0 = No

1 = Yes

39. What proportion of the waking day is the patient "off" on average?

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?

0 = No

1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?

0 = No

1 = Yes

42. Does the patient have symptomatic orthostasis?

(Record the patient's blood pressure, height and weight on the scoring form)

0 = No

1 = Yes

AIMS Score (Abnormal Involuntary Movements Scale)[2]

This scale requires the examiner to observe the patient sitting quietly at rest and again while the patient carries out selected motor tasks (mouth opening, tongue protrusion, finger taps, and walking, among others). Seven body areas are rated: muscles of facial expression, lips and perioral area, jaw, tongue, upper and lower extremities, and trunk. A five-point scheme ranging from 0 (normal) to 4 (severe) is used to assess each body part. The worst dyskinesias seen in each body part are rated for the intensity of the movement and the chosen rating score is reduced by one point if that body region has dyskinesias during the quiet rest phase of the observation. There are also three global rating scales to complete: overall severity, incapacitation for the patient, and the patient's awareness of the dyskinesias. Finally, two interview questions for the patient concentrate on dental hygiene and the wearing of dentures.

Activities of Daily Living (ADL)[3]

The ADL scale measures the impact of PD on 14 categories, including:

- Speech
- Salivation
- Swallowing

- Handwriting
- Cutting food and handling utensils
- Dressing
- Hygiene
- Turning in bed and adjusting bedclothes
- Falling
- Freezing when walking
- Walking
- Left-sided tremor
- Right-sided tremor
- Sensory complaints.

Each category is scored on a 0-4 scale, with 0 indicating normal or unaffected functioning, and 4 signifying a patient who is helpless or non-ambulatory. For example, the response scale for cutting food and handling utensils is as follows:

0 = Normal

1 = Somewhat slow and clumsy, but no help needed

2 = Can cut most foods, although clumsy and slow; some help needed

3 = Food must be cut by someone, but can still feed slowly

4 = Needs to be fed

The scores for the 14 categories are summed to give an overall ADL score. The overall score ranges from 0 to 56, with higher scores reflecting greater disability and the need for assistance.

Barthel Index[4]

Full credit is not given for an activity if the patient needs even minimal help/supervision. A score of 0 is given when patient cannot meet criteria as defined.

1. Feeding

A(10 pts). Independent; feeds self from tray or table; can put on assistive device if needed; accomplishes feeding in reasonable time.

B(5 pts). Assistance necessary with cutting food, etc.

C(0 pts). Cannot meet criteria

2. Moving (from wheelchair to bed and return)

A(15 pts). Independent in all phases of this activity.

B(10 pts). Minimal help needed or patient needs to be reminded or supervised for safety of 1 or more parts of this activity.

C(5 pts). Patient can come to sitting position without help of second person but needs to be lifted out of bed and assisted with transfers.

D(0 pts). Cannot meet criteria

3. Personal Toilet

A(5pts). Can wash hands, face; combs hair, cleans teeth. Can shave (males) or apply makeup (females) without assistance; females need not brain or style hair.

B(0 pts). Cannot meet criteria

4. Getting On and Off Toilet

A(10 pts). Able to get on and off toilet, fastens/unfastens clothes, can use toilet paper without assistance. May use wall bar or other support if needed; if bedpan necessary patient can place it on chair, empty, and clean it.

B(5 pts). Needs help because of imbalance or other problems with clothes or toilet paper.

C(0 pts). Cannot meet criteria

5. Bathing Self

A(5 pts). May use bath tub, shower or sponge bath. Patient must be able to perform all functions without another person being present.

B(0 pts). Cannot meet criteria

6. Walking on Level Surface

A(15 pts). Patient can walk at least 50 yards without assistance or supervision; may use braces, prostheses, crutches, canes, or walkerette but not a rolling walker. Must be able to lock/unlock braces, assume standing or seated position, get mechanical aids into position for use and dispose of them when seated (putting on and off braces should be scored under dressing). 15

B(10pts). Assistance needed to perform above activities, but can walk 50 yards with little help.

C(0 pts). Cannot meet criteria

7. Propelling a Wheelchair

Do not score this item if patient gets score for walking.

A(5 pts). Patient cannot ambulate but can propel wheelchair independently; can go around corners, turn around maneuver chair to table, bed toilet, etc. Must be able to push chair 50 yards.

B(0 pts). Cannot meet criteria

8. Ascending and Descending Stairs

A(10 pts). Able to go up and down flight of stairs safely without supervision using canes, handrails, or crutches when needed and can carry these items as ascending/descending.

B(5 pts). Needs help with or supervision of any of the above items.

C(0 pts). Cannot meet criteria

9. Dressing/Undressing

A(10 pts). Able to put on, fasten and remove all clothing; ties shoelaces unless necessary adaptions used. Activity includes fastening braces and corsets when prescribed; suspenders, loafer shoes and dresses opening in the front may be used when necessary.

B(5 pts). Needs help putting on, fastening, or removing clothing; must accomplish at least half of task alone within reasonable time; women need not be scored on use of brassiere or girdle unless prescribed.

C(0 pts). Cannot meet criteria

10. Continence of Bowels

A(10 pts). Able to control bowels and have no accidents. Can use a suppository or take an enema when necessary (as for spinal cord injury patients who have had bowel training)

B(5 pts). Needs help in using a suppository or taking an enema or has occasional accidents.

C(0 pts). Cannot meet criteria

11. Controlling Bladder

A(10 pts). Able to control bladder day and night. Spinal injury patients must be able to put on external devices and leg bags independently, clean and empty bag, and must stay dry day and night.

B(5 pts). Occasional accidents occur, cannot wait for bed pan, does not get to toilet in time or needs help with external device.

C(0 pts). Cannot meet criteria.

Beck Depression Inventory[5]

This is a twenty question survey to be completed by the patient. Answers are scored on 0 to 3 scale, 0 = minimal, and 3 = severe.

1. Sadness
2. Hopelessness
3. Past failure
4. Anhedonia
5. Guilt
6. Punishment
7. Self-dislike
8. Self-blame
9. Suicidal thoughts
10. Crying

11. Agitation
12. Loss of interest in activities
13. Indecisiveness
14. Worthlessness
15. Loss of energy
16. Insomnia
17. Irritability
18. Decreased appetite
19. Diminished concentration
20. Fatigue
21. Lack of interest in sex

<15 = Mild Depression
15-30 = Moderate Depression
>30 = Severe Depression

Brief Psychiatric Rating Scale (BPRS)[6]

This scale consists of 24 symptom constructs, each to be rated in a 7-point scale of severity ranging from 1 (not present) to 7 (extremely severe). Total score ranges from 24-168, with higher scores indicating more severe psychosis.

1. Somatic concern
2. Anxiety
3. Depression
4. Suicidality
5. Guilt
6. Elated
7. Grandiosity

8. Suspiciousness
9. Hallucinations
10. Unusual thought content
11. Bizarre behavior
12. Self-neglect
13. Disorientation
14. Conceptual disorganization
15. Blunted affect
16. Emotional withdrawal
17. Motor retardation
18. Tension
19. Uncooperativeness
20. Excitement
21. Distractibility
22. Motor hyperactivity
23. Mannerisms and posturing

Columbia University Rating Scale (CURS)[7]

This scale was presented in 1970 by researchers from Columbia University who used it in their initial L-dopa trials. Total scores range from 0-65, 0 is normal and 65 is maximum disability. This scale was a modification of the Webster scale (see page C22), which was published in 1968. In addition to the activities measured in the Webster scale, this scale also measures salivation, arising from a chair, postural stability and rapid movements of fingers, hands and feet. Subsequent modifications of this scale include NYU Scale and Kings College Hospital Scale.

1. Facial Expression

0 = Normal

1 = Minimal hypomimia, could be normal ‘poker face’

2 = Slight but definitely abnormal dimunition of facial expression

3 = Moderate hypomimia

4 = Masked or fixed facies with severe or complete loss of facial expression

2. Seborrhea

0 = Normal

1 = Greasy forehead, no dermatitis

2 = Mild dermatitis, erythema, and scaling

3 = Moderate dermatitis

4 = Severe dermatitis

3. Sialorrhea

0 = None

1 = Slight but definite excess of saliva in pharynx (patients may be unaware of it); no drooling

2 = Moderately excessive saliva with minimal drooling, if any

3 = Marked excess of saliva with some drooling

4 = Marked drooling, requiring special measures

4. Speech Disorder

0 = Normal

1 = Slight loss of expression, diction, and/or volume

2 = Monotone, slurred but understandable

3 = Marked impairment, difficult to understand

4 = Unintelligible

5. **Arising from chair** (with straight back)

   0 = Normal

   1 = Slow

   2 = Pushes self up from arms or seat

   3 = Tends to fall back and may have to try several times but can get up without help

   4 = Unable to arise without help

6. **Posture**

   0 = Normal erect

   1 = Not quiet erect, slightly stooped, could be normal for older people

   2 = Moderate simian posture, definitely abnormal

   3 = Marked simian posture with kyphosis

   4 = Severe flexion with extreme abnormality of posture

7. **Postural Stability** (If Romberg is normal, judge response to sudden posterior displacement produced by push of sternum)

   0 = Normal

   1 = Retropulsion, but recovers unaided

   2 = Absence of postural response; would fall if not caught

   3 = Very unstable, tends to fall

   4 = Unable to stand without assistance

8. **Gait Disturbance**

   0 = Freely ambulatory, good stepping, turns readily

   1 = Walks slowly, may shuffle with short steps; no festination or propulsion

   2 = Walks with great difficulty, with festination, short steps; shows freezing and pulsing but requires little or no assistance

3 = Severe disturbance, requires frequent assistance

4 = Cannot walk, even with help

9. **Tremor** (Head and four limbs are scored separately; maximum score = 20.)

   0 = Absent

   1 = Slight and infrequently present

   2 = Moderate in amplitude but only intermittently present

   3 = Moderate and present most of the time

   4 = Marked in amplitude and present most of the time

10. **Finger Dexterity** (Tested in both hands; maximum score = 8; patients taps thumb with forefinger, then with each finger in rapid succession.)

    0 = No dysfunction

    1 = Slightly slow, may be normal

    2 = Definite dysfunction

    3 = Very slow with frequent errors

    4 = Unable to perform test

11. **Succession Movements** (Tested in both hands; maximum score = 8; patient taps knees alternatively with palm and dorsum of hands.)

    0 = No dysfunction

    1 = Slightly slow; may be normal

    2 = Definite dysfunction

    3 = Very slow with frequent errors

    4 = Unable to perform test

12. **Foot Tapping** (Tested in both feet; maximum sore = 8; using heel as fulcrum, patients taps floor with ball of foot.)

    0 = Normal

1 = Slightly slow

2 = Slow

3 = Markedly slow

4 = Unable to perform test

13. Bradykinesia (Combining both slowness and poverty of movement in general.)

0 = None

1 = Minimal slowness giving movement a deliberate character

2 = Mild degree of slowness and poverty of movements; definitely abnormal

3 = Moderate slowness; occasional hesitation on initiating movements and arrests of ongoing movements

4 = Marked slowness and poverty of movement; frequent freezing and long delays in initiating movements

Dyskinesia Rating Scale[8]

Several variations of the rating scale for dyskinesia are used. This Dyskinesia Scale Score is the arithmetic mean of the intensity and duration scores, and is only assessed in the "on" state.

The intensity score is given as score and definition:

0 = absent

1 = minimal severity: patient is not aware of dyskinesias

2 = patient is conscious of the presence of dyskinesias but there is no interference with voluntary motor acts

3 = dyskinesias may impair voluntary movements but patient is normally capable of undertaking most motor tasks

4 = intense interference with movement control, and daily life activities are greatly limited

5 = violent dyskinesias, incompatible with any normal motor task

The duration score is given as score and definition:

0 = absent

1 = only present when carrying out motor tasks

2 = present between 25-50% of waking hours

3 = present between 51-75% of waking hours

4 = present between 76-99% of waking hours

5 = continuous throughout the day, 100%

Hamilton Depression Scale (HAM-D)[9]

This is a twenty one question survey to be completed by a physician. The range is 0-64 points, higher score = more severe depression.

1. Depressed mood (0 to 4)
2. Feelings of guilt (0 to 4)
3. Suicide (0 to 4)
4. Insomnia
    5. Early (0 to 2)
    6. Middle (0 to 2)
    7. Late (0 to 2)
8. Work activities (0 to 4)
9. Retardation to stupor (0 to 4)
10. Agitation (0 to 2)
11. Fear (0 to 4)
12. Anxiety (0 to 4)
13. Gastrointestinal symptoms (0 to 2)
14. Systemic somatic symptoms (0 to 2)

15. Decreased libido or menstrual disturbance (0 to 2)

16. Hypochondiasis (0 to 4)

17. Weight loss (0 to 2)

18. Diminished insight (0 to 2)

19. Symptom diurnal variation (1 to 2)

20. Feelings of unreality (0 to 4)

21. Paranoid symptoms (0 to 3)

22. Obsessive Compulsive Symptoms (0 to 2)

10-13: Mild depression
14-17: Moderate depression
>17: Severe depression

Hoehn and Yahr Clinical Staging Scale[10]

Stages I-V, lower stage indicates better function.

Stage I.
Unilateral involvement only, usually with minimal or no functional impairment.

Stage II.
Bilateral or midline involvement, without impairment of balance.

Stage III.
First sign of impaired righting reflexes. This is evident by unsteadiness as the patient turns or is demonstrated when he is pushed from standing equilibrium with the feet together and eyed closed. Functionally the patient is somewhat restricted in his activities but may have some work potential depending upon the type of employment. Patients are physically capable of leading independent lives, and their disability is mild to moderate.

Stage IV.
Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.

Stage V.
Confinement to bed or wheelchair unless aided.

Modified Hoehn and Yahr Staging

Stage 0 = No signs of disease.

Stage 1 = Unilateral disease.

Stage 1.5 = Unilateral plus axial involvement.

Stage 2 = Bilateral disease, without impairment of balance.

Stage 2.5 = Mild bilateral disease, with recovery on pull test.

Stage 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

Stage 4 = Severe disability; still able to walk or stand unassisted.

Stage 5 = Wheelchair bound or bedridden unless aided.

This rating system has been largely replaced by the Unified Parkinson's Disease Rating Scale (UPDRS).

Levodopa Equivalent Units (LEU)[11]

Conversion formula:

100 LEU = 100 mg regular L-dopa, given with a peripheral decarboxylase inhibitor = 133 mg L-dopa plus DCI in controlled-release tablets = 10 mg bromocriptine = 1 mg pergolide mesylate.

Mini-Mental Status Exam (MMSE)[12]

Range 0-30, lower scores indicate more severe impairment.

This scale is widely used for assessing cognitive mental status. As a clinical instrument, the MMSE has been used to detect impairment, follow the course of an illness, and monitor response to treatment. While the MMSE has limited specificity with respect to individual clinical syndromes, it represents a brief, standardized method by which to grade cognitive mental status. It assesses orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands. Furthermore, it provides a total score that places the individual on a scale of cognitive function.

Northwestern University Disability Scale (NUDS or NWUDS)[13]

Clinical experience suggested that the symptoms of Parkinson's Disease make themselves felt most frequently in the areas of walking, personal hygiene, dressing, eating and feeding, and

speaking. These five areas constitute the range of this scale. It was decided to assign a maximum of 20 points to each of the five sub-scales, in this way a total of 100 points is possible, so that the degree of disability may be expressed as a percentage. Lower score represents greater disability.

Scale A: Walking

Never Walks Alone

0 Cannot walk at all, even with maximum assistance.

1 Needs considerable help even for short distances; cannot walk outdoors with help.

2 Requires moderate help indoors; walks outdoors with considerable help.

3 Requires potential help indoors and active help outdoors.

Sometimes Walks Alone

4 Walks from room to room without assistance, but moves slowly and uses external support; never walks alone outdoors.

5 Walks from room to room with only moderate difficulty; may occasionally walk outdoors without assistance.

6 Walks short distances with ease; walking outdoors is difficult but often accomplished without help; rarely walks longer distances alone.

Always Walks Alone

7 Gait is extremely abnormal; very slow and shuffling; posture grossly affected; there may be propulsion.

8 Quality of gait is poor and rate is slow; posture moderately affected; there may be a tendency toward mild propulsion; turning is difficult.

9 Gait only slightly deviant from normal in quality and speed; turning is the most difficult task; posture essentially normal.

10 Normal.

Scale B: Dressing

Requires Complete Assistance

0 Patient is a hindrance rather than a help to assistant.

1 Movements of patient neither help nor hinder assistant.

2 Can give some help through bodily movements.

3 Gives considerable help through bodily movements.

Requires Partial Assistance

4 Performs only gross dressing activities alone (hat, coat).

5 Performs about half of dressing activities independently.

6 Performs more than half of dressing activities alone, with considerable effort and slowness.

7 Handles all dressing alone with the exception of fine activities (tie, buttons).

Complete Self-Help

8 Dresses self completely with slowness and great effort

9 Dresses self completely with only slightly more time and effort than normal

10 Normal

Scale C: Hygiene

Requires Complete Assistance

0 Unable to maintain proper hygiene even with maximum help.

1 Reasonably good hygiene with assistance, but does not provide assistant with significant help.

2 Hygiene maintained well; gives aid to assistant

Requires Partial Assistance

3 Performs a few tasks alone with assistant nearby.

4 Requires assistance for half of toilet needs.

5 Requires assistance for some tasks not difficult in terms of co-ordination.

6 Manages most of personal needs alone; has substituted methods for accomplishing difficult tasks (electric razor).

Complete Self-Help

7 Hygiene maintained independently, but with effort and slowness; accidents are not infrequent; may employ substitute methods.

8 Hygiene activities are moderately time-consuming; no substitute methods; few accidents.

9 Hygiene maintained normally, with exception of slight slowness.

10 Normal.

Scale D: Eating and Feeding

Eating

0 Eating is so impaired that a hospital setting is required to get adequate nutrition.

1 Eats only liquids and soft food; these are consumed very slowly.

2 Liquids and soft food handled with ease; hard foods occasionally eaten, but require great effort and much time.

3 Eats some hard food routinely, but these require time and effort.

4 Follows a normal diet, but chewing and swallowing are labored.

5 Normal

Feeding

0 Requires complete assistance.

1 Performs only a few feeding tasks independently.

2 Performs most feeding activities alone, slowly and with effort; requires help with specific tasks (cutting meat, filling cup).

3 Handles all feeding alone with moderate slowness; still may get assistance in specific situations (cutting meat in restaurant); accidents not infrequent.

4 Fully feeds self with rare accidents; slower than normal.

5 Normal

Scale E: Speech

0 Does not vocalize at all.

1 Vocalizes but rarely for communicative purposes.

2 Vocalizes to call attention to self.

3 Attempts to use speech for communication, but has difficulty in initiating vocalization; may stop speaking in middle of phrase and be unable to continue.

4 Uses speech for most of communication, but articulation is highly unintelligible; may have occasional difficulty in initiating speech; usually speaks in single words or short phrases.

5 Speech always employed for communication, but articulation is still very poor; usually uses complete sentences.

6 Speech can always be understood if listener pays close attention; both articulation and voice may be defective.

7 Communication accomplished with ease, although speech impairment detracts from content.

8 Speech easily understood, but voice or speech rhythm may be disturbed.

9 Speech entirely adequate; minor voice disturbances present.

10 Normal.

Phenyl Ethyl Alcohol or Detection Threshold (PEA)[14]

Detection threshold is a measure of the lowest concentration of a particular olfactory stimulus required to activate peripheral receptors and trigger the perception of the stimulus. To assess olfactory threshold, ascending (10^{-7} –1 mol) dilutions of phenyl-ethyl-alcohol are administered; the threshold value is defined as the lowest concentration that is perceived.

Parkinson Psychosis Rating Scale (PPRS)[15]

This scale was designed to assess the severity of specific symptoms of levodopa-induced psychosis in patients with Parkinson's disease.

Visual Hallucinations

1. Absent
2. Mild: Occasional; complete or partial insight; nonthreatening
3. Moderate: Frequent; absence of full insight; can be convinced; may be threatening
4. Severe: Persisitent hallucinations; no insight; associated with heightened emotional tone, agitation, agression

Illusions and Misidentification of Persons

1. Absent
2. Mild: Occurring infrequently
3. Moderate: Occurring very often
4. Severe: Occurring persistently

Paranoid Ideation (persecutory and/or jealous type)

1. Absent
2. Mild: Associated with suspiciousness
3. Moderate: Associated with tension and excitement
4. Severe: Accusations of family members, aggression and/or lack of cooperation (i.e., refusal to eat and/or take medication)

Sleep Disturbances

1. Absent
2. Mild: Associated with anxiety
3. Moderate: Night terrors with recurrent awakening and feeling of danger
4. Severe: Nightmares with recurrent awakenings, associated with agitation and confusion

Confusion

1. Absent
2. Mild: Disorientation in time/place/person

3. Moderate: Confusion combined with impaired attention/concentration/ registration/recall/interruption of goal-directed actions

4. Severe: Very confused with or without delirium

Sexual Preoccupation

1. Absent

2. Mild: Thoughts, dreams, worry about sexual competence

3. Moderate: Increased demand for sexual activity

4. Severe: Violent sexual impulsiveness

8-12: Mild disease
13-18: Moderate disease
19-24: Severe disease

Proposed Diagnostic Criteria for Parkinson's Disease[16]

Criteria for POSSIBLE diagnosis of Parkinson disease:

At least 2 of the 4 features in Group A* are present; at least 1 of these is tremor or bradykinesia
AND
EITHER None of the features in Group B** is present
OR Symptoms have been present for less than 3 years, and none of the features in Group B is present to date
AND
EITHER Substantial and sustained response to levodopa or a dopamine agonist has been documented
OR Patient has not had an adequate trial of levodopa or dopamine agonist

Criteria for PROBABLE diagnosis of Parkinson disease:

At least 3 of the 4 features in Group A are present
AND
None of the features in Group B is present (note: symptom duration of at least 3 years is necessary to meet this requirement)
AND
Substantial and sustained response to levodopa or a dopamine agonist has been documented

Criteria for DEFINITE diagnosis of Parkinson disease:

All criteria for POSSIBLE Parkinson disease are met

AND

Histopathologic confirmation of the diagnosis is obtained at autopsy***

*Group A features: Characteristic of Parkinson disease

1. Resting tremor

2. Bradykinesia

3. Rigidity

4. Asymmetric onset

**Group B features: Suggestive of alternative diagnoses

1. Prominent postural instability in the first 3 years after symptom onset

2. Freezing phenomena in the first 3 years

3. Hallucinations unrelated to medications in the first 3 years

4. Dementia preceding motor symptoms or in the first year

5. Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades

6. Severe, symptomatic dysautonomia unrelated to medications

7. Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

***Proposed criteria for histopathologic confirmation of Parkinson disease:

A. Substantial nerve cell depletion with accompanying gliosis in the substantia nigra

B. At least 1 Lewy body in the substantia nigra or in the locus ceruleus
(note: it may be necessary to examine up to 4 nonoverlapping sections in each of these areas before concluding that Lewy bodies are absent)

C. No pathologic evidence for other diseases that produce parkinsonism
(eg, progressive supranuclear palsy, multiple system atrophy, cortical-basal ganglionic degenration)

Schwab & England Activities of Daily Living Scale (S&E) or (SEADL)[17]

Range 0-100%, with higher % meaning less severe disease

The rating can be assigned by the rater or by the patient.

- **100%**-Completely independent. Able to do all chores without slowness, difficulty, or impairment.
- **90%**-Completely independent. Able to do all chores with some slowness, difficulty, or impairment. May take twice as long.
- **80%**-Independent in most chores. Takes twice as long. Conscious of difficulty and slowing.
- **70%**-Not completely independent. More difficulty with chores. 3 to 4X along on chores for some. May take large part of day for chores.
- **60%**-Some dependency. Can do most chores, but very slowly and with much effort. Errors, some impossible.
- **50%**-More dependant. Help with 1/2 of chores. Difficulty with everything.
- **40%**-Very dependant. Can assist with all chores but few alone.
- **30%**-With effort, now and then does a few chores alone of begins alone. Much help needed.
- **20%**-Nothing alone. Can do some slight help with some chores. Severe invalid.
- **10%**-Totally dependant, helpless.
- **0%**-Vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden.

Sickness Impact Profile (SIP)[18]

The Sickness Impact Profile (SIP) is a general quality of life scale. It consists of 136 items (statements) which measure 12 distinct domains of quality of life:

- Ambulation

- Movement and mobility
- Body care
- Social interaction
- Communication
- Alertness
- Emotional behavior
- Sleep
- Eating
- Work
- Household management
- Recreation

The SIP can be administered by an interviewer or by the patients themselves. Although it is easy to administer and score, it is relatively time-consuming, taking approximately 30 minutes to complete.

Patients identify those statements which describe their experience. Each item is weighted depending on the severity of dysfunction. For each category, the scores are summed and expressed as a percentage of the maximum score possible. Higher scores represent greater dysfunction. Although scores can be calculated for each of the 12 individual domains, three summary scores are typically calculated and reported: total score (includes all domains), a physical score (ambulation, body care, and movement and mobility), and a psychosocial score (emotional behavior, social interaction, alertness, and communication).

UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria[19]

1. Diagnosis of PARKINSONIAN SYMPTOMS:

BRADYKINESIA (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions).
And at least one of the following:

a. muscular rigidity

b. 4-6 Hz rest tremor

c. postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

2. Exclusion criteria for Parkinson's disease:

a. history of repeated strokes with stepwise progression of Parkinsonian features

b. history of repeated head injury

c. history of definite encephalitis

d. oculogyric crises

e. neuroleptic treatment at onset of symptoms

f. more than one affected relative

g. sustained remission

h. strictly unilateral features after three years

i. supranuclear gaze palsy

j. cerebellar signs

k. early severe autonomic involvement

l. early severe dementia with disturbances of memory, language and praxis

m. Babinski sign

n. presence of a cerebral tumor or communicating hydrocephalus on CT scan

o. negative response to large doses of levodopa (if malabsorption excluded)

p. MPTP exposure

3. Supportive prospective criteria for PARKINSON'S DISEASE. Three or more required for diagnosis of definite Parkinson's Disease.

a. unilateral onset

b. rest tremor present

c. progressive disorder

d. persistent asymmetry affecting the site of onset most

e. excellent response (70-100%) to levodopa

f. severe levodopa-induced chorea

g. levodopa response for 5 years or more

h. clinical course of 10 years or more

University of Pennsylvania Smell Identification Test (UPSIT)[14]

This is a standardized tool that has been widely used in the evaluation of patients affected by neurodegenerative disorders. This “scratch and sniff” test consists of 40 multiple-choice items. The range of scores is 0-40, 40 being the best score. The patient is required to mark one of the four alternatives even if no smell is perceived. To establish the meaning of a given individual’s test score, it is compared to scores from normal persons of equivalent age and gender using tables providing an easy-to-interpret measure of an individual’s performance. In this classification scheme, anosmia is defined as total inability to perceive qualitative odor sensations, whereas microsmia is defined operationally as decreased ability to smell. Microsmia can be further subdivided into “severe,” “moderate,” and “mild” classes. The 40-item UPSIT can be used in both clinical and experimental settings to test patients affected by PD and related disorders.

Webster's Parkinson’s Disease Rating Scale (WPDRS)[20]

This scale was developed as a simple rating scale that can be used to evaluate the degree of total parkinsonian disabilities. It applies a gross clinical rating to each of the 10 listed items, assigning value rating of 0-3 for each item, where 0 = no involvement and 1, 2, and 3 are equated to early, moderate, and severe disease, respectively. Scores range from 0 to 30, and decline represents decrease in severity of PD signs. Values of 1 to 10 indicate early illness; 11 to 20, moderate disability; and 21 to 30, severe or advanced disease.

Bradykinesia of Hands – Including Handwriting

0 = No involvement.

1 = Detectable slowing of the supination-pronation rate, evidenced by beginning difficulty in handling tools, buttoning clothes, and with handwriting.

2 = Moderate slowing of supination-pronation rate, one or both sides, evidenced by moderate impairment of hand function. Handwriting is greatly impaired, micrographia present.
3 = Severe slowing of supination-pronation rate. Unable to write or button clothes. Marked difficulty in handling utensils.

Rigidity

0 = Non-detectable.

1 = Detectable rigidity in neck and shoulders. Activation phenomenon is present. One or both arms show mild, negative, resting rigidity.

2 = Moderate rigidity in neck and shoulders. Resting rigidity is positive when patient not on medication.

3 = Severe rigidity in neck and shoulders. Resting rigidity cannot be reversed by medication.

Posture

0 = Normal posture. Head flexed forward less than 4 inches.

1 = Beginning poker spine. Head flexed forward up to 5 inches.

2 = Beginning arm flexion. Head flexed forward up to 6 inches. One or both arms raised but still below waist.

3 = Onset of simian posture. Head flexed forward more than 6 inches. One or both hands elevated above the waist. Sharp flexion of hand, beginning interphalangeal extension. Beginning flexion of knees.

Upper Extremity Swing

0 = Swings both arms well.

1 = One arm definitely decreased in amount of swing.

2 = One arm fails to swing.

3 = Both arms fail to swing.

Gait

0 = Steps out well with 18-30 inch stride. Turns about effortlessly.

1 = Gait shortened to 12-18 inch stride. Beginning to strike one heel. Turn around time slowing. Requires several steps.

2 = Stride moderately shortened – now 6-12 inches. Both heels beginning to strike floor.

3 = Onset of shuffling gait, steps less than 3 inches. Occasional stuttering-type or blocking gait. Walks on toes-turns around very slowly.

Tremor

0 = No detectable tremor found.

1 = Less than one inch of peak-to-peak tremor movement observed in limbs or head at rest or in either hand while walking or during finger to nose testing.

2 = Maximum tremor envelope fails to exceed 4 inches. Tremor is severe but not constant and patient retains some control of hands.

3 = Tremor envelope exceeds 4 inches. Tremor is constant and severe. Patient cannot get free of tremor while awake unless it is a pure cerebellar type. Writing and feeding himself is impossible.

Facies

0 = Normal. Full animation. No stare

1 = Detectable immobility. Mouth remains closed. Beginning features of anxiety or depression.

2 = Moderate immobility. Emotion breaks through at markedly increased threshold. Lips parted some of the time. Moderate appearance of anxiety or depression. Drooling may be present.

3 = Frozen facies. Mouth open ¼ inches or more. Drooling may be severe.

Seborrhea

0 = None.

1 = Increased perspiration, secretion remaining thin.

2 = Obvious oiliness present. Secretion much thicker.

3 = Marked seborrhea, entire face and head covered by thick secretion.

Speech

0 = Clear, loud, resonant, easily understood.

1 = Beginning of hoarseness with loss of inflection and resonance. Good volume and still easily understood.

2 = Moderate hoarseness and weakness. Constant monotone, unvaried pitch. Beginning of dysarthria, hesitancy, stuttering, difficult to understand.

3 = Marked harshness and weakness. Very difficult to hear and to understand.

Self-Care

0 = No impairment.

1 = Still provides full self-care but rate of dressing definitely impeded. Able to live alone and often still employable.

2 = Requires help in certain critical areas, such as turning in bed, rising from chairs, etc. Very slow in performing most activities but manages by taking much time.

3 = Continuously disabled. Unable to dress, feed himself, or walk alone.

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Appendix B. Work Plan

Objective

To conduct a systematic review of the literature to assess the quantity and quality of available evidence regarding diagnosis and treatment of Parkinson's disease (PD).

The following 12 specific questions will be addressed in the systematic review:

1. What are the results of neuroimaging studies (CT, MRI, PET, SPECT) or other diagnostic tests in determining the diagnosis of PD?

2. What are the results of L-dopa challenge in PD? What is the accuracy, sensitivity and specificity of this test for diagnosing PD?

3. What is the efficacy of medication used to treat early PD? What is the efficacy of initial treatment with L-dopa vs. a dopamine agonist?

4. What is the evidence for neuroprotection with selegiline, Vitamin E, or Vitamin C?

5. What is the efficacy of medication used to treat late PD? What is the efficacy of medication used to treat patients who have an insufficient response to L-dopa? What are the outcomes of treatment of medication-induced side effects?

6. What are the outcomes of treatment for patients who experience motor fluctuations and/or dyskinesias while taking L-Dopa?

7. What serious adverse events are associated with medications used to treat PD?

8. What are the outcomes of treatment of PD patients with psychotic symptoms or non-psychotic behavioral and psychological dysfunction?

9. When is surgery performed on PD patients? What types of surgeries are performed and what are their outcomes?

10. What are the outcomes of rehabilitation in PD?

11. What are the results of recent review articles regarding diagnosis and genetic testing in PD.

12. What is the evidence that PD patients are treated differently or have different outcomes based on the following: age, presentation of symptoms, cognitive status, duration of illness, co-morbidities, gender, race, ethnicity, or income level?

Background

The topic "Parkinson's Disease" was nominated by the American Academy of Neurology (AAN) to assist in answering several key questions of diagnosis and management of patients with this disease.

PD is a progressive disorder of the central nervous system characterized clinically by tremor, rigidity, and bradykinesia. PD affects 1% of the population over age 60, and up to 2.5% over age 70.[1] Mayo Clinic researchers have estimated the lifetime risk of developing PD at 7.5%.[2] This could have serious health and economic implications as the baby boom generation ages. Annual societal costs related to PD were estimated in 1994 to be $20 billion,[1] and are likely to be much higher now and in the future.

The design and interpretation of all prevention and treatment studies are made more difficult by the fact that PD has a variable and unpredictable clinical course. Furthermore, numerous outcome measures and formats have been developed, which complicate efforts to pool results across studies.[3]

The twelve key questions can be broken down into 4 basic categories: diagnosis, pharmacological treatment, (early and late), surgical treatment, and other modalities.

Not all "parkinsonism" is PD. The incidence of misdiagnosis has been estimated at up to 24% of patients.[4] The goal of this portion of the task order is to establish the evidence base of clinical trials that present sensitivity and specificity data pertaining to clinical and neuroimaging tests that are used to diagnose PD.

Treatment may be subdivided into early, overall, and late treatment, although there is significant overlap between the categories.

The standard treatment for PD has been levodopa (L-DOPA), which, once it reaches the brain, is converted to dopamine to correct the deficiency which characterizes PD. L-DOPA has been a mainstay of therapy since its introduction 40 years ago. However, questions of when to initiate therapy, and long term neurotoxicity, remain chief concerns to patients and practitioners. Several other drugs are often used, either in combination with L-DOPA to enhance its effects, or instead of L-DOPA, when its efficacy wanes or when response fluctuations or toxicity become unmanageable. These can be categorized chiefly as anticholinergics or dopamine agonists. Although there were very few new agents introduced for nearly 3 decades after the introduction of L-DOPA, several new agents, such as new dopamine agonists and the catechol-O-methyl transferase (COMT) inhibitors, with different mechanisms of action have recently been approved by the FDA. None, however, including L-DOPA, have been shown to impact the natural history of PD. They are useful for symptom control only, primarily motor dysfunction.

Research into agents capable of preventing or slowing progression of the disease is currently underway. These include antioxidants such as Vitamin E and coenzyme Q-10, the monoamine oxidase inhibitors selegiline and rasagiline, and glutamate antagonists such as riluzole.

The role of invasive methods such as pallidotomy and deep brain stimulation as additional treatment options require expert assessment. Neural growth factors

and neural cell implants (fetal cells from humans or animals, and genetically engineered stem cells) are the focus of increasingly intense research efforts.

The safe and effective use of co-medications to treat depression, psychosis, and cognitive changes of PD is also the subject of considerable new research.

The role of non-pharmacologic interventions, such as physical rehabilitation therapy, remains uncertain.

The goal of this portion of the task order is to review the evidence base of clinical trials pertaining to the treatment of PD. Given that PD is a chronic condition, and that patients stay on medications for years, the most clinically relevant data will come from long-term trials. For this reason, only trials of greater than or equal to 24 weeks duration will be accepted. Furthermore, the most useful data for analysis concerning pharmacological treatment of PD will be in randomized controlled trials (RCTs); therefore, only RCTs will be accepted for studies pertaining to pharmacological treatment. Studies pertaining to surgery and rehabilitation will not be limited to RCTs.

Genetic testing of relatives of patients with early onset PD is another area of current controversy. This is an area where there would be limited information to be derived from RCTs or even clinical trials; therefore, review articles pertaining to Genetics and PD will be reviewed and summarized for the Final Report.

Methods

MetaWorks will apply the latest and established best methods in the evolving science of review research.[5-9]

A flow diagram outlining the systematic review process is located in Attachment A.

The following tasks will proceed sequentially, and a project timeline has previously been submitted.

Topic Assessment & Refinement

A technical expert panel (TEP) will be assembled, in consultation with the Task Order Officer (TOO), through networking with our nominating partner, our academic collaborator, professional organizations, purchasers of health care, and relevant consumer groups.

After a preliminary assessment of the state of the literature, the TEP, in conjunction with the nominating partner (AAN), the TOO and our co-principal investigator at the Leonard Davis Institute of Health Economics (LDI), will assist in determining all primary and secondary objectives of this task order.

After a preliminary review of the literature, MetaWorks will develop two causal pathways that identify the critical diagnostic and treatment interventions in PD:

a) work-up of Parkinson's symptoms (diagnostic testing, treatment initiation, neuroimaging, genetic testing and neuroprotection)

b) pharmacologic and nonpharmacologic (including surgery and rehabilitation) management of patients with PD.

These causal pathways will serve as guides during this systematic review, and may be updated during the review process. They are not intended to be clinical practice guidelines or algorithms for decisions in patient care.

A report will be developed in consultation with the TOO which will identify which questions, if any, have insufficient evidence to pursue using literature sources, and will suggest specific areas for future research to fill these gaps. The report will clearly state whether or what evidence exists for diagnosis and management of PD in the adult population and, within that population, evidence related to age, gender, race/ethnicity, and income level.

Literature Screening

This task involves identifying and retrieving all potentially relevant literature on the diagnosis and treatment of PD, categorizing by study design, test, results and other key study, patient, and treatment level details for each of the thirteen key questions. Studies which meet the eligibility criteria (see below) will undergo data extraction and data entry.

The published literature will be searched from 1990 to 2000, with the following exceptions:

- Literature pertaining to pharmacological treatment of PD will be searched from 1985 to 2000, in an attempt to identify studies pertaining to anticholinergic medications.

- Literature pertaining to genetic testing will be searched from 1997-2000.

The search cut-off date will be November 9, 2000, and the retrieval cut-off date will be determined after all abstracts have been screened. The search will begin with a Medline screening search using the following search strategies:

I. Diagnosis:

1. (PD OR parkinsonism OR Parkinson) AND [diagnosis OR medical errors OR accuracy OR sensitivity OR specificity OR (diagnosis AND antiparkinson agents)]

II. Treatment:

2. (PD OR parkinsonism OR Parkinson) AND (treatment OR Levodopa OR carbidopa OR amantadine OR anticholinergic OR selegiline OR deprenyl OR dopamine agonist OR tolcapone OR entacapone)

3. (PD OR parkinsonism OR Parkinson) AND (selegiline OR Vitamin E OR Vitamin C OR neuroprotective agents)

4. (PD OR parkinsonism OR Parkinson) AND (psychological OR psychotic OR mental disorder) AND (drug therapy OR drug interactions)

5. (PD OR parkinsonism OR Parkinson) AND (surgery OR pallidotomy OR brain tissue transplant OR deep brain stimulation)

6. (PD OR parkinsonism OR Parkinson) AND rehabilitation

7. #1 OR #2 OR #3 OR #4 OR #5 OR #6 AND limit to clinical trials.

III. Genetics:

(PD OR parkinsonism OR Parkinson) AND genetics AND limit to review articles January 1, 1997-August 1, 2000.

In addition to the MedLine search described above, MetaWorks will search other suitable electronic databases, including Current Contents®, Cochrane Controlled Trials Register (CCTR) as well as a manual search of accepted study references and recent review articles. The Cochrane Library and the National Guidelines Clearinghouse will also be searched for additional information on these topics. In addition, pertinent Internet sites will be checked for potential leads to additional studies.

All citations and abstracts will be printed and screened at MetaWorks for any mention of diagnosis and/or treatment of PD (Level 1 screening) and reviewed for the following exclusion criteria:

Exclusion criteria

Abstracts demonstrating any of the following characteristics will be rejected:

- Reviews (except those regarding diagnosis and genetics), meta-analyses, letters, case reports, editorials, and commentaries.

- Crossover studies.

- Unpublished study reports and abstracts.

- Pharmacokinetic and pharmacodynamic studies.

- Animal or *in vitro* studies.

- Studies where results for PD population cannot be separated from results from other populations.

- Studies not pertaining to diagnosis or treatment of PD.

- Studies written in languages other than English.

- Studies containing < 10 patients as total sample size.

- Pharmacological treatment studies with < 24 weeks of treatment and followup.

While screening for eligibility, abstracts will be sorted and categorized. In some cases, it may not be possible from the abstract alone to determine the relevance of the study. All abstracts lacking obvious exclusion criteria will be included even if the categorization is unclear. Full papers for all studies passing Level 1 screening will be retrieved for second screening (Level 2), where inclusion and exclusion criteria will be applied.

Inclusion Criteria

Diagnosis:

- The following study designs will be accepted: observational [prospective, retrospective, and cross sectional (XS)], or interventional [RCTs, non-randomized controlled trials (nRCTs), and uncontrolled case series (UCSs), XS].

- Adult patients with potential diagnosis of PD.

- Studies addressing any diagnostic test to establish or support a diagnosis of PD.

Pharmacological Treatment:

- RCTs only

- $\geq$ 24 weeks treatment and follow-up duration

- Studies reporting at least one clinical objective outcome measure (efficacy or safety) on at least one of the following drugs or category of drugs:

    - L-DOPA/Carbidopa (Sinemet) – L-DOPA/decarboxylase inhibitor

    - Amantadine (Symmetrel)

- Dopamine agonists:
    - Bromocriptine (Parlodel)
    - Pergolide (Permax)
    - Ropinirole (Requip)
    - Pramipexole (Mirapex)
    - Andropinole
    - Cabergoline (Dostinex)
    - Apomorphine
    - Lisuride (Dopergin)
- Monoamine oxidase B (MAO-B) inhibitors:
    - Selegeline (Deprenyl)
    - Rasagiline (TVP-1012)
- Catechol-O-methyltransferase (COMT) inhibitors:
    - Tolcapone (Tasmar)
    - Entacapone (Comtan)
- Anticholinergic agents:
    - Trihexylphenidyl (Artane)
    - Benztropine (Cogentin)
    - Procyclidine
    - Other

- Studies involving neuroprotection with selegiline, Vitamine E (tocopherol), or Vitamin C.

- Studies addressing use of antipsychotic medications in conjunction with antiparkinsonian agents.

- Studies addressing the use of atypical antipsychotic medications in management of adult patients with PD.
    - Clozapine (Clozaril)
    - Olanzapine (Zyprexa)
    - Quetiapine (Seroquel)

Nonpharmacological Treatment:

- The following study designs will be accepted: observational [prospective, retrospective, and cross sectional], or interventional (RCTs, nRCTs, and UCSs).
- $\geq$ 24 weeks study and followup duration
- Must report at least one clinical objective outcome measure.
- Studies addressing surgery in adult patients with PD including:
    - Ablative or destructive surgery (thalmotomy, pallidotomy)
    - Stimulation surgery or Deep Brain Stimulation (DBS)
    - Transplantation or restorative Surgery (cell transplants)
- Studies addressing treatment of non-psychotic behavioral and psychological dysfunction in adult patients with PD.
- Studies addressing treatment of psychotic symptoms in adult patients with PD.
- Studies reporting at least one of the following specific interventions:
    - Allied health interventions
        - Occupational therapy (OT)
        - Physical therapy (PT)
        - Psychotherapy (counseling)
        - Speech therapy

- Studies reporting at least one of the following specific outcomes:
    - Acute hospitalization
    - Rehabilitation hospitalization
    - Nursing home admission
    - Work absenteeism
    - Quality of Life (QoL)
    - Activities of Daily Life (ADL) assessment

Genetics:

- The study design will be limited to review articles only.
- Adult patients undergoing genetic testing to establish or support a diagnosis of PD.

Upon completion of Level 2 screening, all accepted articles will be eligible for data extraction.

Assessment of Quality in the Primary Studies

All studies will be appraised according to a previously published Level of Evidence (Attachment B). Each accepted RCT will also be scored for quality (features of randomization method used, blinding of treatments, and accounting for all patients entered and withdrawn) by the Jadad Quality Score Assessment (Attachment C).

Data Extraction

Data extraction forms (DEFs) will be created specifically for this project. Data will be extracted onto the DEF independently by one reviewer and the completed DEF will be 100% checked against the original articles by a second reviewer. Any differences will be resolved by consensus; thus, two reviewers must agree on all data. In all cases, at least one physician reviews all data points. The data will then be entered in MetaWorks' relational database, MetaHub™. At this time, it is anticipated that the following data elements will be extracted.

These preliminary selections may change prior to finalization of the DEF as a result of input from the TEP and/or subsequent revisions to this Work Plan.

Study level characteristics

- Publication year
- Geographical location of study
- Study design (observational - retrospective or prospective interventional – RCT, nRCT, UCS, XS)
- Methodological assessment
    - Level of Evidence (I-V) – all studies
    - Jadad Quality Score – RCT's
- Total number of patients enrolled
- If RCT, number of patients randomized
- Primary study objective
- Funding source/industry sponsorship (name if yes or no/NR)
- Diagnostic test or treatment intervention studied
- Study duration
- Follow-up period
- Study type
    - Diagnostic
    - Treatment: pharmacologic or nonpharmacologic
        - Early
        - Late
        - General

Patient characteristics (by group)

- Age: years (mean, median, and range)
- Gender distribution
- Race and/or ethnicity
- Socioeconomic status
- Age at diagnosis
- Family history of PD
- Presenting symptoms (resting tremor, gait disturbance, rigidity, bradykinesia, motor dysfunction, etc.)
- Criteria used for Diagnosis of PD
- Patient exclusion criteria
- Stage of PD (early, moderate, advanced)
- Prior treatments received for PD
- Treatment resistance (# and type of antiparkinsonian agents tried previously)
- Criteria for establishing dementia diagnosis and for documenting presence of psychosis
    - Type of dementia diagnosed
    - Measures of cognitive impairment
- Other co-morbid conditions

Intervention Characteristics (by group)

- Diagnostic interventions
    - History and physical examination
    - Neuroimaging:
        - Computed tomography (CT)

        - Magnetic resonance imaging (MRI)
        - Fluorodopa positron emission tomography (PET) scans
        - Single proton emission computed tomography (SPECT) scans using dopamine transporter ligands
    - Other
        - Blood (serum ceruloplasmin concentration)
        - Urine (24 hour copper excretion)
        - Slit lamp examination
        - Liver biopsy (to rule out Wilson's disease)
    - Genetic testing
    - Other tests to rule out coexisting organic disease
    - Response to L-DOPA

Treatment interventions (by group)

- **Pharmacological interventions**
    - Treatment type, dose, frequency and duration
        - L-DOPA/Carbidopa
        - Dopamine agonists
        - MAO-B inhibitors
        - COMT-inhibitors
        - Anticholinergic Agents
        - Neuroprotective Agents
        - Antipsychotic medications
        - Other

- Comparison group, if any (placebo or active controls)
    - Concomitant medication (protocol prescribed or allowed)

- **Nonpharmacological interventions**
    - **Surgical**
        - Indications for surgery
        - Type of surgery performed
    - **Other**
        - OT
        - PT
        - Psychotherapy
        - Speech Therapy

Outcomes (by group)

Diagnostic tests

- Sensitivity
- Specificity
- Accuracy
- Negative Predictive Value (NPV)
- Positive Predictive Value (PPV)

Treatment Outcomes

Efficacy

- Hospitalizations or admissions to chronic care facilities
- Symptomatic improvement or worsening (documented motor improvement and other manifestations of disease severity)

- Work absenteeism
- Clinical, objective outcome measures
- QoL
- ADL assessment
- Other

Safety

- Adverse Events (related to treatment)
    - Grade 3 and 4
- Deaths (related to treatment)
- Patient withdrawals due to adverse events or lack of efficacy

Database Development

All consensed data will be entered into the MetaWorks MetaHub™ database. 100% of entered data is checked back to the DEFs after each form is completely entered. In addition, a 20% random sampling of data in the completed database will be checked by the QC group at MetaWorks against the data extraction forms. All discrepancies in data are reconciled by referring back to the original papers. Error rates in excess of 2% of checked data will trigger a 100% check of all data elements in the data base.

Once the accuracy of the database has been verified as described above, it is locked. No further changes are allowed after the data is locked. This is the dataset that will be used by the statisticians for analysis and to create raw data tables displaying key data elements of interest, by study.

All data are maintained in the MetaHub database, in a manner suitable to allow outputs to: a) spreadsheet programs for customized evidence table displays; b) to statistical programs for analysis.

Statistical Analyses

Statistical analyses will be performed as the data permit. The search criteria for the 12 questions have been restricted to allow us to select only those studies most likely to contribute data that could be analyzable. Further details of analysis will be developed later in an analysis plan.

However, we also note that several questions are related to management of patients with PD. Studies in the literature addressing clinical practice or medical

management are typically very limited, and will probably only allow for descriptive analysis.

Synthesis & Reporting

This task involves bringing together all of the evidence into a coherent report and presenting the raw data in a tabular format as well as performing both qualitative and quantitative data syntheses as data permit and as protocol objectives require.

MetaWorks will prepare and submit to the TOO evidence tables for each step in the causal pathways, as data permits.

Technical Experts

MetaWorks will identify a TEP through networking with our nominating partner, our academic collaborators, professional organizations and relevant consumer groups. The TEP will be composed of six to eight individuals with specific expertise in general neurology, PD, neurosurgery, internal medicine, and at least one consumer representative. The TEP will review and provide timely feedback to all draft Work Plans and deliverables on an ongoing basis. MetaWorks will consult with these individuals as appropriate in carrying out the tasks required under this task order.

Peer Review

In addition to the TEP described above, MetaWorks will identify up to 12 additional individuals who are experts in the topic area, to serve as peer reviewers of the draft evidence report. These individuals will be chosen from the fields of neurology, general practice and internal medicine, as well as consumers who have experienced PD. These individuals will be sought from professional organizations which have been instrumental in developing guidelines in aspects of PD treatment or diagnosis, such as the American Academy of Neurology. Consumers will be sought from consumer groups such as the National Parkinson Foundation Inc., the Parkinson's Disease Foundation, Inc., the Parkinson's Institute and others active in PD initiatives.

Names of potential reviewers will come from our technical expert panel, the nominating partner, LDI, AHRQ, and from the literature being reviewed by the project team. The profile of the peer review group will be similar to that of the TEP, and may also include representatives from manufacturers of the medications and diagnostics included in the evidence report.

A copy of the draft evidence report will be sent to each peer reviewer, along with a reviewer's form to be completed and returned to MetaWorks. This form will contain a checklist of items to be assessed as well as provide room for free-

form text comments. The form will be pre-screened by the TEP and the TOO prior to being sent to the peer reviewers. Reviewers will be given 3 weeks to respond, after which they will be contacted. All feedback will be stored in a project folder at MetaWorks. A statement of response to each reviewer's comments will be prepared and stored with each reviewer's comments. This response will also be returned to the reviewer.

A summary of the main comments and responses will be prepared and shared with the TOO. Reviewer comments and additional analyses and text resulting from the response to reviewer critique will be incorporated into the final iteration of the evidence report.

Implementation and Dissemination

An implementation plan will be prepared with the nominator, the American Academy of Neurology. Dissemination will occur via AHRQ. MetaWorks/LDI will prepare a manuscript describing key aspects of the work for publication in peer reviewed journals. Abstracts of same may also be submitted for presentation at professional meetings.

References

1. Marsh L. Neuropsychiatric aspects of Parkinson's disease. Psychosomatics 2000; 41:15-23.

2. Research Digest: Parkinsonism more common than previously thought. Aug. 24, 1999. Mediconsult.com

3. Clarke CE, Speller JM. Pergolide versus bromocriptine for levodopa-induced motor complications in Parkinson's disease. and Hilten JJ van, Ramaker C, Beek WJT van de, Finken MJJ. Bromocriptine for levodopa-induced motor complications in Parkinson's disease. (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software).

4. Clarke CE. Managing early Parkinson's disease. The Practitioner 1999; 243: 41-46.

5. Chalmers TC, Lau J. Meta-analytic stimulus for changes in clinical trials. Statistical Methods in Medical Research 1993; 2: 161-72.

6. Sacks HS, Berrier J, Reitman D, Pagano D, Chalmers T. Meta-analyses of randomized controlled trials. N Engl J Med 1987; 316: 450-5.

7. Sacks HS, Berrier J, Reitman D, Pagano D, Chalmers T. Meta-analyses of randomized control trials: an update of the quality and methodology. In: Bailar JC III, Mosteller F, editors. Medical Uses of Statistics. 2nd Edition. Boston: NEJM Books 1992; 427-42.

8. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. Ann Intern Med 1997; 126: 376-80.

9. Mulrow CD, Oxman AD (eds). Cochrane Collaboration Handbook. The Cochrane Library. The Cochrane Collaboration; Issue 1. Oxford: Update Software; 1997. Updated quarterly.

Work Plan Acceptance

AHRQ

By: _____
Name: _____
Title: _Task Order Officer_____

American Academy of Neurology:

By: _____
Name: _____
Title: AAN Representative_____

MetaWorks Inc.

By: _____
Name: _____
Title: Principal Investigator, MetaWorks

LDI

By: _____
Name: _____
Title: Co-Principal Investigator, LDI

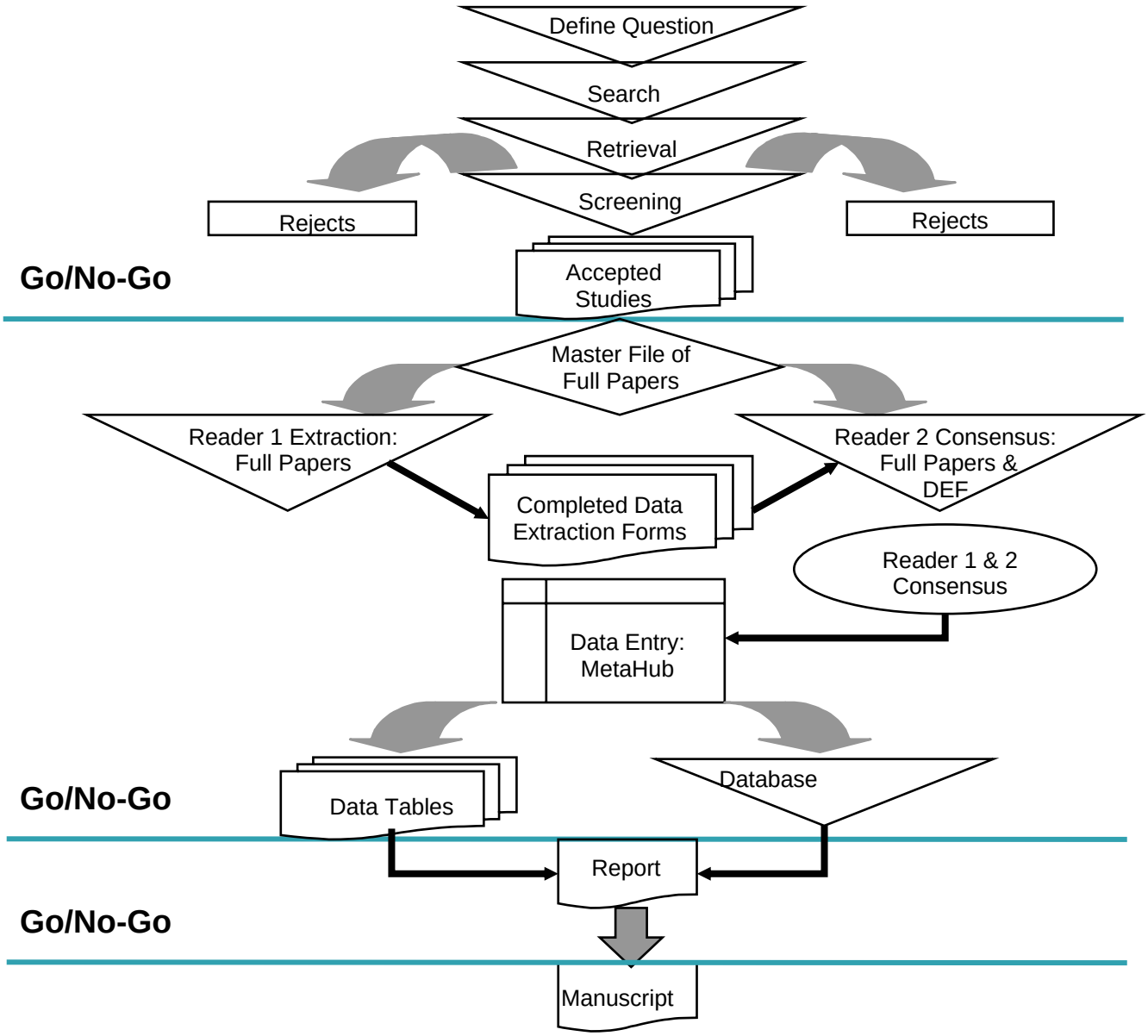
Attachments:

Attachment A: Flow Diagram Systematic Review

Attachment B: Levels of Evidence

Attachment C: Jadad Quality Score Assessment

Attachment A: MetaWorks Flow Diagram



Attachment B: Levels of Evidence

I. Evidence based on randomized controlled clinical trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false-negative results.

II. Evidence based on randomized controlled trials that are too small to provide level I evidence. These may show either positive trends that are not statistically significant or no trends and are associated with a high risk of false-negative results.

III. Evidence based on nonrandomized, controlled or cohort studies, case series, case-controlled studies or cross-sectional studies.

IV. Evidence based on the opinion of respected authorities or that of expert committees as indicated in published consensus conferences or guidelines.

V. Evidence which expresses the opinion of those individuals who have written and reviewed these guidelines, based on their experience, knowledge of the relevant literature and discussion with their peers.

These 5 levels of evidence do not directly describe the quality or credibility of evidence. Rather, they indicate the nature of the evidence being used. In general, a randomized, controlled trial has the greatest credibility (level I); however, it may have defects that diminish its value, and these should be noted. Evidence that is based on too few observations to give a statistically significant result is classified as level II. In general, level III studies carry less credibility than level I or II studies, but credibility is increased when consistent results are obtained from several level III studies carried out at different times and in different places.

Decisions must often be made in the absence of published evidence. In these situations it is necessary to use the opinion of experts based on their knowledge and clinical experience. All such evidence is classified as "opinion" (levels IV and V). Distinction is made between the published opinion of authorities (level IV) and the opinion of those who have contributed to these guidelines (level V). However, it should be noted that by the time level V evidence has gone through the exhaustive consensus-building process used in the preparation of these guidelines, it has achieved a level of credibility that is at least equivalent to level IV evidence.

from: The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. CMAJ 1998:158

Attachment C: Jadad Quality Score Assessment

Please read the articles and try to answer the following questions (see attached instructions):

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?

2. Was the study described as double-blind?

3. Was there a description of withdrawals and drop outs?

Scoring the items:

Either give a score of 1 point for each 'yes' or 0 for each 'no'. There are no in-between marks.

Give an additional point if:	For question 1, the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, coin tossing, etc.)
and/or:	If for question 2 the method of double-blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)
Deduct 1 point if:	For question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)
and/or:	For question 2 the study was described as double-blind but the method was inappropriate (e.g., comparison of tablet vs.injection with no double dummy)

Guidelines for assessment

1. Randomization:

A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers or alternation should not be regarded as appropriate.

2. Double-blinding:

A study must be regarded as double-blind if the word double-blind is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned.

3. Withdrawals and drop outs:

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

from: Jadad AR, Moore A, Carroll D, et al: Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? Controlled Clinical Trials 1996; 17:1-12.

Appendix C. Topic Assessment and Refinement

Objective

The objective of this Task Order is to conduct a systematic review of the literature to assess the quantity and quality of available evidence regarding diagnosis and treatment of Parkinson's Disease (PD).

Project Status to Date

Thirteen key questions were posed by the Agency for Healthcare Research and Quality (AHRQ) and the American Academy of Neurology (AAN). After a preliminary review of the literature, MetaWorks and the Leonard Davis Institute (LDI) worked collaboratively to modify the original key questions, making them more amenable to answers by systematic literature review. The content of the revised questions is unchanged; however, they are now worded differently. In general, where the original questions asked about what kinds of testing or treatment "should" be done, or "what is the role" of a particular test or treatment, the modified questions ask "what are the results," or "what is the evidence."

Causal pathways relevant to the key objectives of this project were developed to help guide the literature review. Many of the elements included in the causal pathways are controversial, particularly the use of MAO-B inhibitors for neuroprotection, and the question of when L-Dopa should be started. One of the goals of this Task Order is to identify the weight of the available evidence regarding these and other issues.

After numerous discussions with representatives from AHRQ, AAN, and LDI, final decisions were made regarding the composition of the Technical Expert Panel (TEP) for this project. The TEP is composed of four neurologists/PD experts, one neurosurgeon/PD expert, one general neurologist, one general internist, and one PD patient, who is a cardiologist. This multidisciplinary approach will provide valuable feedback from a variety of perspectives.

The Work Plan and Causal Pathways were sent to all members of the TEP for review on September 19, 2000. Feedback was requested by October 16, 2000, and has been received from 7 of the 8 members of the TEP.

Based on preliminary assessment of the literature, relevant databases, input from collaborating partners, and feedback received from the TEP, the Work Plan and the Causal Pathways have been modified accordingly.

Twenty people have been invited to participate in the project as Peer Reviewers of our draft evidence report. To date, seven have accepted. More potential peer reviewers are being contacted, with an ultimate goal of at least twelve peer reviewers, from multiple disciplines.

To date, 957 abstracts have been identified from the Medline search, 397 from the Current Contents search, and 590 from the Cochrane Library search, yielding a total of 1,944 citations. After 614 duplicates were identified, a total of 1,330 abstracts were downloaded into Reference Manager at MetaWorks.

Level I screening of all abstracts for exclusion criteria has been completed, and resulted in 560 potential accepted studies. Full papers are being retrieved for all accepted abstracts.

Level 2 screening of the full articles for inclusion and exclusion criteria is nearly complete. All studies that are rejected at Level 2 are required to be reviewed by a second researcher, to insure that there is 100% consensus regarding which studies are to be rejected. Manual bibliography checks of all accepted studies are currently underway, in search of potential accepts that may not have been identified by electronic searches.

After Level 2 screening is complete, data extraction of the accepted articles will commence. The Revised Work Plan describes, in great detail, the remaining steps in the systematic review process. The draft Evidence Report will be submitted to AHRQ by July 2, 2001.

Appendix D. Causal Pathways: Diagnosis and Treatment of Parkinson's Disease

Please Note:
The causal pathways are **not** clinical practice guidelines, nor are they algorithms for decisions in patient care. They have been constructed solely for use as guides during this systematic review of the literature.

Causal Pathway: Diagnosis of Parkinson's Disease Legends

[1]Principal Symptoms Present:

*Two or more present, one of which is resting tremor or bradykinesia

1**. Rigidity** affecting one or more limbs, cogwheel in nature

2. Resting, postural **tremor** most often asymmetrical, 3-7 Hz, hands preferentially affected

3. **Bradykinesia** (akinesia, hypokinesia)

4. **Postural/Gait disturbance** often appears late in disease

[2]Principal Symptoms *May Be* Present:

*One or more *may be* present

1. Rigidity affecting one or more limbs, may or may not be cogwheel in nature

2. Tremor may be asymmetrical, but frequently bilateral and higher frequency (5-12 Hz). Head, voice, tongue, palate, leg and/or trunk tremor may occur

3. Bradykinesia

4. Postural/Gait disturbance

[3]Secondary Symptoms *May Be* Present:

1. Psychiatric symptoms (depression, anxiety, psyshosis)

2. Autonomic dysfunction (sexual dysfunction, orthostatic hypotension)

3. Gastrointestinal dysfunction (constipation, weight loss, dysphagia)

4. Urologic dysfunction

5. Speech and swallowing problems

6. Falls

7. Sleep disturbances

8. Visual disturbances

9. Cognitive dysfunction (dementia)

10. Olfactory dysfunction

11. Difficulty writing

[4]Secondary Symptoms *May Be* Present:
(as above)

[5]Radiology/Laboratory Tests not as useful in diagnosis:

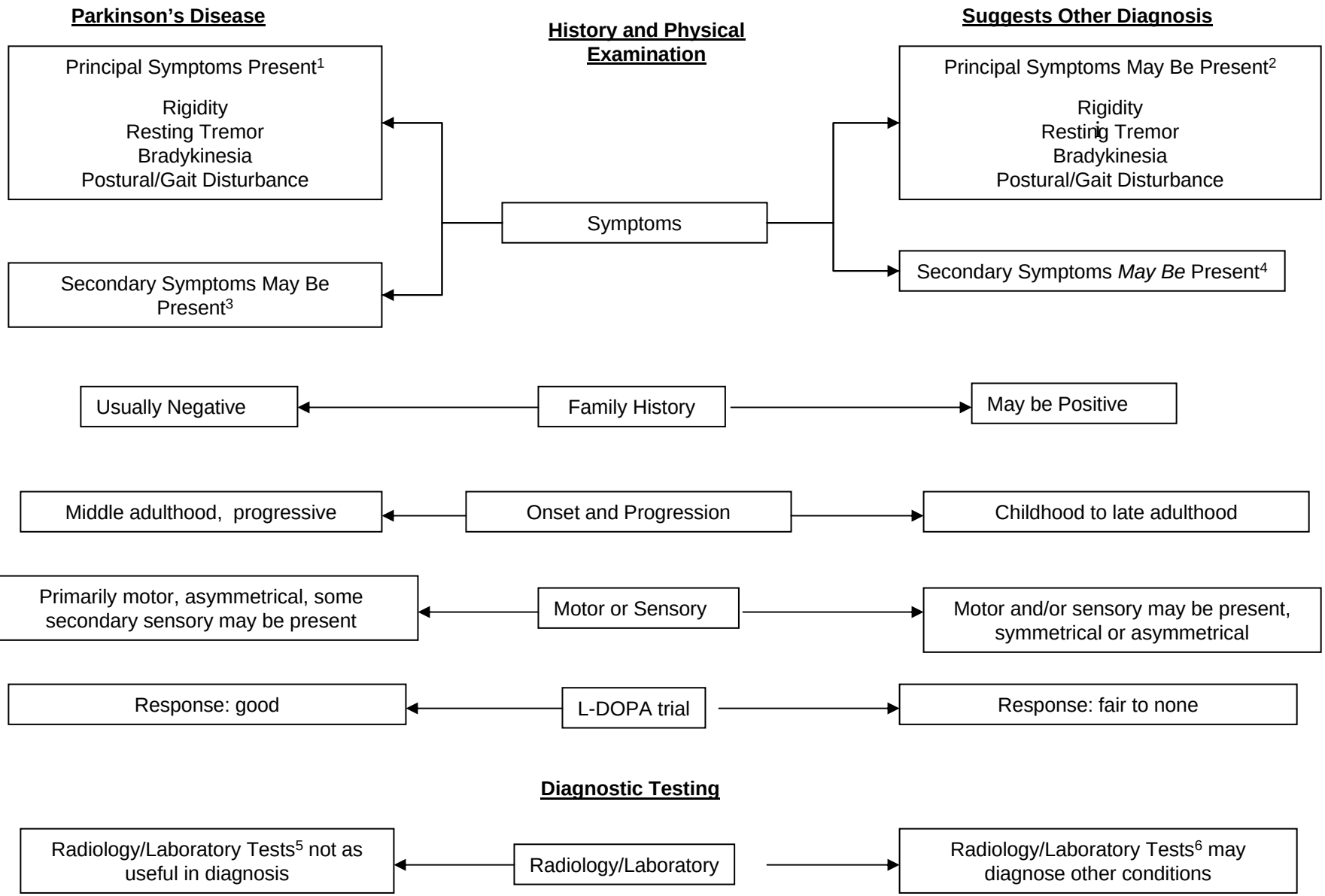
Results of computed tomography (CT), magnetic resonance imaging (MRI), cerebrospinal fluid analysis, and electroencephalography (EEG) are usually normal and of little diagnostic asistance.

Positron-emission tomography (PET scan) using radio-labeled dopa may be helpful in confirming a diagnosis.

[6]Radiology/Laboratory Tests helpful in diagnosis of other conditions:

CT, MRI useful to eliminating other disease processes such as tumors, strokes, hydrocephalus, etc. Laboratory investigation should be performed when atypical symptoms exist, there is a strong family history or early age of onset.

Causal Pathway: Diagnosis of Parkinson's Disease



Causal Pathway: Treatment of Parkinson's Disease Legends

For all medications, start with low dose, increase dose slowly until:

symptoms abate OR
maximum dose is reached OR
intolerable side effects occur.

Only make one medication change at a time.

[1] MAO-B Inhibitors: Monoamine oxidase B inhibitors (for neuroprotection) :

[2] Seligiline, Rasagiline

[3] Dopamine Agonists : Bromocriptine, Pergolide, Pramipexole, Andropinrole,

[4] Cabergoline, Ropinirole, Apomorphine (activate dopamine receptors)

[5] Other Modalities: Rehabilitation, Physical Therapy, Occupational Therapy, Speech Therapy, Counseling, Dietary Changes.

[6] L-DOPA/PDI: Levodopa/Carbidopa (peripheral decarboxylase inhibitor)

[7] Disabling tremor: may occur any time during the course of the disease.

[8] COMT inhibitors: Catechol-O-methylransferase inhibitor: Tolcapone, Entacapone

[9] Anticholinergic agents: Trihexylphenidyl, Benztropine, Procyclidine

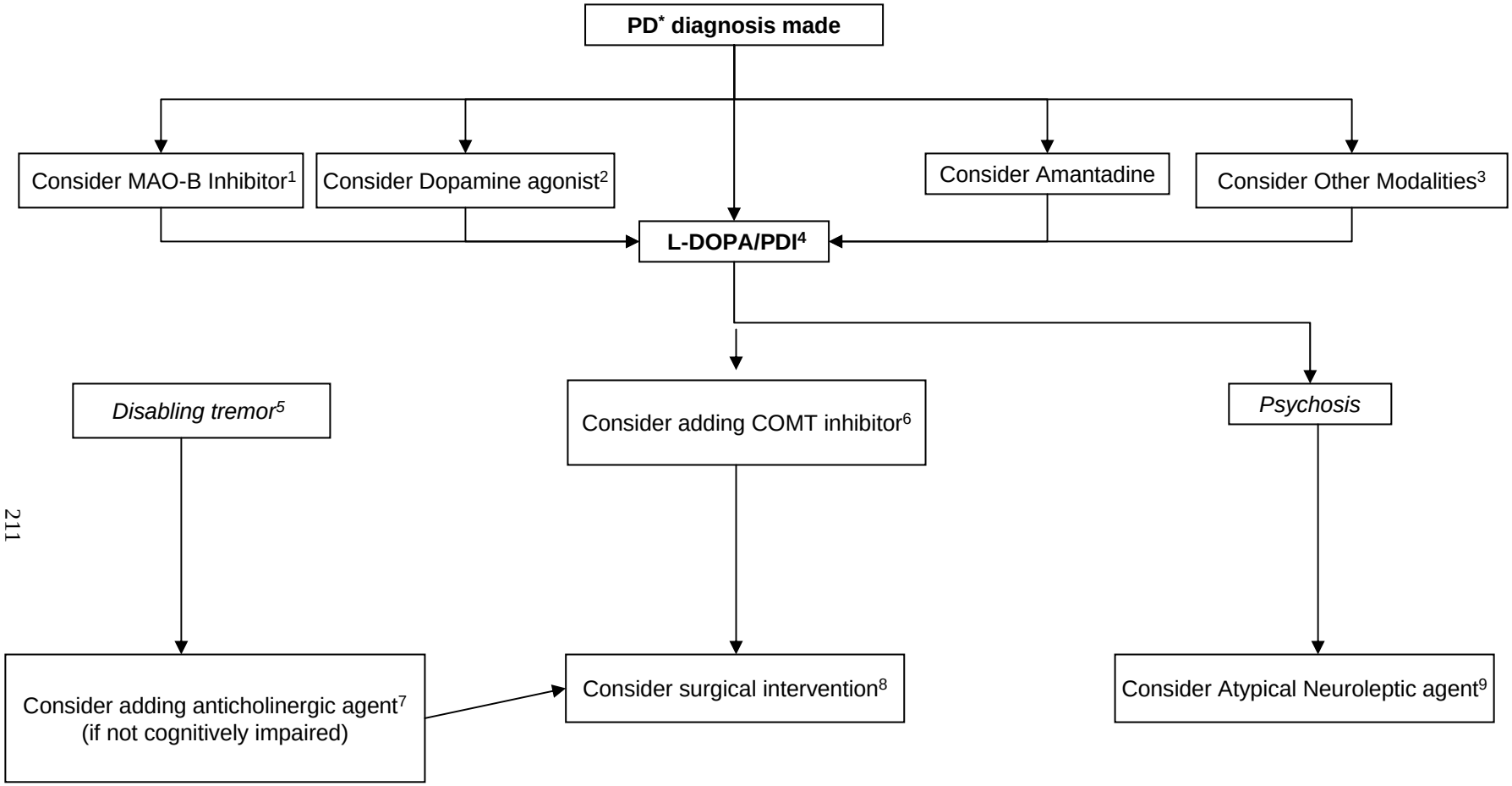
[10] Surgical interventions: pallidotomy, thalamotomy, deep brain stimulation, fetal nigral implants.

[11] Atypical Neuroleptic agents: Clozapine, Olanzapine, Quietipine

Many aspects of this causal pathway are controversial, including when to initiate therapy with L-DOPA, and when to use other agents. Monitoring for toxicities should be done throughout treatment, and is not specifically mentioned in this pathway. Similarly, physical therapy, counseling, speech therapy, and rehabilitation should start as soon as PD is diagnosed, and continue indefinitely.

The causal pathways are **not** clinical practice guidelines, nor are they algorithms for decisions in patient care. They have been constructed solely for use as guides during this systematic review of the literature.

Causal Pathway: Treatment of Parkinson's Disease



* PD = Parkinson's Disease

Appendix E. Screening Sheets and Data Extraction Forms

Extracted by _____
Date _____

Data Extraction Form
Diagnosis of Parkinson's Disease

Consensed by _____
Date _____

Study Characteristics

Study ID: _____ **First Author:**_____ **Pub. Date:** _____

Study Location: ___ North America _____ **Institution** _____

____ Europe _____ **Kin(s)**:_____

____ Other _____ _____

Study Design: _ __ RCT ___nRCT ___UCS ___XS ___Other _____

Level of Evidence: _____ (I) _____ (II) _____(III) _____(IV) _____(V)

Industry Sponsorship: Yes _____
NR

Diagnostic Criteria Category:

_____Apomorphine/L-Dopa Test
_____Autopsy Data
_____Blood/CSF Tests - Levels
_____Evoked Potentials
_____H&P/Clinical Exam
_____ Misc. Tests_____
_____MRI
_____PET
_____SPECT
_____Ultrasound
_____Visual Testing
_____Other _____
_____

Patients Enrolled: _____Total #
_____PD
_____Controls
_____Other _____
_____
_____

Primary Study Objective

Study Conclusion

AHRQ – PARKINSON DISEASE
Level II Screening
DIAGNOSIS

Reviewed by_____ **MetaHub Study ID**_____
First Author_____ **Year Published**_____

Status: Accept Reject

If REJECT, Specify Reason:

Animal or *in vitro* studies

Abstracts, letters, comments, reviews, editorials, case report, meta-analyses

Pharmacodynamic or Pharmacokinetic Study

Study with < 10 patients

Languages other than English

Studies published prior to 1990

Study populations not including Parkinson Disease

Studies not including tests to establish or support diagnosis of Parkinson Disease

Cross-over studies

Mixed populations where results for Parkinson patients not separately extractable

Other _____

If ACCEPT, then record:

Study Design:

____Observational
_____Prospective
_____Retrospective
_____Cross-sectional

_____ Interventional
____RCT
____nRCT
____UCS
____Cross-sectional

Geographic Location: _____North America
_____Europe
_____Other:_____

Patients Enrolled:_____

Diagnostic Test(s): _____
_____
_____
_____

AHRQ – PARKINSON DISEASE
Level II Screening
NON-PHARMACOLOGICAL TREATMENT

Reviewed by_____ **MetaHub Study ID**_____
First Author_____ **Year Published**_____

Status: Accept Reject

If REJECT, Specify Reason:

Animal or *in vitro* studies

Abstracts, letters, comments, editorials, meta-analyses

Studies not including a clinical objective outcome measure of PD activity

Pharmacodynamic or Pharmacokinetic Study

Languages other than English

Studies with <10 patients

Studies published prior to 1990

Studies < 24 weeks of treatment/follow-up

Study populations not including Parkinson Disease

Studies not including treatment or diagnosis

Cross-over studies

Mixed populations where results for Parkinson patients not separately extractable

Other _____

If ACCEPT, then record:

Surgery:
____ Pallidotomy
____ Thalamotomy
____ Deep Brain Stimulation (DBS)
____ Cell transplants
____ Other _____

Geographic Location: _____North America
_____Europe
_____Other_____

Patients Enrolled:_____

Rehabilitation:
____ Occupational therapy (OT)
____ Physical therapy (PT)
____ Psychotherapy (counseling)
____ Speech therapy
____ Other _____
Other: _____
_____

Study Duration: _____months

Outcome Measures: _____
_____
_____
_____

Study Design:

____Observational
_____Prospective
_____Retrospective
_____Cross-sectional

_____Interventional
____RCT
____nRCT
____UCS

AHRQ – PARKINSON DISEASE
Level II Screening
PHARMACOLOGICAL TREATMENT

Reviewed by_____ **MetaHub Study ID**_____
First Author_____ **Year Published**_____

Status: Accept Reject

If REJECT, Specify Reason:

Animal or *in vitro* studies
Abstracts, letters, comments, reviews, editorials, case report, meta-analyses
Pharmacodynamic or Pharmacokinetic Study
Languages other than English
Study populations not including Parkinson Disease
Studies not including clinical objective outcome measure of Parkinson Disease activity
Mixed populations where results for Parkinson patients not separately extractable
Studies that are not RCTs
Studies with <10 patients
Studies < 24 weeks of treatment/follow-up
Studies published prior to 1985
Cross-over studies
Other _____

If ACCEPT, then record:

____Early
____Advanced
____Other
____ Neuroprotection
____ Psychology

Geographic Location: _____North America
_____Europe
____ Other_____

Patients Enrolled: _____

Study Duration: _____months

Outcome Measures: _____
_____
_____
_____

Medication:
____ L-DOPA/Carbidopa* (Sinemet)
____Amantadine (Symmetrel)
Dopamine Agonist:
_____ Andropinole
_____ Apomorphine
_____ Bromocriptine (Parlodel)
_____ Cabergoline (Dostinex)
_____ Lisuride (Dopergin)
_____ Pergolide (Permax)
_____ Pramipexole (Mirapex)
_____ Ropinirole (Requip)

Antipsychotic medications:
____ Clozapine (Clozaril)
____ Olanzapine (Zyprexa)
____ Quetiapine (Seroquel)

Comparison: Placebo / Active _____
_____

Monoamine oxidase B (MAO-B) inhibitors:
____ Rasagiline (TVP-1012)
____ Selegeline (Deprenyl

Catechol-O-methyltransferase (COMT) inhibitors:
____ Entacapone (Comtan)
____ Tolcapone (Tasmar)

Anticholinergic agents:
____ Benztropine (Cogentin)
____ Procyclidine
____ Trihexylphenidyl (Artane)

Neuroprotective agents:
____ Vitamine E (tocopherol)
____ Vitamin C

___Other_____
_____

Extracted by _____
Date _____

Data Extraction Form
Ancillary Treatment of Parkinson's Disease

Consensed by _____
Date _____

Study Characteristics

Study ID: _____ **First Author:** _____ **Pub. Date:** _____

Study Name _____

Study Location: ___ North America _____ Institution _____

____ Europe _____ Kin(s):_____

____ Other _____ _____

Study Design: ___**RCT** ___**nRCT** ___**UCS** ___**XS** ___**Other**

Quality Score: ___(rand) + ___(blind) + ___(w/drwl) = ___(Total)

Level of Evidence: _____ (I) _____ (II) _____ (III) _____ (IV) ____ (V)

Accrual years _____ _____ **Patients Enrolled**

Industry Sponsorship: Yes _____
NR

Intervention:

Inclusion Criteria:

Exclusion Criteria:

Primary study objective

Study conclusion

Extracted by _____
Date _____

Data Extraction Form
Pharmacological Treatment of Parkinson's Disease

Consensed by _____
Date _____

Study Characteristics

Study ID: _____ **First Author:** _____ **Pub. Date:** _____

Study Location: ___ North America _____ Institution _____
____ Europe _____ Kin(s):_____
____ Other _____ _____

Quality Score: ___(rand) + ___ (blind) + ___(w/drwl) = ___(Total)

Level of Evidence: ____ (I) ___ (II) ____ (III) ___ (IV) ____ (V)

Tx Duration:_____ (mos) **F/U Duration:**_____ _____ **Patients Enrolled**

Accrual years _____

Industry Sponsorship: Yes _____

Treatment: ___Early ____Advanced ____General NR

Medications:

Dopamine Agonist:	**MAO-B Inhibitor:**	**Anticholinergic agent:**	**Psychotropic agent:**
__Andropinole	__Rasagiline (TVP-1012)	___Benztropine (Cogentin)	___Clozapine (Clozaril)
__Apomorphine	__Selegeline (Deprenyl)	___Procyclidine	___Olanzapine (Zyprexa)
__Bromocriptine (Parlodel)	__Tranylcypromine	___Trihexylphenidyl (Artane)	___Quetiapine (Seroquel)
__Cabergoline (Dostinex)	__Other _____	___Other _____	___Other_____
__Lisuride			
__Pergolide (Permax)	**COMT Inhibitor:**		**Other**
__Pramipexole (Mirapex)	__Entacapone (Comtan)	**Neuroprotective agent:**	_____
__Rimantadine	__Tolcapone (Tasmar)	___Vitamin E (Tocopherol)	_____
__Ropinirole (Requip)	__ Other _____	___Vitamin C	
__Other_____		___Other _____	**Comparison group:**
	__**L-DOPA/Carbidopa**		___Placebo
__**Amantadine**	__Other _____		___Active

Inclusion Criteria:

Exclusion Criteria:

Primary study objective

Primary efficacy variable

Extracted by _____
Date _____

Data Extraction Form
Psychiatric Treatment of Parkinson's Disease

Consensed by _____
Date _____

Study Characteristics

Study ID:_____ **First Author:**_____ **Pub. Date:**_____

Study Location: ___ North America _____ Institution _____

____ Europe _____ Kin(s):_____

____ Other _____ _____

Study Design: ___**RCT** ___**nRCT** ___**UCS** ___**XS** ___**Other**

Quality Score: ___(rand) + ___(blind) + ___(w/drwl) = ___(Total)

Level of Evidence: _____ (I) _____ _____ (III) _____ (IV ____ (V)

Accrual years _____ _____ **Patients Enrolled**

Industry Sponsorship: Yes _____

NR

Treatment:

____Clozapine
____Risperidone
____Citalopram
___Piracetam
___Quetiapine
___Other _____

Inclusion Criteria:

Exclusion Criteria:

Primary study objective

Study conclusion

Extracted by _____
Date _____

Data Extraction Form
Surgical Treatment of Parkinson's Disease

Consensed by _____
Date _____

Study Characteristics

Study ID:_____ **First Author:**_____ **Pub. Date:**_____

Study Location: ___ North America _____ Institution _____
____ Europe _____ Kin(s):_____
____ Other _____ Industry: Yes_____
NR

Study Design: _ __ RCT ___nRCT ___UCS ___XS ___Other _____

Quality Score: ___(rand) + ___(blind) + ___(w/drwl) = ___(Total)

Level of Evidence: _____ (I) _____ (II) _____ (III) _____ (IV) ____ (V)

F/U Duration:_____**(mos)** _____ **Patients Enrolled**

Accrual years _____

Surgical Intervention	
Deep Brain Stimulation ___ Pallidotomy ___ Unilateral _____ (# pts) Bilateral _____ (# pts) Type _____ _____	Thalmotomy ___ Tissue Transplant ___ Adrenal Medulla ___ Fetal brain cells ___ Other_____ _____

Inclusion Criteria:

Exclusion Criteria:

Primary study objective

	Group 1:	**SD / SEM**	**Group 2:**	**SD / SEM**
# Enrolled / Randomized				
# Analyzed for Saf/Eff				
Age (Mean, Med, Range)				
# Male / # Female				
# R handed / # L handed				
Race or ethnicity				
Socioeconomic status				
Duration of PD (yrs)				
Age @ onset (yrs)				
Family history of PD				
Prior treatments for PD				
Comorbidities				

Appendix F. Statistical Reference

Interpretation of Standardized Mean Differences

Standardized mean differences (δs) are used to represent the difference between two groups when the groups are measured on differently scaled measures across many studies. For instance, in the pharmacological studies, patients are evaluated on as many as seven different measures. A standardized mean difference between groups is simply the mean difference re-scaled so that all measures have the same variance and standard deviation in scores. If we make the assumption that these scales or subscales measure roughly the same construct (past validity studies make this a safe assumption for the scales in question),[1] meta-analysis of standardized mean differences (also commonly referred to as "effect sizes" in this report) becomes both possible and theoretically meaningful.

The value of the standardized mean difference might be best considered as the degree of overlap between the distributions of treatment and control group scores. Because delta (δ) is the standardized score of the treatment group mean in the control group distribution, we can calculate approximately what proportion of the control group scores are less than the *average* score in the treatment group.[2] The table below summarizes percentages for a range of effect sizes.

Effect Size	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	1.00	1.20	1.50
% of treatment group with scores better than the average person in the control group	54%	58%	62%	66%	69%	73%	76%	79%	84%	88%	93%

Thus, someone undergoing a treatment (e.g., bromocriptine) that has an expected effect size of .50 would expect that his symptoms afterwards would be better than 70 percent of those who underwent the "control" procedure (e.g., L-dopa alone).

Even small effects can be important, depending on the importance of the outcome. In past medical studies, small but statistically significant effect sizes have been deemed important enough to prematurely end double-blinding: the 1987 study of the effect of aspirin on reducing the risk of heart attacks found an effect size for aspirin over placebo equivalent to a standardized mean difference of .07.[3]

Calculation of Change Score Standard Deviations

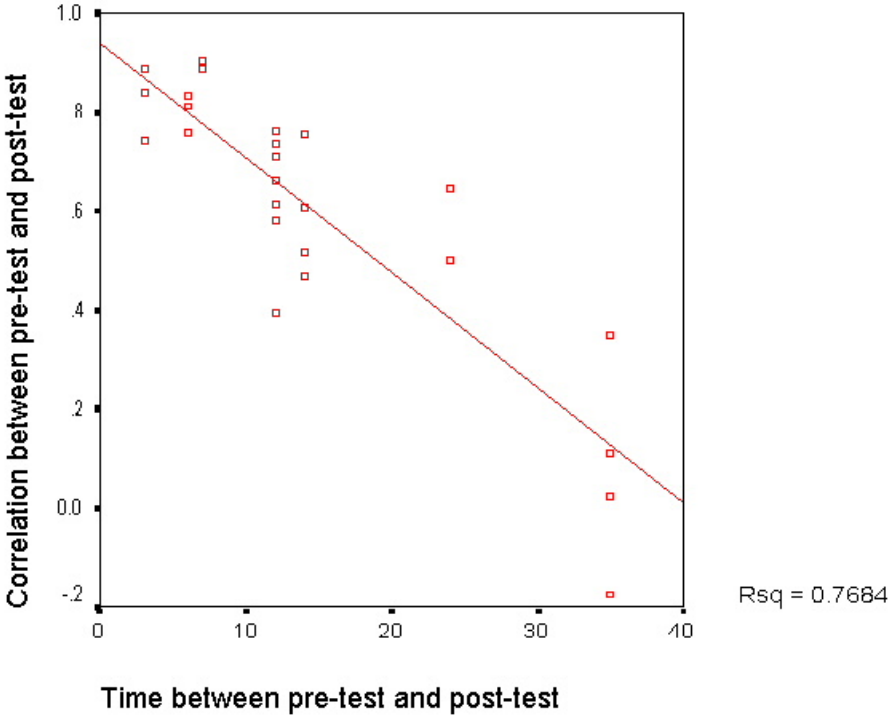
While many studies reported both baseline and outcome data (from which change score means can be calculated), only a few studies (most from the Parkinson's Study Group) reported change score standard deviations. Because controlling for pre-test differences was desired, and the "change score" standardized mean difference was desirable as a meta-analytic outcome, we estimated change score standard deviations when the data was not directly available.

This estimation was possible due to the studies that reported pre-test means and standard deviations, post-test means and standard deviations, and change score means and standard deviations. This data was available for 25 treatment arms, and it allowed for the calculation of 25

pre/post-test correlations. Figure 1 demonstrates that the time between pre-test and post-test scores was strongly related to the correlation between pre-test and post-test scores. In fact, the relationship was strong enough (R^2=.77) to make imputation of the pre/post-test correlation possible. The method used gave slightly more conservative (i.e., lower) correlations than those implied by the figure. For studies with a treatment duration of 10 months or less, a correlation of .8 was used to estimate the change-score standard deviation; .6 was used for those between 10.1 months and 20 months; .4 for those between 20.1 months and 30 months; .2 for those between 30.1 months and 40 months; and .1 for those studies of longer duration. The formula used was

$$s_{CHANGE\_SCORE} = \sqrt{s^2_{BASELINE} + s^2_{OUTCOME} - 2 * r_{PRE-POST} * s_{BASELINE} * s_{OUTCOME}}.$$

Figure 1. Time of evaluation versus pre-test post-test correlation



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Appendix G. Technical Experts and Peer Reviewers

Appendix G. Technical Experts and Peer Reviewers

AHRQ Diagnosis and Treatment of Parkinson's Disease Peer Reviewer Panel

Name	Specialty	Affiliation
Bressman, Susan - MD	PD Expert	Beth Israel Medical Center New York, NY
Brooks, Deborah W.	Consumer Advocate	Executive Director, The Michael J. Fox Foundation New York, NY
Brown, Janet - MA CCC-SLP	Speech-Language Pathology	Associate Director Health Care Services in Speech-Language Pathology American Speech-Language-Hearing Association Rockville, MD
Cohen, Perry - MD	Consumer Advocate	Director, Health Services Research Parkinson's Disease Foundation Washington, DC
Cosgrove, G. Rees - MD, FRCS (C.)	Neurosurgeon	Director, Movement Disorders Center Wang Ambulatory Care Center Massachusetts General Hospital Boston, MA
Langston, J William - MD	PD Expert	Founder, The Parkinson's Institute Sunnyvale, CA
Leurgans, Sue - PhD	Statistician	Department of Preventive Medicine & Neurological Sciences Rush-Presbyterian - St. Lukes Medical Center Chicago, IL
Marder, Karen - MD, MPH	PD Expert	Associate Professor of Clinical Neurology Sergievsky Center, Columbia University New York, NY
Neuman, William "Richey" - MD	Internist	Assistant Professor of General Internal Medicine Presbyterian Medical Center Philadelphia, PA
Nutt, John G. - MD	PD Expert	Oregon Health Sciences University Department of Neurology Portland, OR
Oertel, Wolfgang H. - MD	PD Expert	Philipps University Department of Neurology Director, Center for Nervous Diseases Marburg D 35033 Germany
Pfeiffer, Ron - MD	PD Expert	University of Tennessee, Memphis Department of Neurology Memphis, TN

AHRQ Diagnosis and Treatment of Parkinson's Disease Technical Expert Panel (TEP)

Name	Specialty	Affiliation
Baime, Michael - MD	Internist	Chief of Internal Medicine PENNCare at Rittenhouse Square Philadelphia, PA
Carter, Julie - RN, PhD	PD Expert	Oregon Health Sciences University Department of Neurology Portland, OR
Factor, Stewart A. - MD	PD Expert	Albany Medical Center Department of Neurology Albany, NY
Kieburtz, Karl D. - MD	PD Expert	Chief, Movement and Inherited Neurological Disorders Unit University of Rochester Medical School Rochester, NY
Levy, Sanford - MD	Neurologist	Department of Neurology North Shore Medical Center Salem, MA
Turner, Dennis - MD	PD Expert	Duke University Medical Center Division of Neurosurgery Durham, NC
Wistran, Daniel - MD	Consumer Advocate	Cardiology Physicians Inc. North Shore Medical Center Salem, MA
Zesiewicz, Theresa A. - MD	PD Expert	University of South Florida Parkinson's Disease Movement Disorders Center Tampa, FL

Peer Reviewer Form

AHRQ Task Order: Diagnosis and Treatment of Parkinson's Disease: A Systematic Review of the Literature

Please indicate your level of agreement with each of the following Statements, by placing an "X" in the appropriate column.				
Statements	**Very much agree**	**Moderately agree**	**Not very much in agreement**	**Do not agree at all**
1. This topic is relevant to healthcare decision-making (clinical practice and policy making) in 2001.				
2. The criteria used to select articles for inclusion were appropriate.				
3. Based on selection criteria used, it is not likely that relevant studies were missed.				
4. The validity of the studies was appraised appropriately.				
5. The methods are presented in such a way as to be reproducible.				
6. The statistical analytic methods are appropriate to the material and the objectives.				
7. The results are stated clearly.				
8. Given the nature of the topic and the data, all clinically important outcomes were considered.				
9. I agree with the conclusions presented in the report.				

On the following page, please provide:
a) A brief explanation of both positive and negative answers;
b) Suggestions for improvement of the content or format of this review;
c) Suggestions for additional analyses of this dataset worth including in this report, or in future reports.

**We would prefer that you complete and return this form electronically. However, you may also fax the form back to us, or fax back an annotated version of the draft report if you prefer. Contact information is provided below.

Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please send the completed form and comments to MetaWorks by **July 30, 2001.**

Contact: Rhonda P. Estok, RN, BSN, CNOR
Metaworks Inc.
E-mail: restok@metawork.com
Phone: (781) 395-0700 x254
Fax: (781) 395-7336

Peer Reviewer Form

AHRQ Task Order: Diagnosis and Treatment of Parkinson's Disease: A Systematic Review of the Literature (continued)

Please print legibly or type comments here:

(signature) (date)

(print name)

Appendix H. Accepted Studies Log

Citation

Study Category:Ancillary Treatment

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Study Category: Diagnosis

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Appendix I. Rejected Studies Log

Citation

Rejection Reason: Abstract, letter comment, review, case report, or meta-analysis

1 Bejjani BP, Damier P, Arnulf I, Papadopoulos S, Bonnet AM, Vidailhet M, et al. Deep brain stimulation in Parkinson's Disease: Opposite effects of stimulation in the pallidum. Mov Disord 1998; 13:969-70.

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Rejection Reason: Cross-over studies

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Rejection Reason: Duplicate Study

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Rejection Reason: In vitro studies

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Rejection Reason: Mixed populations where results for PD patients can not be separately extracted

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Rejection Reason: No outcome of interest

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Rejection Reason: Outcomes not extractable

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Rejection Reason: Pharmacodynamic or pharmacokinetic study

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Rejection Reason: Studies not including an objective clinical outcome measure of PD activity

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Rejection Reason: Studies not including tests to establish or support diagnosis of PD

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Rejection Reason: Study populations not including Parkinson Disease

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Appendix J. Studies of Interest Excluded from Database

A few studies did not meet inclusion criteria, but the consulting PD experts recommended that they be mentioned in this review. These studies are discussed below, but were not extracted, entered into the database, or included in the statistical analyses.

Pharmacological Treatment

The Parkinson Study Group conducted a 10-week, multicenter, double-blind RCT comparing placebo with various doses of pramipexole as monotherapy in 264 patients with early PD.[1] The trial did not meet the inclusion criteria for this review, due to its short duration; however, only two studies of pramipexole in early PD are included in the database, and this study is mentioned here for comparison. Pramipexole was well tolerated, and resulted in total UPDRS scores that were significantly improved compared with placebo. Studies of longer duration are necessary to confirm these favorable results.

A French, multicenter, open-label RCT compared tolcapone with bromocriptine in 146 PD patients who experienced "wearing-off" or "on/off" fluctuations on L-dopa/PDI.[2] As the trial lasted only eight weeks, it did not meet the inclusion criteria for this review, but it is the only direct comparison of tolcapone and bromocriptine, and therefore deserves mention. After eight weeks, patients in both groups had similar degrees of motor disability and "on/off" time. Patients in the tolcapone group were able to reduce their daily L-dopa dose more than were patients in the bromocriptine group. The side effect profile varied between the two groups. Studies of longer duration are necessary before conclusions can be made regarding a comparison of the efficacy and safety of bromocriptine and tolcapone.

Three double-blinded, placebo-controlled RCTs that were rejected because of insufficient study duration were readdressed upon the recommendation of a TEP member. One was the French selegiline multicenter trial (FSMT), a three-month study which showed that selegiline was statistically superior to placebo in improving symptoms in patients with early PD.[3] One study reported that pergolide monotherapy had superior efficacy to placebo in a three-month study of patients with early PD.[4] One six-week study of patients with "wearing-off" phenomenon on L-dopa assessed different doses of tolcapone in addition to L-dopa.[5] The addition of tolcapone reduced the "wearing-off" phenomenon. While all of these studies are important, their short duration precludes our ability to statistically compare the results of these studies to other studies in the database, and they remained in the "unaccepted studies" log.

A few studies have been performed using GM1 ganglioside, a normal constituent of nerve cell membranes, in human PD patients.[6,7,8] None of the studies met the criteria for acceptance for this review; only one was an RCT, and the study duration was less than 24 weeks. The study is, nevertheless, mentioned in this review, as GM1 represents a new category of pharmacologic treatment for PD that may receive further attention among researchers, although no studies published after 1998 were found.

After an initial intravenous test dose of GM1 1000 mg or placebo, 48 patients with mild to moderate PD were randomized to self-administered GM1 100 mg or placebo subcutaneously twice a day for 16 weeks.[8] Forty-five patients completed the study, and no withdrawals were

related to the safety or efficacy of GM1. The main adverse events were injection site reaction, including rash, erythema, or swelling, in ten GM1 patients and one placebo patient, and insomnia in five GM1 patients and two placebo patients. Twelve placebo patients and three GM1 patients complained of fatigue. The UPDRS motor scores improved a mean of 7.5 points after 16 weeks of GM1, while remaining essentially unchanged in the placebo patients. Twenty-one patients elected to continue to take GM1 in an open-label extension of the RCT.[7] Eighteen of these 21 patients continued to have UPDRS motor scores better than baseline, while three had worse scores. Patients who took GM1 continuously for two years showed the greatest improvement from their baseline UPDRS motor scores. Three patients who were followed after they discontinued GM1 at the end of the double blind trial all developed worsening of their UPDRS motor scores.

Anticholinergic Drugs

No trials of anticholinergic drugs met the inclusion criteria for this systematic review. In order to present the available information on this category of drugs, eight studies that were rejected for inclusion into the database but are pertinent to anticholinergic drugs in PD are mentioned here. The most recent studies are discussed first.

A cross-sectional study of the prevalence of dementia in PD was performed on 70 consecutive PD outpatients at a clinic of a university hospital.[9] Patients with dementia had received anticholinergic drugs for significantly longer than patients who were not mentally impaired, leading the authors to conclude that anticholinergic drugs should be avoided in PD patients with cognitive decline.

One study tested the cognitive function of 13 patients with newly diagnosed PD, before and after two weeks of treatment with trihexyphenidyl.[10] No patients were demented at baseline, and no significant change was seen in neuropsychological testing before and after the trihexylphenidyl. Given the short duration of the trial and the lack of cognitive impairment at baseline, it is difficult to draw any conclusions from this study.

In a retrospective analysis of 113 PD patients at a movement disorder clinic, the memory performance of patients taking anticholinergics was not significantly different from that of patients on dopaminergic medications alone.[11] This observation held true for patients with early, middle, or advanced disease. The presence of dementia at baseline was not reported, and may confound these findings, as other studies have suggested that anticholinergics impair cognitive function in patients who are already impaired at baseline.[12]

A study of 78 PD patients showed that patients with PD for > 3 years had memory performance that was worse than controls, and patients on benzhexol had dosage-dependent memory impairment compared to patients on L-dopa alone.[13] The authors concluded that memory is impaired in PD, and benzhexol contributes to the memory decline.

Most studies of anticholinergics were published prior to 1990. In a placebo-controlled, double-blind cross-over study published in 1981, 29 men with PD for one year, on stable doses of L-dopa/PDI, were treated with 10 weeks of benztropine or placebo, followed by a five-week washout period, then 10 weeks of the opposite treatment.[14] The authors reported that qualitative and quantitative evaluations showed small but statistically significant improvements for rigidity, finger tapping speed, and ADL for patients on benztropine, compared with patients on placebo. No patients had dementia at baseline. Patients on benztropine had a ten percent decrease in one of the five cognitive measures tested, two patients complained of memory problems, poor

concentration, irritability and confusion, and two patients experienced hallucinations. All adverse effects were reportedly mild and reversible with decreasing the medication dose. Interpretation of this study is limited by its short duration, the absence of results prior to cross-over, and the difficulty in comparing their evaluations with today's UPDRS scores.

A study published in 1978 evaluated 20 patients with early PD who were taking trihexyphenidyl.[15] L-dopa/PDI was openly added for eight weeks. All patients improved in bradykinesia, tremor, rigidity, and disability scale. The authors concluded that adding L-dopa/PDI to anticholinergics improves the therapeutic response in PD. This study is mainly of historic interest, as practitioners at that time were hesitant to use L-dopa, and were often treating PD patients with anticholinergics alone.

A double-blinded RCT comparing L-dopa plus trihexyphenidyl to L-dopa plus placebo was published in 1974.[16] There was no significant difference between the two groups, indicating that L-dopa alone was equivalent to L-dopa plus trihexyphenidyl.

The literature contains limited data regarding the efficacy and safety of anticholinergics in PD. Anticholinergics played an important role in the treatment of PD prior to the development of L-dopa, but their current role is limited to young, cognitively intact PD patients who have resting tremor as the predominant symptom.[17]

Surgery

One study compared overall effects of unilateral vs. bilateral STN in patients with advanced PD.[18] The study was not accepted into the database because no baseline data was reported on the ten patients in the study. They all underwent bilateral STN electrode implants, and the UPDRS scores of nine patients were assessed six months postoperatively, off medication, with stimulation off, on unilaterally, and on bilaterally. For all parameters measured, bilateral stimulation resulted in the greatest improvement, although unilateral STN DBS also led to moderate improvement in all PD symptoms.

One study that was published too late to meet the inclusion criteria for this systematic review was an RCT comparing the outcomes of embryonic tissue transplantation to sham surgery.[19] The active group consisted of 20 patients who underwent transplantation of human embryonic mesencephalic tissue containing dopamine neurons into their putamens. A control group of equal size underwent sham surgery, in which burr holes were drilled into their skulls, without penetration of the dura. The mean subjective global rating scores reported by patients one year after surgery were not significantly different between the two groups. The mean total UPDRS "off" scores one year postoperatively improved in the transplantation group compared to the control group, but the difference was not statistically significant ($p=0.11$). Patients ≤ 60 in the active group had significantly better UPDRS total, motor, rigidity, and bradykinesia scores than patients in the sham surgery group. Patients > 60 in the active group showed mild, not statistically significant improvement in UPDRS total scores, but no improvement in bradykinesia. Tremor did not improve in either age group.

The transplanted embryonic dopamine neurons survived well, as evidenced by 18F-fluorodopa PET scans in 19 transplant recipients, and autopsies in two transplant recipients who died of causes unrelated to their surgeries. Five of the younger patients who initially responded well to transplants developed severe, refractory dystonia and dyskinesia after the first year after transplantation. The researchers postulated that the transplanted embryonic dopamine neurons were producing too much dopamine in these patients.

While the initial results of embryonic tissue transplantation appeared promising in the younger patients, the development of late dystonia and dyskinesia clearly showed that this procedure is not a panacea for PD patients.

Psychological

The **PSY**chosis and **CLO**zapine in **P**arkinson'**S** Disease (PSYCLOPS) trial examined the effects of clozapine on dopaminergic-induced psychosis.[20] As the trial lasted only four weeks, it did not meet the criteria for acceptance into our database, however, the study is worthy of mention due to the paucity of information on treatment of patients with antiparkinsonian drug-induced psychosis. Sixty PD patients with hallucinations or delusions induced by antiparkinsonian drugs were randomized to receive low-dose clozapine (n=30) or placebo (n=30). Dosage was titrated between 6.25 and 50 mg daily, depending on clinical response. In the treatment of schizophrenia, clozapine is generally prescribed at a much higher dosage of 300 to 900 mg daily. Patients in the clozapine group showed improvement in all measures of psychosis, and had no worsening of motor symptoms. There was a statistically significant improvement in tremor in the patients in the clozapine group. During the four weeks of the trial, one patient on clozapine developed leukopenia, and one discontinued clozapine due to sedation. In an open-label extension of the trial, another patient developed leukopenia, and six patients died. The investigators did not believe that any of the deaths were related to clozapine use. While these results are promising, RCTs of longer duration are needed, particularly to evaluate adverse events.

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Appendix K. Acronyms in This Report

AAN = American Academy of Neurology

ACTH = adrenocorticotropic hormone

AD = Alzheimer's Dementia

ADL = activities of daily living

AEs = adverse events

AHRQ = Agency for Healthcare Research and Quality

ASHA = American Speech-Language-Hearing Association

BDI = Beck Depression Inventory

CAPIT = core assessment program for intracerebral transplantations

CAPSIT-PD = core assessment program for surgical interventional therapies in Parkinson's Disease

CBD = corticobasal degeneration

CBF = cerebral blood flow

COMT = catechol O-methyl transferase

CR = controlled release

CSF = cerebrospinal fluid

CT = computerized tomography

DA = dopamine agonist

DATATOP = deprenyl and tocopherol antioxidative therapy for Parkinson's Disease

DBS = deep brain stimulation

DEF = data extraction form

DLBD = diffuse Lewy body disease

EMG = electromyogram

FSMT = French selegiline multicenter trial

GH = growth hormone

GPi = globus pallidus

H&Y = Hoehn & Yahr Disability Scale

HVA = homovanillic acid

IBZM = ^{123}I-iodobenzamide

IPD = idiopathic Parkinson's Disease

ITT = intention to treat

L-dopa = levodopa

LFT = liver function tests

LDI = Leonard Davis Institute

LID = L-dopa-induced dyskinesia

LSVT = Lee Silverman Voice Treatment

MAOB = monoamine oxidase B

MRI = magnetic resonance imaging

MSA = multiple system atrophy

MT = music therapy

NHP = Nottingham Health Profile

NMR = nuclear magnetic resonance

NPV = negative predictive value

nRCT = non-randomized controlled trial

NUDS = Northwestern University Disability Score

ODT = odor discrimination test

OIT = odor identification test

OPT = orofacial physiotherapeutic treatment

OT = occupational therapy

PBL - peripheral blood lymphocyte

PD = Parkinson's Disease

PDI = peripheral decarboxylase inhibitor

PET = positron emission tomography

PIGD = postural instability and gait disturbance

PMT = premotor time

PPV = positive predictive value

PRL = prolactin

PROPATH = a patient education and health promotion program

PSP = progressive supranuclear palsy

PSYCLOPS = **psy**chosis and **clo**zapine in **P**arkinson'**s** Disease

PT = physical therapy

QC = quality control

QoL = quality of life

RAS = rhythmic auditory stimulation

RCT = randomized controlled trial

ROC = receiver operating characteristic

ROI = region of interest

S&E = Schwab and England scale

SLI = somatostatin-like immunoreactivity

SPECT = single photon emission computed tomography

SPM = statistical parametric mapping

SSRI = selectove serotonin reuptake inhibitor

STN = subthalamic nucleus

TCCS = transcranial color-coded real-time sonography

TEP = technical expert panel

TMS = transcranial magnetic stimulation

TOO = task order officer

UCS = uncontrolled case series

UPDRS = Unified Parkinson Disease Rating Scale

UPSIT = University of Pennsylvania Smell Identification Test

VEP = visual evoked potentials

WRS = Webster Rating Scale

XS = cross sectional