Evidence-Based Guide to Key Care Processes in Parkinson's Disease Management

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The  logo on the cover is the official logo of the Parkinson's Disease Research, Education, and Clinical Centers (PADRECCs). More details can be found on page 4.

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The care processes highlighted with a 🎖 were rated by an expert panel of movement disorder specialists to have a high "impact on patient outcomes", yet are likely to reflect areas where there currently is "room for improvement." For more details, see page 4.

Introduction

The goal of this monograph is to serve as a resource guide to evidence-based, "best practices" for clinicians who care for patients with Parkinson's Disease (PD). The monograph contains evidence summaries for 41 key care processes in PD. Each of the care processes was carefully reviewed and rated by a national panel of movement disorder experts - following a scientific process -and met threshold levels for validity.

PD is a chronic, progressive neurological condition and a major cause of disability. Appropriate management of PD is challenging to clinicians because of the availability of a wide range of effective pharmaceutical and non-pharmaceutical interventions. To improve the medical care of PD patients throughout the Veteran's Administration (VA), the VA approved the establishment of six Parkinson's Disease Research, Education, and Clinical Centers (PADRECCs) in February, 2001.

In 2002, a team of PADRECC health services researchers who are also VA neurologists developed and evaluated a set of evidence-based quality indicators for the management of PD. These researchers reviewed the medical literature for existing guidelines, randomized controlled trials, and observational studies relevant to the management of PD patients. After reviewing this literature, the team drafted a list of evidence-based care processes specific to the management of PD patients and prepared written summaries of the existing evidence for each care process. These PD-specific processes are organized into 5 areas of care.

Initial Diagnosis and Treatment of PD
Management of Motor Complications
Management on Non-Motor Complications
Management of Dementia, Depression, and Psychosis
Education and Reporting

Following a specific protocol, in November, 2002, an expert panel of VA movement disorders specialists determined that 41 PD-specific care processes met threshold levels for validity.[2] In this monograph are the evidence summaries and supporting reference citations for these 41 PD-specific care processes.

Of these 41 care processes, the expert panel's ratings for 16 met *additional* threshold criteria for (1) having the potential for a high impact on patient outcomes if the care process is followed, and (2) likely to reflect areas where there currently is "room for improvement." These 16 care processes are highlighted with a  indicating they may be areas to particularly target for care improvement efforts.

The large number of quality indicators developed by the Assessing Care of Vulnerable Elders (ACOVE) project[1] were also reviewed; out of these, 33 generic care processes were identified as particularly relevant to PD patients. These 33 generic care process were in clinical areas such as fall assessment, treatment of urinary incontinence, and

dementia care. These 33 selected ACOVE care processes and evidence summaries are being collected into a *separate* monograph.

As research in PD moves forward, the evidence supporting “best practices” in PD care will evolve. A goal of the VA PADRECCs is to stay abreast of these changes and regularly update and disseminate this monograph as part of a broader effort to take new evidence in PD care “from bench to bedside,” with the ultimate goal of improving the health of all veterans with PD.

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Initial Diagnosis and Treatment of PD

Guide to Level of Evidence*

A:	Methods strong, results consistent – RCTs, no heterogeneity
1:	Effect clear – Clear that benefits do (or do not) outweigh risks
A:	Methods strong, results consistent – RCTs, no heterogeneity
2:	Effect equivocal – Uncertainty whether benefits outweigh risks
B:	Methods strong, results inconsistent – RCTs, heterogeneity present
1:	Effect clear – Clear that benefits do (or do not) outweigh risks
B:	Methods strong, results inconsistent – RCTs, heterogeneity present
2:	Effect equivocal – Uncertainty whether benefits outweigh risks
C:	Methods weak – Observational studies
1:	Effect clear – Clear that benefits do (or do not) outweigh risks
C:	Methods weak – Observational studies
2:	Effect equivocal – Uncertainty whether benefits outweigh risks

* Guyatt GH, Cook DJ, Sackett DL, Eckman M, Pauker S. Grades of Recommendation for Antithrombotic Agents. Chest 1998;114:441S-444S.

Care Process:

1. Before making a diagnosis of PD in a patient who is also receiving medication known to cause parkinsonism (e.g. neuroleptics), performing either (1) a trial of withdrawal of the medication, (2) a trial substituting a low-potency neuroleptic in place of a high-potency neuroleptic (if on a high-potency neuroleptic), or (3) documenting in the medical record that the medication cannot be withdrawn

Evidence sources: Two systematic reviews. Observational studies.

Level of Evidence: C1

Summary: Many drugs have been associated with symptoms of parkinsonism in observational studies. These drugs include typical and most "atypical" neuroleptic medications, dopamine-depleting agents, some calcium channel blocking agents, and a number of other compounds. Observational studies have shown a high prevalence of extrapyramidal side effects in patients receiving neuroleptics. This prevalence is much higher than that of idiopathic PD. Systematic reviews of randomized trials show that "atypical" neuroleptics including risperidone and olanzepine are less likely to cause parkinsonism than older neuroleptics, but that these newer agents still have more extrapyramidal side effects than clozapine.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: Two Cochrane reviews addressed the frequency of extra-pyramidal side effects, including parkinsonism. Tuunainen[1] found that olanzepine and risperidone both had more extra-pyramidal side effects than clozapine (16% vs. 8%). In turn, Kennedy et al[2] found that risperidone had less extra-pyramidal side effects than haloperidol and a group of other, older neuroleptics (OR=0.43; 95% CI 0.34-0.55).

Randomized Controlled Trials: none

Other studies/Reviews/Issues: In 1961, Ayd [3] reported extra-pyramidal reactions in 39 percent of a group of 3775 patients receiving neuroleptic medications. Case-series have also reported parkinsonism as a side-effect of the nausea medications prochlorperazine and metoclopramine.[4,5] In case reports and case series, reserpine [6] and tetrabenazine [7] have also been reported to cause parkinsonism. The calcium-channel blockers flunarazine and cinnarizine are derived from piperazine and have been associated with parkinsonism, as well.[8,9]

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Care Process:

2. Conducting at least one assessment of functional status in a PD patient

Evidence sources: one systematic review of RCTs of all antiparkinsonian medications

Level of Evidence: A1

Summary: According to a Movement Disorder Society systematic review, no medication has been proven to slow the progression of PD. Therefore, the indication for all PD medications is symptomatic treatment. One indication for symptomatic treatment is limitation of functional status. By assessing functional status, providers can determine if initiation of PD medications is warranted.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on pharmacotherapy in Parkinson's disease. [1-15] It reviewed the medical literature between 1966 and January 2001. The review concluded that there was insufficient evidence to determine if any medication could prevent disease progression. However, the review stated that levodopa (regular or sustained-release), selegiline, dopamine agonists, anticholinergic medications, and amantadine were all either EFFICACIOUS or LIKELY EFFICACIOUS as symptomatic monotherapy. Limitations of functional status are an indication to initiate symptomatic treatment.

Randomized Controlled Trials: None

References

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13. MAO-B inhibitors for the treatment of Parkinson's disease. Mov Disord 2002; 17:S38-S44.

14. Anticholinergic therapies in the treatment of Parkinson's disease. Mov Disord 2002; 17:S7-S12.
15. DA agonists - Overview. Mov Disord 2002; 17:S52.

Care Process:

3. Prescribing selegiline, amantadine, levodopa (either sustained-release or regular), or a dopamine agonist to a newly diagnosed PD patient who has impairment in activities of daily living.

Evidence Sources: One practice guideline, one systematic review, and many randomized controlled trials

Level of Evidence: A1

Summary: No medication has been proven to slow the progression of PD. However, based on numerous RCTs, several medications offer symptomatic control of PD symptoms. Both an AAN practice guideline and a Movement Disorder Society systematic review recommended selegiline, levodopa (sustained-release or regular), or dopamine agonists as monotherapy symptomatic treatment for patients with PD.

Details of Literature Review

Practice Guidelines: The American Academy of Neurology published a practice parameter on the initiation of treatment for Parkinson's disease. [1] It reviewed the medical literature between 1966 and 2000. It recommended that selegiline could be used to confer mild, symptomatic benefit prior to institution of dopamineregic therapy, though there was no convincing evidence for a neuroprotective effect. It also recommended levodopa (in slow-release or regular), and the dopamine agonists cabergoline, ropinirole, and pramipexole as effective in ameliorating motor and ADL disability. The practice guideline found no differences in efficacy between sustained-release and regular levodopa. It also found no differences in the rate of developing motor complications between regular and sustained-release levodopa.

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on pharmacotherapy in Parkinson's disease. [2-16] It reviewed the medical literature between 1966 and January 2001. The review concluded that there was insufficient evidence to determine if any medication could prevent disease progression. The MDS assessed levodopa as MORE EFFICACIOUS or LIKELY MORE EFFICACIOUS than any other antiparkinsonian medication monotherapy for symptomatic control. The MDS assessed sustained-release levodopa as EQUALLY EFFICACIOUS as regular levodopa in improving motor symptoms, but also stated that sustained-release levodopa was not useful in preventing the development of levodopa induced motor complications. The MDS assessed selegiline and the dopamine agonists pergolide, pramipexole, and ropinirole as EFFICACIOUS for symptomatic monotherapy. Lastly, the MDS assessed anticholinergic therapies, amantadine, and the dopamine agonists bromocriptine, dihydroergocryptine, and lisuride as LIKELY EFFICACIOUS for symptomatic monotherapy (though this recommendation is not as strong as EFFICACIOUS).

Randomized Controlled Trials: There are no placebo-controlled RCT for levodopa, but it is used as the control group in many RCTs. Two large 5-year RCTs compared sustained-release and regular levodopa on efficacy and development of motor complications, but found them to be equivalent. [17-19]

Selegiline was used in 6 RCTs. [20-25] All but one showed a modest symptomatic benefit to selegiline. The one study that didn't show a benefit to selegiline had a crossover design, but no "washout" phase. [25] Multiple large RCTs show benefit to pramipexole [26-29] and ropinirole [30-32] monotherapy. Cabergoline was used in one RCT. [33] The AAN practice guideline cited this trial as evidence for efficacy, but the MDS cited INSUFFICIENT EVIDENCE for the efficacy of cabergoline monotherapy. Pergolide was cited in one RCT. [34] The MDS cited this trial as EFFICACIOUS, but the AAN practice guideline did not reference this trial.

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Care Process:
4. Discussing the tradeoffs of initiating dopamine agonists versus levodopa with a newly diagnosed PD patient who has impairment in activities of daily living.

Evidence Sources: One practice guideline, two systematic reviews, several RCTs

Level of Evidence: A1

Summary: Both an AAN practice guideline and a Movement Disorder Society systematic review recommend either levodopa or dopamine agonists to reduce disability in patients with PD. However, there are benefits and drawbacks for each option. Levodopa is thought to provide greater symptomatic relief than the dopamine agonists. However, several of the dopamine agonists have been shown to delay motor complications when compared to levodopa-treated patients with PD.

Details of Literature Review

Practice Guidelines: The American Academy of Neurology published a practice parameter on the initiation of treatment for Parkinson's disease. [1] It reviewed the medical literature between 1966 and 2000. It assessed levodopa and the dopamine agonists cabergoline, ropinirole, and pramipexole as effective in ameliorating motor and activities of daily living (ADL) disability. It stated that levodopa was more effective than the dopamine agonists in treating motor and ADL disability. However, levodopa was more likely than the dopamine agonists to be associated with motor complications, such as wearing off, dyskinesias, and on-off motor fluctuations. The dopamine agonists were more likely than levodopa to be associated with adverse events such as hallucinations, somnolence, and edema.

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on the role of levodopa and dopamine agonists in Parkinson's disease. [2-12] It reviewed the medical literature between 1966 and January 2001. It assessed levodopa monotherapy as MORE EFFICACIOUS in relieving symptoms than dopamine agonist monotherapy. However, it also recommended cabergoline, pergolide, pramipexole, and ropinirole as EFFICACIOUS in reducing the long-term risk of motor complications.

Metaworks prepared a systematic review of the literature regarding diagnosis and treatment of patients with PD for the Agency for Healthcare Research and Quality (AHRQ). [13] It searched the English language literature from 1990 to 2000. It found that in studies in which patients were randomized to levodopa versus levodopa plus a dopamine agonist (DA) (levodopa was mandatory in these trials), the combination of levodopa plus a dopamine agonist resulted in better UPDRS scores than levodopa alone. However, in studies in which patients were randomized to levodopa versus DAs, in which additional levodopa was discretionary, levodopa treatment resulted in better UPDRS scores than levodopa plus DA treatment. It concluded that there was not

enough evidence to make conclusions regarding whether initial treatment with levodopa versus a dopamine agonist was more or less beneficial.

Randomized Controlled Trials: A large RCT compared cabergoline versus levodopa as initial therapy for PD in 412 patients. [14] The levodopa group had better improvement in UPDRS scores than the cabergoline group (no statistical comparison made). However, after 3-5 years, fewer patients in the cabergoline group reached the motor complication endpoint than the levodopa group (22% vs. 34%, p<0.02).

A large RCT compared pramipexole versus levodopa as initial therapy for PD in 301 patients. [15] The levodopa group had significantly greater improvement than the pramipexole group in both the motor and ADL portions of the UPDRS (p<0.001). However, after 23.5 months, the pramipexole group (28%) were significantly less likely to develop dopaminergic motor complications than the levodopa group (51%) (p<0.001). Adverse effects caused the early withdrawal of about 15% of subjects. The incidence of somnolence (32% vs. 17%, p<=0.003), hallucinations (9% vs. 3%, p=0.03), generalized edema (18% vs. 8%, p=0.01), and peripheral edema (15% vs. 4%, p=0.002) were higher in the pramipexole group than in the levodopa group.

A large RCT compared ropinirole versus levodopa as initial therapy for PD for PD in 268 patients. [16] The levodopa group had significantly better scores than the ropinirole group in the motor portion of the UPDRS (p<0.001). However, after 5 years, patients in the ropinirole group were significantly less likely to develop dyskinesias as the levodopa group (20% versus 45%, p<0.001). Adverse events caused the early withdrawal of about 30% of subjects. The incidence of hallucinations (17% vs. 6%), edema (14% vs., 6%), and somnolence (27% vs. 19%) were higher in the ropinirole group than in the levodopa group.

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Care Process:

5. Starting a dopamine agonist at a low dose and gradually titrating it to the therapeutic range for a PD patient who is prescribed the agonist as monotherapy.

Evidence sources: One RCT, package inserts

Level of Evidence: A1

Summary: An RCT of the dopamine agonist bromocriptine found that patients on a "low/slow" regimen of bromocriptine were less likely to withdraw from the RCT due to adverse effects than those patients on a "high/fast" regimen. The package insert for the dopamine agonist pramipexole states, "in all clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse effects…[The medication] should be titrated gradually in all patients". The package insert for the dopamine agonist ropinirole states, "in all clinical studies, dosage was initiated at a subtherapeutic level and gradually titrated to therapeutic response. The dosage should be increased to achieve a maximum therapeutic effect balanced against the principal side effects".

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: The UK Bromocriptine Research Group studied 134 patients with untreated PD. [1] Patients were randomized to a "low/slow" or "high/fast" regimen of bromocriptine. The "low/slow" dose started at 0.625 mg/day, then titrated upward at a maximum of 1.25 mg/week until a maximum dose of 25 mg/day. The "high/fast" regimen started at a dose of 2.5 mg/day, then titrated upward at a maximum rate of 5 mg/week until a maximum dose of 100 mg/day. The desired outcome was a 33% improvement in disability scores after 26 weeks. A significantly higher proportion of patients in the "high/fast" group than the "low/slow" group had severe adverse effects that resulted in withdrawal from the trial (36% vs. 20%, $p<0.05$).

Other studies/Review/Issues: The package insert for the dopamine agonist pramipexole states, "in all clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse effects…[The medication] should be titrated gradually in all patients". The package insert for the dopamine agonist ropinirole states, "in all clinical studies, dosage was initiated at a subtherapeutic level and gradually titrated to therapeutic response. The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principal side effects". [2, 3]

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Care Process:

6. Providing education about the timing of intake of dietary amino acids and its impact on response to levodopa to a PD patient with motor fluctuations and who is taking levodopa

Evidence Sources: several observational studies; Physician's Desk Reference

Level of Evidence: C1

Summary: One expert opinion recommends that patients be educated about dietary issues of special concern for PD. This review notes that "Dietary amino acids can compete with levodopa for absorption from the GI tract and for transport into the brain. Therefore, they can cause erratic and unpredictable responses to levodopa therapy (Nutt, et al, 1984; Nutt et al, 1990). Patients with advanced PD should be aware of this interaction because it can lead to delayed "on" and no "on" responses if levodopa is taken with a meal, and the protein content limits the amount of levodopa that can gain entry into the brain…Ideally, PD patients should take levodopa on an empty stomach to facilitate absorption, but nausea may necessitate the administration of levodopa with some food. In this case, it is preferable for patients to take levodopa with a low-protein meal." (from Olanow et al, 2001, page S73). The Physician's Desk Reference (PDR) under "Precautions" with respect to Sinemet states that patients "should be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation …The above factors may reduce the clinical effectiveness of the levodopa or carbidopa-levodopa therapy" (from PDR 2000, page 977). Other expert opinion also support education about timing of dietary protein intake.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: none

Other sources: The expert opinion and algorithm of Olanow et al (2001) recommends that patients be educated about dietary issues of special concern for PD. They note that "Dietary amino acids can compete with levodopa for absorption from the GI tract and for transport into the brain. Therefore, they can cause erratic and unpredictable responses to levodopa therapy (Nutt, et al, 1984; Nutt et al, 1990). Patients with advanced PD should be aware of this interaction because it can lead to delayed "on" and no "on" responses if levodopa is taken with a meal, and the protein content limits the amount of levodopa that can gain entry into the brain…Ideally, PD patients should take levodopa on an empty stomach to facilitate absorption, but nausea may necessitate the administration of levodopa with some food. In this case, it is

preferable for patients to take levodopa with a low-protein meal." (from Olanow et al, 2001, page S73).

The Physician's Desk Reference (PDR) under "Precautions" with respect to Sinemet states that patients "should be advised that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation…The above factors may reduce the clinical effectiveness of the levodopa or carbidopa-levodopa therapy" (from PDR 2000, page 977).

Other expert opinion supports educating patients about timing of dietary protein intake and levodopa.

References

Physician's Desk Reference 2000. 54th Edition. Medical Economics Company. Montvale, New Jersey, page 977.

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Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): Treatment guidelines. *Neurology* 2001;56 (Suppl 5):S72-73.

Adler, CH; Ahlskog JE. Parkinson's Disease and Movement Disorders. 2000 Totowa: Humana Press, p. 167-168.

Care Process:

7. Referring to physical therapy a PD patient who has impairment of ADLs or in walking ability.

Evidence sources: four systematic reviews, multiple small RCTs.

Level of Evidence: A2

Summary: Two systematic reviews by the Movement Disorders Society and by the Agency for Healthcare Research and Quality, as well as a meta-analysis, recommend physical therapy for all PD patients who have impairment of ADLs or in walking ability. Though physical therapy programs studied in RCTs differ by study participants, specific exercise therapies, and measured outcomes, there is a consistent improvement in function seen across the studies, with no mention of adverse effects.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on the role of physical therapy in Parkinson's disease. [1] They reviewed the medical literature between 1966 and January 2001. They stated that no specific physical therapy regimen can be recommended over another due to lack of evidence. Nonetheless, given the consistent benefits seen in most studies of physical therapy, they considered physical therapy as LIKELY EFFICACIOUS for improving function while the patient is receiving therapy.

A meta-analysis prepared for the Agency of Healthcare Research and Quality (AHRQ) concluded that physical therapy improved function while patients were enrolled in such programs. They caution that a few studies show a worsening to baseline impairment after the physical therapy sessions have been discontinued. [2]

A meta-analysis by de Goede et al analyzed the results of 12 studies of physical therapy for PD patient. Significant summary effect sizes (SES) were found for Activities of Daily Living (SES=0.40. CI=0.17-0.64), walking speed (SES=0.49. CI=0.21-0.77), and stride length (SES=0.46. CI=0.12-0.82). No significant SES was found for neurologic signs (such as rigidity and tremor). [3] They conclude that PD patients benefit from physical therapy added to their medical regimen.

A meta-analysis prepared for the Cochrane database of systematic reviews could not reach a conclusion whether physical therapy was effective in PD patients because all found trials had methodological flaws; none could be included for their meta-analysis. [4]

Randomized Controlled Trials:

There are multiple small randomized trials. [5-12] Most of the trials showed benefit for PD patients in the physical therapy program. One study showed that benefits did not persist, [10] two studies showed some persistent improvement [8, 12], and the other studies did not have a long-term evaluation. Only one study used the UPDRS as an outcome measure. [10]

References

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12. Katsikitis M, Pilowsky I. A controlled study of facial mobility treatment in Parkinson's disease. J Psychosom Res 1996; 40:387-96.

Care Process:

8. Reassessing a PD patient for complications of PD (such as worsening functional status, excessive daytime somnolence, speech and swallowing difficulties, dementia, depression, and psychosis) on at least an annual basis

Evidence sources: ACOVE indicators

Level of Evidence: C1 (for performing periodic reviews)

Summary: There are no RCTs on the optimal time interval for the reassessment of PD symptoms. Some ACOVE (Assessing Care of Vulnerable Elders) quality indicators state that certain assessments (drug regimen review, asking about falls, etc.) should be repeated on an annual basis. Given the progressive nature of PD, patients are likely to develop new symptoms or worsening of current symptoms over time. Periodic assessments that detect these symptoms can lead to early intervention.

Details of Literature Review

Practice Guidelines: None

Systematic Reviews: ACOVE (Assessing Care of Vulnerable Elders) was a large-scale study undertaken several years ago by RAND researchers. The project's goals were to "develop a comprehensive set of quality-assessment tools for ill older persons." Over 200 quality indicators for 22 "diseases, geriatric syndromes, physiologic impairments, and clinical situations" were developed under ACOVE, with the aid of several expert panels. Several of the ACOVE indicators state that an assessment should be repeated on an annual basis. These ACOVE indicators include annual assessment of falls, annual periodic drug regimen review, annual assessment of pain in symptomatic osteoarthritis, annual counseling of smoking cessation, and annual documentation of the presence or absence of urinary incontinence. [1]

Randomized Controlled Trials: None

References

1. Shekelle PG, MacLean CH, Morton SC, Wenger NS. Acove quality indicators. Ann Intern Med 2001; 135:653-67.

Management of Motor Complications

Guide to Level of Evidence*

A: Methods strong, results consistent – RCTs, no heterogeneity
1: Effect clear – Clear that benefits do (or do not) outweigh risks

A: Methods strong, results consistent – RCTs, no heterogeneity
2: Effect equivocal – Uncertainty whether benefits outweigh risks

B: Methods strong, results inconsistent – RCTs, heterogeneity present
1: Effect clear – Clear that benefits do (or do not) outweigh risks

B: Methods strong, results inconsistent – RCTs, heterogeneity present
2: Effect equivocal – Uncertainty whether benefits outweigh risks

C: Methods weak – Observational studies
1: Effect clear – Clear that benefits do (or do not) outweigh risks

C: Methods weak – Observational studies
2: Effect equivocal – Uncertainty whether benefits outweigh risks

* Guyatt GH, Cook DJ, Sackett DL, Eckman M, Pauker S. Grades of Recommendation for Antithrombotic Agents. Chest 1998;114:441S-444S.

Care Process:
9. Assessing for the presence of motor complications (wearing-off, on-off fluctuations, or dyskinesia) at least every six months in a PD patient who is receiving therapy with a dopaminergic medication (levodopa or a dopamine agonist).

Evidence sources: Five observational studies

Level of Evidence: C1

Summary: The literature on the impact of motor complications on quality of life shows mixed results. In general, studies of patients with less severe complications do not show an impact on quality of life. However, studies of more advanced patients do find an adverse impact of motor complications on quality of life. Because some patients are likely to be adversely affected by motor complications, and because therapeutic interventions can modify motor complications, it is reasonable to assess patients for the presence of these problems on a regular basis.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: none

Other studies/Reviews/Issues: Karlsen et al[1] and Schrag et al[2] found no relationship between the presence of motor complications and standard measures of quality-of-life in community-based samples of patients with relatively mild PD. A specialty-clinic based study of slightly more advanced patients[3] had similar findings.

By contrast, Diamiano et al[4] and Pechevis et al[5] found that patients with motor complications had lower scores on standard measures of QOL including the PDQ-39 and SF-36. These studies were conducted in patients with more advanced disease. The mean disease duration in these studies was 9.0 and 8.8 years, respectively.

References

1. Karlsen KH, Tandberg E, Aarsland D, Larsen JP. Health related quality of life in Parkinson's disease: a prospective longitudinal study. Journal of Neurology, Neurosurgery and Psychiatry, 69: 584-589.
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3. Siderowf A, Ravina B, Glick HA. Preference-based quality of life in patients with Parkinson's disease. Neurology, 59: 103-108.

4. Damiano AM, McGrath MM, William MK, Snyder DF, LeWitt PA, Richter RR. Evaluation of a measurement strategy for Parkinson's disease: patients health-related quality-of-life. Quality of Life Research, 9: 87-100.
5. Pechevis, M., Clarke, C. E., Vieregge, P., Ziegler, M., Berdeaux, G., Barland, J. C., and Gardiner, J. Direct and indirect osts of Parkinson's disease and L-dopa induced dyskinesia: A prospective European study. Parkinsonism and Related Disorders 7(suppl), S106. 2001.

Care Process:

10. Offering a PD patient with end-of-dose wearing-off and with impairments of daily living one of the following options:

1) addition of a dopamine agonist (bromocriptine, pergolide, pramipexole or ropinirole),
2) addition of a COMT inhibitor (entacapone),
3) more frequent dosing of levodopa, OR
4) addition of a selective MAO-B inhibitor or amantadine.

Evidence sources: Twelve systematic reviews (eleven Cochrane and one by the Movement Disorder Society). Many RCTs

Level of Evidence: A1 (for the use of dopamine agonists and COMT inhibitors)

Summary: A large number of clinical trials support the role of dopamine agonists in treating wearing-off symptoms. Several trials also support the use of entacapone for wearing off. Both of these strategies reduce “off” time by about 30%. Two trials comparing dopamine agonists (pergolide and bromocriptine) to a COMT inhibitor (tolcapone) found no difference in efficacy. The strategy of reducing the interval between levodopa doses is widely practiced, although not formally studied.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: Cochrane reviews have compiled information on the large number of clinical trials of dopamine agonists for wearing-off symptoms. [1-9] These systematic reviews have shown that the dopamine agonists approved in the US are all efficacious in reducing wearing-off symptoms, and that no agonist is clearly superior to any other agonist.

In reviewing this literature, the reviewers for the Movement Disorders Society concluded that all dopamine agonists approved in the United States are either LIKELY EFFICACIOUS or EFFICACIOUS in reducing wearing-off symptoms.

In reviewing the literature on the efficacy of entacapone for treatment of wearing off, the Movement Disorders Society concluded that entacapone is EFFICACIOUS in the management of motor fluctuations.[10]

Randomized Controlled Trials: The many clinical trials of dopamine agonists are summarized in the “systematic reviews” section, above.

Two large-scale randomized, controlled trials have shown that entacapone is effective in reducing wearing-off symptoms. The Parkinson Study Group (1997)[11] found that entacapone treatment significantly increased the (absolute) percent "on" time by 5.0 percentage points (equal to about 1h) when compared to placebo. The effect of

entacapone was more prominent in patients with a smaller percent "on" time (<55%) at baseline, and increased as the day progressed. Nomecomt Study (1998)[12] found that entacapone significantly increased the mean "on" time by 1.4 h and correspondingly decreased the "off" time by 1.1 hour. The average benefit derived from the (first) morning levodopa dose as related by the patients was increased significantly by 0.24 h. The daily levodopa dose was reduced significantly in the entacapone group by 113 mg (12%).

Two randomized, controlled studies compared tolcapone to pergolide and bromocriptine for treatment of early wearing-off.[13,14] These studies found no difference between the two strategies. (Portions of the preceding text were adapted from Management of Parkinson's Disease, Movement Disorders, Volume 17; suppl.4)

Other studies/Reviews/Issues: Although widely practiced, the strategy of increasing the dosage of levodopa or reducing the interval between levodopa doses has not been formally studied.

References

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2. Clarke CE, Deane KH. Cabergoline for levodopa-induced complications in Parkinson's disease. Cochrane Database of Systematic Reviews 2002;(Issue:3):3.
3. Clarke CE, Deane KD. Cabergoline versus bromocriptine for levodopa-induced complications in Parkinson's disease. Cochrane Database of Systematic Reviews 2002;(Issue:3):3.
4. Clarke C, Speller J. Lisuride for levodopa-induced complications in Parkinson's disease. Cochrane Database of Systematic Reviews 2002;(Issue:3):3.
5. Clarke C, Speller J. Lisuride versus bromocriptine for levodopa-induced complications in Parkinson's disease. Cochrane Database of Systematic Reviews 2002;(Issue:3):3.
6. Clarke C, Speller J. Pergolide for levodopa-induced complications in Parkinson's disease. Cochrane Database of Systematic Reviews 2002;(Issue:3):3.
7. Clarke C, Speller J, Clarke J. Pramipexole for levodopa-induced complications in Parkinson's disease. Cochrane Database of Systematic Reviews 2002;(Issue:3):3.
8. Clarke CE, Deane KHO. Ropinirole for levodopa-induced complications in Parkinson's disease. Cochrane Database of Systematic Reviews 2002;(Issue:3):3.
9. Clarke CE, Deane KHO. Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's disease. Cochrane Database of Systematic Reviews 2002;(Issue:3):3.

10. Goetz CG, Koller WC, Poewe W, Rascol O, Sampaio C. Management of Parkinson's Disease: An Evidence-based review. Movement Disorders 2002; 17(suppliment 4).
11. Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Ann Neurol 1997; 42:747-755.
12. Rinne UK, Larsen JP, Siden A, Worm Petersen J, and the Nomecomt Study Group. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Neurology 1998; 51:1309-1314.
13. Koller W, Lees A, Doder M, Hely M, Tolcapone/Pergolide Study Group. Randomized trial of tolcapone versus pergolide as add-on to levodopa therapy in Parkinson's disease patients with motor fluctuations. Movement Disorders 2001; 16(5):858-866.
14. Efficacy and tolerability of tolcapone compared with bromocriptine in levodopa-treated parkinsonian patients. Tolcapone Study Group. Movement Disorders 1999; 14(1):38-44.

Care Process:

11. Offering a PD patient with end-of-dose wearing-off that has persisted after an initial medication adjustment one of the following options:

1) Addition of a dopamine agonist or COMT inhibitor (if the initial adjustment was increasing the frequency of levodopa dosing),

2) Addition of a COMT inhibitor or more frequent levodopa dosing (if the initial adjustment was adding a dopamine agonist),

3) Adding a dopamine agonist or increasing the frequency of levodopa dosing (if the initial adjustment was adding a COMT inhibitor), OR

4) Adding another adjunctive medication (selegiline or amantadine).

Evidence sources: Twelve systematic reviews (eleven Cochrane and one by the Movement Disorder Society) and many RCTs

Level of Evidence: A1 (for COMT inhibitors)

Summary: Dopamine agonists were allowed as concomitant therapy in trials of COMT inhibitors. Therefore, there is high-quality evidence to support the use of COMT inhibitors as adjunct to levodopa and agonist combination therapy. However, all trials of dopamine agonists as adjunctive therapy for treatment of motor complications were conducted before the availability of COMT inhibitors. Therefore, there is only indirect evidence for adding dopamine agonists to the combination of levodopa and a COMT inhibitor. As is the case for indicator 2 in this category, although it is widely practiced, there are no controlled trials to support the use of more frequent levodopa to reduce motor complications.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: Cochrane reviews have compiled information on the large number of clinical trials of dopamine agonists for wearing-off symptoms. [1-9] In reviewing this literature, the reviewers for the Movement Disorders Society concluded that all dopamine agonists approved in the United States are either LIKELY EFFICACIOUS or EFFICACIOUS in reducing wearing-off symptoms.

In reviewing the literature on the efficacy of entacapone for treatment of wearing off, the Movement Disorders Society concluded that entacapone is EFFICACIOUS in the management of motor fluctuations.[10]

Randomized Controlled Trials: The very large number of clinical trials of dopamine agonists are summarized in the “systematic reviews” section, above.

Two large-scale randomized, controlled trials have shown that entacapone is effective in reducing wearing-off symptoms. The Parkinson Study Group (1997)[13] found that

entacapone treatment significantly increased the (absolute) percent "on" time by 5.0 percentage points (equal to about 1h) when compared to placebo. The effect of entacapone was more prominent in patients with a smaller percent "on" time (<55%) at baseline, and increased as the day progressed. Nomecomt Study (1998)[14] found that entacapone significantly increased the mean "on" time by 1.4 h and correspondingly decreased the "off" time by 1.1 hour. The average benefit derived from the (first) morning levodopa dose as related by the patients was increased significantly by 0.24 h. The daily levodopa dose was reduced significantly in the entacapone group by 113 mg (12%).

Two randomized, controlled studies compared tolcapone to pergolide and bromocriptine for treatment of early wearing-off.[1;12] These studies found no difference between the two strategies. (Portions of the preceding text were adapted from Management of Parkinson's Disease, Movement Disorders, Volume 17; suppl.4)

Other studies/Reviews/Issues: Although widely practiced, the strategy of increasing the dosage of levodopa or reducing the interval between levodopa doses has not been formally studied.

References

1. Efficacy and tolerability of tolcapone compared with bromocriptine in levodopa-treated parkinsonian patients. Tolcapone Study Group. Movement Disorders. 14:38-44, 1999
2. Clarke C, Speller J: Lisuride for levodopa-induced complications in Parkinson's disease. Cochrane Database of Systematic Reviews3, 2002
3. Clarke C, Speller J: Lisuride versus bromocriptine for levodopa-induced complications in Parkinson's disease. Cochrane Database of Systematic Reviews3, 2002
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13. Parkinson Study Group: Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Ann Neurol 42:747-755, 1997
14. Rinne UK, Larsen JP, Siden A, et al: Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Neurology 51:1309-1314, 1998

Care Process:

12. Prescribing a peripheral decarboxylase inhibitor (carbidopa) and levodopa to a PD patient who is also prescribed COMT inhibitors.

Evidence sources: One systematic review. FDA approved drug package insert

Level of Evidence: C1

Summary:
Catechol-O-methyl transferase (COMT) inhibitors work by increasing the plasma half-life of levodopa. Their mechanism of action suggests that they would not have anti-parkinsonian activity when administered as monotherapy. No trials have investigated their effects as monotherapy.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on the use of COMT inhibitors to treat symptoms of Parkinson's disease. No qualified studies of monotherapy with a COMT inhibitor were identified.

The reviewers concluded that COMT inhibitors are "EFFICACIOUS in improving "on" motor function. Tolcapone is also EFFICACIOUS in patients without motor complications. However, use of this medication requires specialized monitoring of hepatic function."[1]

Randomized Controlled Trials: none

Other studies/Reviews/Issues: The FDA approved package inserts for both entacapone[2] and tolcapone[3] both state that it is indicated only as adjunctive therapy for patients receiving levodopa.

References

1. Goetz, CG, Koller WC, Poewe W, Rascol O, Sampaio. Management of Parkinson's Disease: An evidence-based review. *Movement Disorders.* 2002; 17(suppl. 4).
2. Entacopone package insert, PDR, 2002: pp. 2328-2332.
3. Tolcapone package insert. PDR, 2002: pp. 3010-3014

Care Process:
13. Prescribing tolcapone for a PD patient only if (1) entacopone is contraindicated or (2) entacopone has been tried and found to be ineffective.

Evidence sources: One systematic review. FDA drug warning and approved drug package insert.

Level of Evidence: C1

Summary: Occasional liver function abnormalities were noted in clinical trials of tolcapone. However, in the post-marketing period, at least three cases of fatal liver injury (plus six cases of hepatitis) were reported in patients receiving tolcapone. These cases led to the suspension of tolcapone within the European Union. In the US, the Food and Drug Administration (FDA) recommends serum ALT and AST testing be performed biweekly for the first year, every four weeks for the next six months and every eight weeks thereafter. Roche Laboratories (the maker of tolcapone), in consultation with the FDA, issued a letter to physicians on November 16, 1998, stating that tolcapone should only be used in patients who are either not responding to or are not candidates for other anti-parkinsonian therapies.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on the use of COMT inhibitors to treat symptoms of Parkinson's disease. The reviewers concluded that in non-fluctuating and in fluctuating patients who can be adequately treated with other drugs, tolcapone carries "an UNACCEPTABLE RISK. In fluctuating patients who have failed other therapies, tolcapone has an ACCEPTABLE RISK, BUT REQUIRES SPECIALIZED MONITORING as defined by regulatory authorities in different countries where available (e.g., liver function)."[1]

Randomized Controlled Trials: none

Other studies/Reviews/Issues: At least nine cases of serious liver function abnormalities occurred in the post marketing period, including at least six cases of hepatitis and at least three fatal cases of liver injury[2,3] The European Agency of the Evaluation of Medicinal Products issued a recommendation for the suspension of the marketing authorization for tolcapone in November of 1998.[4] In the US, the Food and Drug Administration required that a boxed warning be added to the approved product labeling warning about potential hepatic injury and recommended regular serum ALT and AST monitoring for patients on tolcapone.[5,6]

References

1. Goetz, CG, Koller WC, Poewe W, Rascol O, Sampaio. Management of Parkinson's Disease: An evidence-based review. *Movement Disorders.* 2002; 17(suppl. 4).
2. Colosimo C. The rise and fall of tolcapone. *J Neurol* 1999; 246(10):880-882.
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5. http:///www.fda.gov/medwatch/safety/1998/tasmar.htm
6. Tolcapone package insert. PDR, 2002: pp. 3010-3014

Care Process:
14. Performing liver function testing on a regular basis on a PD patient who is prescribed tolcapone

Evidence sources: One systematic review, 8 randomized controlled trials, one FDA safety report, one European Union safety report

Level of Evidence: A1 (based on results from RCTs. Post-marketing results are level C2.)

Summary: Occasional liver function abnormalities were noted in clinical trials. However, in the post-marketing period at least three cases of fatal liver injury were reported in patients receiving tolcapone. These cases lead to the suspension of tolcapone within the European Union. In the USA, the Food and Drug Administration (FDA) recommends serum ALT and AST testing be performed biweekly for the first year, every four weeks for the next six months and every eight weeks thereafter.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on the use of catechol-o-methyl transferase (COMT) inhibitors for the treatment of Parkinson's Disease, including safety of these medications.

The objectives of this review were to review the literature and identify the clinical evidence that supports specific treatments chosen because they are commonly used for treatment of PD; to determine which studies are scientifically sound so they can be used as evidence to support or condone specific treatments in clinical practice; and to identify where specific evidence is lacking so future research efforts may be directed toward addressing these specific areas of need.

In reviewing the available information from randomized controlled trials and post-marketing experience, this review concluded that in fluctuating patients who can be adequately treated with other drugs, tolcapone carries "an UNACCEPTABLE RISK. In fluctuating patients who have failed other therapies, tolcapone has an ACCEPTABLE RISK, BUT REQUIRES SPECIALIZED MONITORING as defined by regulatory authorities in different countries where available (e.g., liver function)."[1]

Randomized Controlled Trials:
Three of the eight studies[2-9] report elevated liver transaminases, and the occurrence was 3% to 4%. Of these patients, 37.5% withdrew from the study. Reports on the recovery rate after withdrawal are scarce. Four of the ten patients remaining on treatment were followed and all recovered.

Other studies/Reviews/Issues:

At least nine cases of serious liver function abnormalities occurred in the post marketing period, including at least six cases of hepatitis and at least three fatal cases of liver injury.[10,11] The European Agency of the Evaluation of Medicinal Products issued a recommendation for the suspension of the marketing authorization for tolcapone in November of 1998.[12] In the USA, the Food and Drug Administration required that a boxed warning be added to the approved product labeling warning about potential hepatic injury and recommended regular serum ALT and AST monitoring for patients on tolcapone.[13] (Portions adapted from Management of Parkinson's Disease, Movement Disorders, Volume 17; suppl.4)

References

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Care Process:

15. Offering a PD patient with impairments in activities of daily living or social function as a result of treatment-related dyskinesia (choreiform involuntary movements) one of the following options:

1) **reduce the amount of levodopa at each dosing period,**
2) **add amantadine, OR**
3) **begin discussion of surgical therapy.**

Evidence Sources: One systematic review; 3 randomized controlled trials; eight case series.

Level of Evidence: A1 for amantadine; C1 for surgical interventions

Summary: Although disabling dyskinesias should be treated, no single strategy has been shown to be superior to another. Reducing the dose size of levodopa is a common strategy, but has not been tested in high-quality trials. Several randomized controlled trials have shown that amantadine reduces dyskinesia severity. Case series of surgical interventions have shown dramatic effects of both pallidal and subthalamic nucleus ablation/stimulation on dyskinesia severity.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on the use of several drugs as well as surgery to treat levodopa-related dyskinesias.

The objectives of this review were to review the literature and identify the clinical evidence that supports specific treatments chosen because they are commonly used for treatment of PD; to determine which studies are scientifically sound so they can be used as evidence to support or condone specific treatments in clinical practice; and to identify where specific evidence is lacking so future research efforts may be directed toward addressing these specific areas of need.

The reviewers concluded that there is INSUFFICIENT EVIDENCE to support the efficacy of modifying the dosage or timing of standard levodopa to control motor fluctuations. They concluded that amantadine is EFFICACIOUS in controlling dyskinesias. They concluded that there is INSUFFICIENT EVIDENCE for the efficacy of pallidotomy or deep brain stimulation for the control of dyskinesias due to the lack of controlled trials.[1]

Randomized Controlled Trials: Verhagen et al [2] found a 60% reduction in dyskinesias using amantadine up to a dose of 400mg per day in a double-blind, placebo-controlled crossover study. Snow [3] performed a similar study using doses of amantadine up to 200mg per day, and also found a significant reduction in dyskinesia. Luginger et al [4]

also found that dyskinesias were reduced by about 50% in a double-blind, placebo-controlled crossover study.

Other studies/Reviews/Issues: Although there have been no randomized, controlled trials, a number of case-series have examined the effect of surgery on dyskinesias. A number of case series[5-11] have shown dramatic reductions in dyskinesias following pallidotomy. The Deep Brain Stimulation of Parkinson's Disease Study Group[12] compared patients who had undergone pallidal and sub-thalamic deep brain stimulation, and found that both groups had a significant reduction in dyskinesia relative to before surgery.

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Care Process:

16. Offering surgical options to a PD patient who is not demented, and who is under the age of 75, and with motor fluctuations (including dyskinesias, or on-off fluctuations) that are refractory to optimal medical management. These surgical options could include pallidotomy, pallidal stimulation or subthalamic nucleus stimulation, but not thalamic stimulation or thalamotomy.

Evidence Sources: One systematic review; eight case series.

Level of Evidence: C1

Summary: Case series have shown robust effects of several surgical procedures in treating parkinsonian symptoms. These procedures include pallidotomy, pallidal stimulation and subthalamic nucleus stimulation. However, these procedures have not been compared to placebo or to each other in large-scale randomized trials. Patients in these case series are generally under 75 years of age, have marked motor fluctuations, and are not demented. Case series suggest that thalamotomy is effective for parkinsonian tremor, but not other signs of PD, and does not change functional status.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on the surgical procedures available to treat parkinsonism.

The objectives of this review were to identify from the literature and review the clinical evidence that supports specific treatments chosen because they are commonly used for treatment of PD; to determine which studies are scientifically sound so they can be used as evidence to support or condone specific treatments in clinical practice; and to identify where specific evidence is lacking so future research efforts may be directed toward addressing these specific areas of need.

The reviewers concluded that there is INSUFFICIENT EVIDENCE to support the efficacy of any surgical procedure in controlling the symptoms of PD. This conclusion is based on the lack of high-quality (randomized, controlled) trials.[1]

Randomized Controlled Trials: none

Other studies/Reviews/Issues: Although there have been no randomized, controlled trials, a number of case-series have examined the effect of surgery on symptoms of parkinsonism. A number of cases [2-8] have shown improvements in parkinsonism in the short-term. The long-term effects of pallidotomy in case series are mixed.[9,10] A number of series have shown improvement in parkinsonism with sub-thalamic nucleus stimulation.[11,12] The Deep Brain Stimulation of Parkinson's Disease Study Group [13] compared patients who had undergone pallidal and sub-thalamic deep brain stimulation,

and found that both groups had a significant reduction in parkinsonism relative to before surgery. Case-series of thalamic stimulation for PD have found an improvement in tremor but no change in functional capacity.[14] (Portions of the preceding text were adapted from Management of Parkinson's Disease, Movement Disorders, Volume 17; suppl.4)

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Care Process:
17. Not offering surgical treatment to a PD patient who is demented, has severe impairments of activities of daily living in the "on" state (Schwab and England <75% when "on") or has co-morbid medical conditions that substantially raise the risk of surgical complications

Evidence Sources: One systematic review; eight case series.

Level of Evidence: No published studies have included subjects with these characteristics; thus, no evidence of benefit for PD patients with these characteristics exists.

Summary: Surgical series have not included patients who do not retain a robust response to dopaminergic medications, are over the age of 75 or who have dementia. As a result, evidence suggesting a beneficial effect for surgery does not extend to these patient groups. Some reports have associated pallidotomy with cognitive decline. There have been no such reports for subthalamic nucleus stimulation. Although complications rates are acceptable for appropriate patients, deep brain surgery is associated with intracranial hemorrhage, infection and death. Patients with severe medical conditions may be more prone to complications, and less likely to benefit from surgery.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on the surgical procedures available to treat parkinsonism.

The objectives of this review were to review the literature and identify the clinical evidence that supports specific treatments chosen because they are commonly used for treatment of PD; to determine which studies are scientifically sound so they can be used as evidence to support or condone specific treatments in clinical practice; and to identify where specific evidence is lacking so future research efforts may be directed toward addressing these specific areas of need.

The reviewers concluded that there is ACCEPTABLE RISK for unilateral pallidotomy, and pallidal and sub-thalamic stimulation with SPECIALIZED MONITORING that included *choice of appropriate patients*, adequate surgical expertise and careful follow-up.[1]

Randomized Controlled Trials: none

Other studies/Reviews/Issues: Case series of patients undergoing pallidotomy[2-8] have excluded demented patients and few patients over the age of 75 are included in

these studies. Patients in case series of deep brain stimulation are also young and non-demented.[9,10,11] The mean age in these studies is under 60 years.

Complications in patients who had unilateral pallidotomy have included intracerebral hemorrhages, speech impairment and visual field defects. Transient adverse experiences occurred in up to 20% of cases, and long-term complications have been noted in up to 10% of cases.[12,13] The reported complication rates following deep brain stimulation are somewhat lower. Intracerebral hemorrhage is reported in up to 5% of cases. Other adverse events include seizures and infection.[11]

Perrine [14] found no change in neuropsychological performance following pallidotomy. However, Trepanier and colleagues [15] found an increase in "frontal" deficits following pallidotomy. Burchiel[16] found no change in neuropsychological functioning following sub-thalamic nucleus stimulation. (Portions adapted from Management of Parkinson's Disease, Movement Disorders, Volume 17; suppl.4)

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Care Process:
18. Offering tissue transplantation procedures (including adrenal medullary transplantation and transplantation of fetal or stem cells) to a PD patient only in the context of Institutional Review Board-approved research protocols.

Evidence Sources: One systematic review; 2 randomized controlled trials.

Level of Evidence: A2

Summary: Fetal transplantation showed great promise in uncontrolled case-series. However, controlled trials have not substantiated this promise. One small trial showed no effect of transplantation and a second, larger trial showed no improvement over sham surgical patients and a high rate of adverse experiences in the transplanted patients. As a result, transplantation should not be performed outside of carefully controlled research environments.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on fetal transplantation and implantation of alternative sources of dopaminergic tissue.

The objectives of this review were to review the literature and identify the clinical evidence that supports specific treatments chosen because they are commonly used for treatment of PD; to determine which studies are scientifically sound so they can be used as evidence to support or condone specific treatments in clinical practice; and to identify where specific evidence is lacking so future research efforts may be directed toward addressing these specific areas of need.

The reviewers concluded that there is INSUFFICIENT EVIDENCE to support the efficacy of fetal or porcine dopaminergic transplantation. They also concluded that transplantation should be INVESTIGATIONAL and should be restricted to research centers performing studies under high-quality surveillance.[1]

Randomized Controlled Trials: Freed and colleagues[2] performed a randomized, sham-surgery controlled trial of fetal mesencephalic transplantation. After one year of observation, there was no significant difference in the primary outcome of global change in function. Furthermore, 15% of subject who received transplants developed severe dyskinesias that persisted after withdrawal of dopaminergic therapy. Spencer et al [3] found no improvement after transplantation in a randomized, open trial in 7 patients.

Other studies/Reviews/Issues: A number of open trials of fetal transplantation have been performed. In total, several hundred transplants have been performed around the world. Examples of these studies include those by Freedman,[4] Hauser[5] and Lindvall[6]

These studies generally show very robust improvement in “off” medication parkinsonian symptoms.

Safety reports from these open trials have suggested that transplantation is well-tolerated. There have not been reports of uncontrollable dyskinesias as seen in the study by Freed and colleagues. In addition to occasional operative complications including hematomas and transient confusion, there was one report of transplanted tissue migrating into the fourth ventricle, producing brainstem compression and obstructive hydrocephalus.[7]

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Management of Non-Motor Complications

Guide to Level of Evidence*

A:	Methods strong, results consistent – RCTs, no heterogeneity
1:	Effect clear – Clear that benefits do (or do not) outweigh risks
A:	Methods strong, results consistent – RCTs, no heterogeneity
2:	Effect equivocal – Uncertainty whether benefits outweigh risks
B:	Methods strong, results inconsistent – RCTs, heterogeneity present
1:	Effect clear – Clear that benefits do (or do not) outweigh risks
B:	Methods strong, results inconsistent – RCTs, heterogeneity present
2:	Effect equivocal – Uncertainty whether benefits outweigh risks
C:	Methods weak – Observational studies
1:	Effect clear – Clear that benefits do (or do not) outweigh risks
C:	Methods weak – Observational studies
2:	Effect equivocal – Uncertainty whether benefits outweigh risks

* Guyatt GH, Cook DJ, Sackett DL, Eckman M, Pauker S. Grades of Recommendation for Antithrombotic Agents. Chest 1998;114:441S-444S.

Care Process:
19. Avoiding the use of metoclopramide (Reglan) and avoiding the use of cisapride (Propulsid) in a PD patient.

Evidence Sources: two systematic reviews

Level of Evidence: C1 (Risks of cisapride and metoclopramide are well-documented in case reports).

Summary: Patients with PD can experience reduced gastric motility that can impair absorption of L-dopa medications. The benefit of cisapride was shown only in five non-controlled case series. Indirect evidence reviewed in a Cochrane report suggests that cisapride is associated with cardiac arrhythmias and sudden deaths, and its use in several countries is now restricted. It also has also been suggested that cisapride exerts dopamine antagonist properties that may aggravate parkinsonian symptoms. There are a number of case reports that metoclopramide can compromise the antiparkinsonian effects of levodopa and other dopamine agonists.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: "Given the limited available level III evidence and the diversity in outcome variables reported, there is INSUFFICIENT EVIDENCE TO MAKE CONCLUSIONS regarding efficacy of cisapride to treat gastrointestingal motility problems patients with PD. Because of the risk of arrhythmia, sudden death, and aggravation of parkinsonism, cisapride has an UNACCEPTABLE RISK in treating gastrointestinal problems in patients with PD. The use of cisapride in clinical practice is currently considered UNACCEPTABLE for treatment of gastrointestinal problems in patients with PD…. There is INSUFFICIENT EVIDENCE TO MAKE CONCLUSIONS on the efficacy of metoclopramide in treating nausea and vomiting in patients with PD. Because of the metoclopramide-induced parkinsonism in non-PD patients and aggravation of symptoms in PD, metoclopramide has an UNACCEPTABLE RISK in patients with PD. The clinical usefulness of metoclopramide in patients with PD is considered DOUBTFUL."[1] [quoted from Movement Disorder Society. Management of Parkinson's disease: An evidence-based review. Movement Disorders 2002; 17:S1-S166.]

A 2001 Cochrane Review highlights the absence of evidence to support the use of cisapride in spinal cord injured people. Rare but life-threatening arrhythogenic side effects have led to its withdrawal in some countries. It can also provoke high reflex contractions in hyperactive spinal cord injury bladders. The review cautioned its use in other neurological conditions. Cisapride was only recommended to be carefully and empirically tried in individuals with severe slow transit constipation who are resistant to other modifications of their bowel programme.[2]

Randomized Controlled Trials: none

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Care Process:
20. Counseling to a PD patient about diet, bulk, fluid intake, and/or exercise for the treatment of constipation.

Evidence Sources: one systematic review, one prospective study, two expert opinions

Level of Evidence: C1

Summary: Constipation is common in PD. One small, prospective clinical trial showed that psyllium increased stool frequency in PD patients. Counseling about diet, bulk, fluid intake, and exercise for constipation in PD patients is recommended by two expert opinions. A Cochrane systematic review on management of fecal incontinence and constipation in adults with neurologic disorders found seven small studies. [1] One trial assessed the effect of psyllium on stool frequency in patients with PD (see below). Due to the poor quality in all the studies, this systematic review did not make any recommendation for bowel care in people with neurological diseases.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: A Cochrane systematic review on management of fecal incontinence and constipation in adults with neurologic disorders found seven small studies. [1] One trial assessed the effect of psyllium on stool frequency in patients with PD (see below). Due to the poor quality in all the studies, this systematic review did not make any recommendation for bowel care in people with neurological diseases.

Randomized Controlled Trials: none

Other studies: Asraf et al assessed the effect of psyllium in seven PD subjects with constipation. [2] Stool diaries were used to measure stool frequency. They found that psyllium increased stool frequency and weight but did not alter colonic transit or anorectal function.

Expert opinion: Olanow et al recommended, “Dietary modification is aimed primarily at increasing the bulk and softening the stool. This should be the first treatment strategy and is efficacious in most patients. Helping patients become aware of their dietary habits and educating them about the elements of a balanced diet and the techniques to successfully alter poor eating habits are essential…

Within the boundaries of an individual patient’s physical capability, exercise should be as vigorous as possible. Increasing physical activity can be helpful in managing constipation.

Referral to a nutritionist for evaluation and dietary recommendations may occasionally be valuable.” [3]

A PD textbook states that dietary bulk, increased fluid intake, regular exercise, stool softeners, and osmotic laxatives, and cessation of anticholinergic drugs are first-line therapies for constipation. [4]

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Care Process:
21. Offering a PD patient without dementia and who has urinary frequency, daytime urgency, or nocturia resistant to fluid restriction one of the following options:

1. peripherally acting anticholinergic medications such as oxybutynin, propantheline, or tolterodine (Detrol),

2. referral to a urologist.

Evidence Sources: two systematic reviews, multiple RCTs, expert opinion

Level of Evidence: A1 for evidence from non-PD populations; no PD-specific study.

Summary: No clinical trials or observational studies were found that were conducted specifically in Parkinson's populations. To the extent that urinary problems in individuals with PD are analogous to those in non-PD subjects, drugs whose efficacy has been established in multiple Level-I trials (i.e., oxybutynin and tolterodine) in non-PD patients may be considered as initial treatment options. However, the Cochrane review for non-PD patients felt benefit of improvement in urinary problems may be outweighed by dry mouth side effects.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorder Society review concludes, "There is INSUFFICIENT EVIDENCE to make conclusions on the efficacy [or safety] of oxybutynin, tolterodine, flavoxate, propiverine, and prazosin in the treatment of urinary symptoms in patients with PD… Based on the absence of clinical study data in patients with PD, oxybutynin, tolterodine, flavoxate, propiverine, and prazosin are considered INVESTIGATIONAL.[1]

A Cochrane review concludes, "The administration of anticholinergic drugs for overactive bladder syndrome does result in statistically significant differences compared to placebo medication. Those receiving anticholinergic therapy were more likely to report cure/improvement of symptoms, and a reduction in micturitions and leakage episodes. However, the value of these improvements - one less void and one less leakage episode per 48 hours - to people with overactive bladder syndrome is unclear. There was a marked placebo response…..these limited benefits need to be balanced with the risk of side effects, notably dry mouth. Depending on the type of medication being offered, the risk of dry mouth is increased by two and a half to three times."[2]

Randomized Controlled Trials: The following is an example of an RCT reviewed in the Cochrane report: A double-blind, placebo-controlled, multicenter study was carried out; after a 1-week run-in period to establish baseline values, 81 patients were randomized to receive placebo or tolterodine 0.5, 1, 2 or 4 mg twice daily for 2 weeks. The frequency of micturition, episodes of incontinence and pad use were reduced by 20%, 46% and 29%, respectively, while the volume at first contraction increased by 89

mL.The 4 mg dosage was associated with a large increase in residual urinary volume and an increased incidence of dry mouth. The incidence of adverse events was comparable with placebo at tolterodine dosages of < or = 2 mg. No serious adverse events were observed and tolterodine had no clinically significant impact on electrocardiographic or laboratory findings.[3]

Expert Opinion: In cases in which curtailing fluid intake after the evening meal is not effective, peripherally acting anticholinergics can be used. "Oxybutynin (5–10 mg at bedtime or tid), propantheline (7.5–15 mg at bedtime or tid), or tolterodine (Detrol) (1–2 mg bid on individual response and tolerability) can be used as initial pharmacologic treatment. If these are ineffective, hyoscyamine (Levsin, Cystospaz, Levbid, Anaspaz, Levsinex) administered at doses of 0.15–0.30 mg at bedtime or on a qid schedule can be tried. Anticholinergic agents reduce detrusor contractions and may be useful in the treatment of detrusor hyperactivity but may worsen voiding problems and even produce urinary retention in patients who have detrusor hypoactivity or outlet obstruction. Anticholinergic drugs should be administered with caution to patients with clinically significant GI obstructive disorders because of the risk for induction of gastric retention."[4, p. S56]

References

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Care Process:
22. Offering a a trial of sildenafil citrate (Viagra) to an optimally managed PD patient who is experiencing erectile dysfunction, does not have medication and depression as a cause of erectile dysfunction, and is not receiving nitraties.

Evidence Sources: one randomized controlled trial, one open-label trial

Level of Evidence: B2

Summary: A randomized, placebo-controlled study of sildenafil citrate (Viagra) with 12 PD patients found significant improvement in ability to sustain an erection and quality of sex life. An open-label trial with 10 PD patients in the treatment group produced similar results. Orthostatic hypotension is cited as a potential temporary side effect.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: One study recruited 12 PD patients and 12 with multiple system atrophy, all of whom had erectile disease, into a randomised, double blind, placebo controlled, crossover study of sildenafil citrate. The starting dose was 50 mg active or placebo medication with the opportunity for dose adjustment depending on efficacy and tolerability. The international index of erectile function questionnaire (IIEF) was used to assess treatment efficacy and a quality of life questionnaire to assess the effect of treatment on sex life and whole life. Sidenafil citrate was efficacious in men with parkinsonism with a significant improvement, as demonstrated in questionnaire responses, in ability to achieve and maintain an erection and improvement in quality of sex life. In multiple system atrophy, three men showed a severe drop in blood pressure 1 hour after taking the active medication. As Parkinson's disease may be diagnostically difficult to distinguish from multiple system atrophy, especially in the early stages, measurement of lying and standing blood pressure is recommended before prescribing sildenafil to men with parkinsonism. Furthermore, such patients should be counseled to seek medical advice if they develop symptoms on treatment suggestive of orthostatic hypotension.[1]

Other: One open-label trial, included ten men with idiopathic Parkinson's disease (PD) and erectile dysfunction were prescribed 50-100 mg sildenafil citrate to use in eight sexual encounters over a 2-month period. Patients underwent Unified Parkinson's Disease Rating Scale (UPDRS) evaluations and completed a Beck's Depression Inventory (BDI) and a Sexual Health Inventory-M version (SHI-M) at baseline and after 8 weeks. There was statistically significant improvement in total SHI-M scores (23.8 +/- 2.0 vs 16.6 +/- 2.8; p = 0.01), overall sexual satisfaction (p = 0.03), satisfaction with sexual desire (p = 0.04), ability to achieve erection (p = 0.02), ability to maintain erection (p = 0.03), and ability to reach orgasm (p = 0.04) with use of sildenafil citrate. UPDRS

and BDI scores were not significantly changed. Side effects included headache in one patient during three sexual encounters. In this open-label study, sildenafil citrate significantly improved sexual function in men with PD and erectile dysfunction.[2]

References

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Care Process:
23. Offering a PD patient with symptomatic orthostatic hypotension one of the following options:

1) increasing salt intake and elevate the head of the bed, OR
2) decreasing antihypertensive medication (s) in a PD patient receiving antihypertensive medications

Evidence Sources: One expert opinion

Level of Evidence: C1

Summary: Autonomic dysfunction, including orthostatic hypotension, is a common complication in patients with Parkinson's disease. There are no clinical trials on behavioral modifications (such as increasing salt intake and elevating the head of the bed, or adjusting antihypertensive medications) in treating orthostatic hypotension in PD patients. However, a published algorithm/expert opinion recommends the use of these therapies prior to the initiation of pharmacologic treatment.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: none

Other studies/Review/Issues: An algorithm/expert opinion statement developed by movement disorder specialists was published in 2001.[1] Despite the lack of clinical trial data, these experts recommended that non-pharmacological interventions should be tried first in the management of orthostatic hypotension. Such interventions include increasing salt intake and elevating the head of the bed. They also recommend decreasing or discontinuing antihypertensive medications.

References

1. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology 2001; 56:S1-S88.

Care Process:

24. Prescribing midodrine or fludrocortisone to a PD patient with symptomatic orthostatic hypotension resistant to behavioral modification (increasing salt intake, raising the head of the bed, or adjusting antihypertensive medications).

Evidence Sources: One systematic review, two RCTs that included PD and non-PD patients, as well as several small observational studies.

Level of Evidence: A1 for midodrine (RCTs included non-PD patients)
C1 for fludrocortisone

Summary: Autonomic dysfunction, including orthostatic hypotension, is a common complication in patients with PD. Though there are no RCTs on the management of orthostatic hypotension solely in PD patients, two moderate-size RCTs on the management of orthostatic hypotension have included PD patients. These studies showed that midodrine significantly increased standing blood pressures and reduced orthostatic hypotension symptoms. Several small observational studies support the use of fludrocortisone for orthostatic hypotension.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on the management of orthostatic hypotension in Parkinson's disease. [1] It reviewed the medical literature between 1966 to January 2001. They could not find sufficient evidence to make specific recommendations on pharmacological management of orthostatic hypotension in PD. However, based on RCTs that included non-PD subjects, it stated, "midodrine may be considered as a practical treatment option in patients with PD."

Randomized Controlled Trials: An RCT of 171 patients with orthostatic hypotension compared midodrine 10 mg tid to placebo. [2] Ten of the 79 midodrine patients (13%) had PD; 9 of the 83 placebo patients (11%) had PD. After 6 weeks, patients taking midodrine had improvements in standing systolic BP ($P<0.001$), and reported fewer symptoms ($p=0.001$) than patients taking placebo. A statistical analysis concluded that the etiology of autonomic failure did not influence response to therapy.

An RCT of 97 patients with orthostatic hypotension compared three different doses of midodrine to placebo.[3] After 4 weeks, patients receiving 30 mg midodrine per day had significant increases in standing systolic blood pressure and diastolic blood pressure compared to controls. A subgroup analysis of 19 PD patients showed that 16 had received midodrine and 3 had received placebo. Eleven of the 16 PD patients (69%) responded to midodrine, a higher response rate than that seen in the total group of intervention subjects (47%).

Other studies/Review/Issues: Fludrocortisone has been evaluated for orthostatic hypotension in PD patients in several small observational studies. [4-6] It has not been evaluated in any large RCT for the management of orthostatic hypotension.

A consensus conference composed of movement disorder specialists was held in 1997 to construct algorithms for the management of Parkinson's Disease. These recommendations were updated in a publication in 2001.[7] The authors acknowledge that no RCTs have evaluated pharmacologic treatment of orthostatic hypotension solely in patients with PD. Nevertheless, they recommend the use of either fludrocortisone or midodrine in PD patients with symptomatic orthostatic hypotension when it is refractory to behavioral modification.

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Care Process:
25. Asking a PD patient about daytime sleepiness at the next visit if the patient is begun on a new dopaminergic medication or the dosage of a current dopaminergic medication is increased

Evidence sources: RCTs, multiple observational studies

Level of Evidence: A1

Summary: Placebo-controlled RCTs of dopamine agonists in early PD show that somnolence is reported more frequently by the group taking dopamine agonists versus the placebo group (22% vs. 9% for pramipexole; 40% vs. 6% for ropinirole). Observational studies show an association between higher Epworth Sleepiness Scale scores (greater somnolence) and greater dose of antiparkinsonian medications.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: The package insert for pramipexole summarizes the incidence of adverse events in three double-blind, placebo-controlled trials in patients with early PD.[1] There were 388 patients treated with pramipexole and 235 patients treated with placebo. 22% of the pramipexole group reported somnolence versus 9% in the control group.

The package insert for ropinirole summarizes the incidence of adverse events in one double-blind, placebo-controlled trial in patients with early PD. [2] There were 157 patients treated with ropinirole and 147 patients treated with placebo. 40% of the ropinirole group reported somnolence versus 6% in the placebo group.

A pramipexole versus levodopa RCT reported adverse events according to the "escalation (titration) phase" or the "maintenance phase" of the trial. A greater proportion of pramipexole subjects reported somnolence than levodopa subjects during the "escalation phase" (23.2% vs. 8.7%, $p<0.01$), but an equal number reported somnolence during the "maintenance phase" (9.9% vs. 9.0%). **[3]**

Other studies/Review/Issues: The Epworth Sleepiness Scale (ESS) was developed to assess a subject's tendency to fall asleep. [4] Higher ESS scores indicate a greater degree of somnolence. ESS scores greater than 10 "suggest pathological hypersomnolence." [5] Recent prospective studies have shown that increasing dopaminergic medications are associated with higher ESS scores.

Two studies compared hypersomnolence scores between PD patients and a control group. O'Suilleabhain et al compared 368 PD patients at a movement disorders clinic

with 243 patients at the same clinic without a diagnosis of PD. [6] They found that PD patients had higher mean ESS scores (10.8 vs. 8.5 in the non-PD patients, p<0.001), indicating greater somnolence. They also showed that greater severity of disease and increased dosages of dopaminergic medication were associated with higher ESS scores.

Tan et al compared 201 PD patients with 214 age, sex-matched controls. [7] They showed greater proportion of PD patients had ESS scores >10 than in control subjects (19.9% vs. 9.8%, p=0.0005). They report that "sleep attacks" were much more common in PD patients (13.9% vs. 1.9%, p<0.001). Higher doses of levodopa and greater duration of disease were associated with "sleep attacks".

Ondo et al prospectively surveyed 320 consecutive clinic patients with PD. [5] The average ESS score was 11.1. In 152 (50.2%) of the patients, ESS scores were above 10. Duration of PD, male sex, use of any dopamine agonist, and higher Hoehn and Yahr stage were associated with higher ESS scores (p<0.01). Falling asleep while driving was reported by 63/279 (22.6%) of current drivers. Older age (p<0.003), use of dopaminergic medications (p<0.05), and higher ESS scores (p<0.03) were associated with falling asleep while driving.

Arnulf et al studied 54 PD patients who complained of excessive daytime sleepiness with polysomnography and daytime multiple sleep latency (MSL) tests. [9] The mean ESS score was 14.3. The mean daytime sleep latency was 6.3 minutes (normal < 8 minutes). There was a correlation between ESS scores and sleep latency (p=0.02). There was also a correlation between severity of sleepiness (measured by MSL) and daily dose of levodopa (p=0.03).

In 1999, Frucht et al first reported nine PD patients who were taking the non-ergot dopamine agonists pramipexole and ropinirole fell asleep while driving. [10] These episodes were labeled "sleep attacks". They reported that sleep attacks ceased upon cessation of the dopamine agonist. Since that report, other antiparkinsonian medication, including ergot dopamine agonists [11, 12], and levodopa [13] have been implicated in "sleep attacks". Homann et al reviewed all reports of sleep attacks in PD patients between July 1999 and May 2001. [14] They found 20 publications that described 124 patients with sleep events. Of these events 17 occurred while driving, leading to 10 automobile accidents. They conclude that sleep attacks are distinct from severe somnolence, and that any dopaminergic medication can cause them. They state that prospective population based data is necessary to provide effective guidelines.

Excessive somnolence can have adverse outcomes for patients. Two studies assessed excessive daytime somnolence in PD patients, and looked for predictors of driving risk. Hobson et al studied 638 patients seen in 18 Canadian movement disorder clinics. [8] The mean ESS score was 7.4. They found that higher ESS scores are associated with falling asleep at the wheel (p<0.001). 49/420 (12%) drivers experienced dozing while driving. 16/420 (3.8%) drivers experienced at least one episode of sudden onset of sleep while driving.

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Care Process:
26. Assessing a PD patient for excessive daytime somnolence
All veterans with PD should be assessed for excessive daytime somnolence.

Evidence Sources: multiple observational studies

Level of Evidence: C1

Summary: Observational studies show that the incidence of excessive daytime somnolence in PD patients is higher than the general population. PD symptoms such as bradykinesia, rigidity, and impaired ability to turn in bed can exacerbate sleep problems. Though dopaminergic medications can improve PD symptoms, thereby resulting in better sleep, dopaminergic medications can also have a somnolent effect. Therefore, assessment of daytime somnolence is important when adjusting a medical regimen. Assessment of daytime somnolence can identify patients at potentially higher risk of motor vehicle accidents. Such patients will need counseling about the safety risks of driving.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: none

Other studies/Review/Issues: The Epworth Sleepiness Scale (ESS) was developed to assess a subject's tendency to fall asleep. [1] Higher ESS scores indicate a greater degree of somnolence. ESS scores greater than 10 "suggest pathological hypersomnolence." [2]

Two studies compared hypersomnolence scores between PD patients and a control group. O'Suilleabhain et al compared 368 PD patients at a movement disorders clinic with 243 patients at the same clinic without a diagnosis of PD. [3] They found that PD patients had higher mean ESS scores (10.8 vs. 8.5 in the non-PD patients, $p<0.001$), indicating greater somnolence. They also showed that greater severity of disease and increased dosages of dopaminergic medication were associated with higher ESS scores.

Tan et al compared 201 PD patients with 214 age, sex-matched controls. [4] They showed greater proportion of PD patients had ESS scores >10 than in control subjects (19.9% vs. 9.8%, $p=0.0005$). They report that "sleep attacks" were much more common in PD patients (13.9% vs. 1.9%, $p<0.001$). Higher doses of levodopa and greater duration of disease were associated with "sleep attacks".

Two studies assessed excessive daytime somnolence in PD patients, and looked for predictors of driving risk. Hobson et al studied 638 patients seen in 18 Canadian movement disorder clinics. [5] The mean ESS score was 7.4. They found that higher ESS scores are associated with falling asleep at the wheel ($p<0.001$). 49/420 (12%) drivers experienced dozing while driving. 16/420 (3.8%) drivers experienced at least one episode of sudden onset of sleep while driving.

Ondo et al prospectively surveyed 320 consecutive clinic patients with PD. [2] The average ESS score was 11.1. In 152 (50.2%) of the patients, ESS scores were above 10. Duration of PD, male sex, use of any dopamine agonist, and higher Hoehn and Yahr stage were associated with higher ESS scores ($p<0.01$). Falling asleep while driving was reported by 63/279 (22.6%) of current drivers. Older age ($p<0.003$), use of dopaminergic medications ($p<0.05$), and higher ESS scores ($p<0.03$) were associated with falling asleep while driving.

Arnulf et al studied 54 PD patients who complained of excessive daytime sleepiness with polysomnography and daytime multiple sleep latency (MSL) tests. [6] The mean ESS score was 14.3. The mean daytime sleep latency was 6.3 minutes (normal < 8 minutes). There was a correlation between ESS scores and sleep latency ($p=0.02$). There was also a correlation between severity of sleepiness (measured by MSL) and daily dose of levodopa ($p=0.03$).

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6. Arnulf I, Konofal E, Merino-Andreu M, et al. Parkinson's disease and sleepiness: an integral part of PD. Neurology 2002; 58:1019-24.

Care Process:
27. Asking a PD patient about his or her ability to operate a motor vehicle
All veterans diagnosed with PD should be asked about their ability to operate a motor vehicle.

Evidence Sources: multiple observational studies

Level of Evidence: C1

Summary: PD can impair the motor and cognitive skills necessary to operate a motor vehicle. One cross-sectional comparison study found that patients with more severe PD reported higher accident rates than patients with less severe PD and than a group of normal control subjects. Multiple observational studies show that patients with greater severity of PD are more likely to have their driving skills impaired than age- and sex-matched drivers. PD patients with impaired driving skills may need referral for assessment of their driving skills as well as counseling and education about the risks of continued driving.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: none

Other studies/Review/Issues: Dubinsky et al interviewed 150 PD patients and 100 controls about their driving habits. [1] In this study, patients with greater severity of PD (as measured by the Hoehn and Yahr stage) had higher motor vehicle accident rates per mile of travel than patients with less severity of PD, patients in the control group, and the calculated accident rate for the United States. They also found that PD patients with cognitive impairment (as measured by MMSE) had higher accident rates than PD patients who were cognitively normal.

Prospective studies show that PD patients who drive have impaired driving skills when compared to age, sex-matched controls. Heikkila et al compared the driving ability of 20 consecutive drivers with PD with 20 age-matched patients with similar driving habits.[2] The patient's driving ability was estimated by a neurologist, by a psychologist through tests and an interview, and by a traffic instructor through a driving test. The same neurologist and driving instructor evaluated all the patients. PD patients had significantly worse scores on psychologic testing compared to controls, especially visual memory, choice reactions, and information processing ($p<0.01$). PD patients also had significantly more faults and offences on the driving test than controls ($p<0.05$). The neurologist's evaluation was consistently more optimistic than either the psychologist or the traffic instructor ($p<0.001$). The study did not assess sleepiness or the effect of anti-parkinsonian medication.

Madeley et al compared 10 PD drivers with 10 age- and sex-matched drivers and with 4 PD patients who were not driving. [3] Patients underwent a computerized simulator study. On their tests, PD patients had slower reaction times, decreased accuracy of steering, and more missed red lights. Greater severity of PD was associated with worse test scores.

Lings et al compared the driving ability of 28 PD patients with 109 healthy controls through the use of a driving simulator. [4] 15 of the 28 PD patients were currently not driving. Overall, the PD patients had slower pedal and steering wheel reaction times. 21% of the PD group committed two or more errors, compared to 6% in the control group ($p<0.01$).

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Care Process:
28. Referring a PD patient to a swallowing expert if the patient reports trouble swallowing (for example, repeated coughing, choking during meals, or weight loss)

Evidence Sources: 2 systematic reviews, 1 observational study, 1 expert opinion.

Level of Evidence: C1

Summary: One systematic review and one expert in PD care support referral to a swallowing expert when a PD patient reports trouble swallowing. The Metaworks systematic review reviewed a single study of ten PD patients and 12 healthy volunteers, which suggested that swallowing training might be beneficial. The other systematic review (Cochrane) found no level I evidence to support the use of swallowing evaluation.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: Metaworks reviewed one observational study by Nagaya, Kachi et al.[1], described below and concluded that swallowing training showed benefit for PD patients but "studies of longer duration are needed to assess the clinical significance and durability of these results."[2]

The Cochrane systematic review reports that, "no randomised controlled trials were found that examined the efficacy of non-pharmacological swallowing therapy for dysphagia in Parkinson's disease."[3]

Randomized Controlled Trials: none

Other Studies: The effect of swallowing training on PD patients with swallowing disorders was evaluated in ten PD patients and 12 healthy volunteers.[1] Subjects underwent an initial evaluation which consisted of a modified barium swallow and electromyogram (EMG) to evaluate the time it took to initiate their swallowing reflex (premotor time, or PMT). Subjects were then given one session of swallowing training. PMTs were initially elongated in the PD patients, and decreased significantly after the training, while they were normal and unchanged in healthy controls. [Adapted from Metaworks]

Expert Opinion: "PD patients who experience clinically significant swallowing dysfunction should be evaluated by a speech and swallowing expert."[4 p. S60]

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Care Process:
29. Referring a PD patient to a short course of speech therapy if the patient reports difficulty with speech function

Evidence Sources: 3 systematic reviews, 5 RCTs, 2 observational studies

Level of Evidence: B1

Summary: The Cochrane systematic review concludes that there is insufficient evidence to support or refute the benefit of speech therapy. Two additional systematic reviews conclude that speech therapy emphasizing prosody and speech loudness is possibly useful. Long-term evidence is limited to one study with 22 patients. Short-term evidence includes five clinical trials of four weeks or less and one trial of a 3-month treatment. Therapies emphasizing prosody or speech loudness were most effective.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Cochrane systematic review summarizes that improvements in speech impairments were noted in the 41 patients from two studies, [1] some of which may be clinically useful and have had an impact on intelligibility. Another study[2] could not be evaluated due to lack of raw numerical data. “Considering the methodological flaws in many of the studies, the small number of patients examined, and the possibility of publication bias, there is insufficient evidence to support or refute the efficacy of speech and language therapy in Parkinson's disease.”[3]

The Movement Disorder Society Review evaluated five randomized controlled trials.[1, 2, 4-6] “Very few well-controlled studies of speech therapy have been performed. Based on those cited, randomized, controlled (Level I) clinical evidence demonstrates that speech therapy that emphasizes prosody and perhaps speech loudness is LIKELY EFFICACIOUS for short-term speech improvement. There are not enough data at the present time to comment on the duration of benefit. In all studies cited, the speech therapy involved frequent therapy sessions. Based on the Level-I evidence and the absence of morbidity associated with the reports of speech therapy in PD, speech therapy is SAFE and has an ACCEPTABLE RISK, WITHOUT SPECIALIZED MONITORING. In the practical therapeutic setting, because most reported speech therapy has been very intensive and outside the range of sessions usually prescribed in the community, speech therapy is POSSIBLY USEFUL.”[7]

The AHRQ funded Metaworks Evidence Report evaluated four studies,[5, 6, 8, 9] which looked at the benefits of speech therapy in PD. “Short-term (≤ one month) studies of…speech therapy…demonstrated improvements in speech….but their short duration precludes any conclusions regarding their long-term efficacy. Intensive speech therapy has been shown to improve vocal intensity up to twelve months after treatment; however, long-term results are from only one study of 22 patients”[10]

Randomized Controlled Trials. Two studies (n=80), both by the same author, evaluated the effects of intensive speech treatment (LVST) versus respiratory exercises in PD patients[5, 6]. Thirty-two patients had the same number of placebo speech therapy sessions, in which they were trained to increase their respiratory muscle activity during inspiration and expiration. Both studies supported the efficacy of LSVT for improving vocal intensity and decreasing the impact of PD on communication. In the 12-month study, 22 patients were evaluated and the LSVT group improved or maintained vocal intensity above pretreatment levels 12 months after their training was completed, whereas the placebo group had statistically significant deterioration of vocal intensity levels from before treatment. [Adapted from Metaworks]

Robertson & Thomson (1984)[2] studied 18 PD subjects randomized to speech therapy versus no treatment. The speech therapy involved two weeks of daily exercises. A significant improvement was still demonstrable three months after the speech program compared to controls. The evaluations were not blinded. [Adapted from MDS]

Johnson & Prang (1990)[1] randomized twelve patients to a four-week speech program versus no therapy. The study was blinded and raters evaluated tapes of speech. After four weeks of therapy, the speech therapy group showed significant improvement in the primary and several other secondary speech measures. The control group showed decline. [Adapted from MDS]
Scott and Cairn[4] randomized patients to either regular speech therapy or to the same therapy with the addition of a Vocalite apparatus that was used as a vocal reinforcement tool. Ratings were performed by two evaluators, one blinded to treatment assignment and one not. Treatment sessions were 2-3 times weekly for approximately three weeks. Patients were assigned in random order with 13 subjects in each group. With both therapies, there was significant improvement in both outcome measures; no additional benefit occurred with the vocal reinforcement. [Adapted from MDS]

Observational Studies: Speech was tested in a cross-sectional study of ten patients while listening to white noise.[8] All ten PD patients showed a marked increase in speech intensity while listening to white noise. Speaking rate and speech intelligibility did not improve consistently with the white noise, and in fact worsened in some cases. [Adapted from Metaworks]

The effect of a one-month voice rehabilitation program on 20 moderate-severity PD patients was evaluated.[9] After the one-month program, patients had increased vocal intensity. Twelve of the patients complained of dysphagia prior to the program, compared with zero complaints afterwards. [Adapted from Metaworks]

References

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2. Robertson SJ, Thomson F. Speech therapy in Parkinson's disease: a study of the efficacy and long term effects of intensive treatment. 1984; 19:213-224.
3. Deane KH, Whurr R, Playford ED, Ben-Shlomo Y, Clarke CE. Speech and language therapy versus placebo or no intervention for dysarthria in Parkinson's disease. Cochrane Database of Systematic Reviews 2002.
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Management of Dementia, Depression, and Psychosis

Guide to Level of Evidence*

A: Methods strong, results consistent – RCTs, no heterogeneity
1: Effect clear – Clear that benefits do (or do not) outweigh risks

A: Methods strong, results consistent – RCTs, no heterogeneity
2: Effect equivocal – Uncertainty whether benefits outweigh risks

B: Methods strong, results inconsistent – RCTs, heterogeneity present
1: Effect clear – Clear that benefits do (or do not) outweigh risks

B: Methods strong, results inconsistent – RCTs, heterogeneity present
2: Effect equivocal – Uncertainty whether benefits outweigh risks

C: Methods weak – Observational studies
1: Effect clear – Clear that benefits do (or do not) outweigh risks

C: Methods weak – Observational studies
2: Effect equivocal – Uncertainty whether benefits outweigh risks

* Guyatt GH, Cook DJ, Sackett DL, Eckman M, Pauker S. Grades of Recommendation for Antithrombotic Agents. Chest 1998;114:441S-444S.

Care Process:
30. Assessing decision-making capacity in a PD patient diagnosed with dementia

Evidence Sources: two practice guidelines on dementia; several observational studies of impaired capacity in mild and moderate dementia

Level of Evidence: C1

Summary: Both the California Workgroup's Guidelines on Alzheimer's Disease Management and the American Medical Associations' Guide on dementia recommend making an assessment of decision-making capacity. Decision-making capacity for medical care refers to the "ability to understand information and to make informed decisions based on such information" (AMA Guide, page 16). Loss of capacity to make medical decisions is common in dementia and has critical medical-legal implications for patients, their families, and health care providers. Because of the progressive nature of degenerative dementia, the California AD Guidelines recommend that designation of a durable power of attorney for health care (i.e., a health care agent) and of advance directives be done early in the course of the disease, while the patient has the capacity to make these decisions. However, to designate an agent and/or to specify future treatment preferences, the decision-making capacity of the patient must be determined and documented.

Details of Literature Review

Practice Guidelines: Both the California Workgroup's Guidelines on Alzheimer's Disease Management and the American Medical Associations' Guide on dementia recommend making an assessment of decision-making capacity. Decision-making capacity for medical care refers to the "ability to understand information and to make informed decisions based on such information" (AMA Guide, page 16). Because of the progressive nature of degenerative dementia, the California AD Guidelines recommend that designation of a durable power of attorney for health care (i.e., a health care agent) and of advance directives be done early in the course of the disease, while the patient has the capacity to make these decisions (Cummings, et al, 2002). However, to designate an agent and/or to specify future treatment preferences, the decision-making capacity of the patient must be determined and documented.

Systematic Reviews: none

Randomized Controlled Trials: none

Other Studies: Several studies have shown that loss of capacity to make medical decisions is common in dementia, and can occur in mild or moderate stages (Marson, et al, 1995; Marson et al, 1997). The issue of decision-making capacity has critical medical-legal implications for dementia patients, their families, and health care providers because of the principles of informed consent for medical care (President's Commission, 1982).

References

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A report on the ethical and legal implications of informed consent in the patient-practitioner relationship. In: *Making health care decisions: President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.* Washington, CD: US Government Printing Office, 1982.

Care Process:

31. Assessing a PD patient for depression

Evidence Sources: practice guideline, systematic review, observational studies

Level of Evidence: A1

Summary: Multiple observational studies have estimated the risk of depression in PD patients to be 40-50%. In PD patients, depression may be due to underlying biochemical deficiencies, and/or because PD patients are suffering from a disability. The US Preventive Services Task Force (USPTF) recently recommended screening for depression in all adults. A systematic review for the USPTF shows that screening programs lower the risk of persistent depression.

Details of Literature Review

Practice Guidelines: The role of the United States Preventive Services Task Force (USPSTF) is to devleop evidence-based recommendations for clinicians about preventive health care. In 2002, the USPSTF published the following recommendation about screeing for depression in adults: "The U.S. Preventive Services Task Force recommends screening adults for depression in clinical practices that have systems in place to assure accurate diagnosis, effective treatment, and followup." (http://www.ahrq.gov/clinic/uspstf/uspsdepr.htm)

Systematic Reviews: The USPSTF updated their prior recommendation on depression screening by reviewing the medical literature from 1994 to 2001.[1] Their meta-analysis suggests that screening and feedback significantly lowered the risk for persistent depression 0.87 [95% CI, 0.79 to 0.95]. Programs that coordinate screening results with followup and treatment had greater impact than programs that simply feed back screening results to the clinician.

Randomized Controlled Trials: Recent studies indicate that shorter screening tools may be as effective as longer screening instruments.[2] One RTC shows that asking two simple questions ("Over the past 2 weeks, have you ever felt down, depressed, or hopeless?" and "Have you felt little interest or pleasure in doing things?") was as effective as some other established depression screening tools.[3]

Other studies/Review/Issues: Multiple observational studies indicate that the rate of depression in PD patients is quite common.[4-6] Dooneief et al studied 339 patients with PD. [5] They found that the prevalence of depression was 47%. Using medical record review, they calculated the incidence rate of depression in this cohort of patients was 1.86% per year. In comparision, the incidence rate of depression in the general population has been estimated to be between 0.17-0.29%/year. Mayeux et al studied 55 consecutive patients with PD. [6] Using the Beck depression inventory, 47% of patients met criteria for depression.

References

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4. Brown RG, MacCarthy B, Gotham AM, Der GJ, Marsden CD. Depression and disability in Parkinson's disease: a follow-up of 132 cases. Psychol Med 1988; 18:49-55.
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Care Process:
32. Avoiding either tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) in a PD patient with depression being treated with MAO-A inhibitors (such as moclobemide)

Evidence Sources: one systematic review

Level of Evidence: C1

Summary: The combination of an MAO-A inhibitor such as moclobemide and either a tricyclic antidepressant or selective serotonin reuptake inhibitors is unacceptable due to the risk of serotonin syndrome.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: The Movement Disorders Society (MDS) performed a systematic review on the management of depression in Parkinson's disease. [1] It reviewed the medical literature between 1966 to January 2001. This review stated that treatment of depressed PD patients with MAO-A inhibitors (such as moclobemide) and either a tricyclic antidepressants or a SSRI is UNACCEPTABLE due to the risk of serotonin syndrome.

Randomized Controlled Trials: none

Other studies/Review/Issues: none.

References

1. Treatment of depression in idiopathic Parkinson's disease. Mov Disord 2002; 17:S112-S119.

Care Process:

33. Discontinuing or reducing anticholinergics, amantadine, selegiline, dopamine agonists, and/or levodopa in a PD patient with hallucinations or delirium before initiating quetiapine or clozapine

Evidence Sources: 1 RCT, 2 observational studies, multiple other sources

Level of Evidence: A1 (for anticholinergics); C1 (for others)

Summary: A few small observational studies have shown that transient withdrawal of levodopa reduced hallucinations in patients with PD. Pharmaceutical package inserts describe hallucinations and delirium side effects for anticholinergics, amantadine, selegiline, dopamine agonists and levodopa. One RCT demonstrated that symptoms of mild delirium occurred more often in the group treated with anticholinergics, potentially supporting their discontinuation before discontinuation of dopamine agonists or levodopa.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: The cognitive performance of 82 newly diagnosed PD patients was assessed after randomization to one of three monotherapies: levodopa, bromocriptine or anticholinergic agents. 1 Motor function improved in all three groups at four months. However, at four months, immediate registration skills were worse in the anticholinergic group while other cognitive functions reliant on working memory and sequencing improved in the other two groups.

Observational Studies: Four of six PD patients with hallucinations, who were given brief periods off levodopa, remained free of psychiatric manifestations for an entire year. 2 In another study, hallucinosis was ameliorated in all 16 patients given a period of transient levodopa withdrawal. 3

Other Sources: Pharmacy company package inserts for anticholinergics (Cogentin, Artane), Symmetrel, Eldepryl, Requip, Mirapex, and Sinemet describe delirium and hallucinations as side effects. 4-10

References

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2. Koller WC. Weiner WJ. Perlik S. Nausieda PA. Goetz CG. Klawans HL. Complications of chronic levodopa therapy: long-term efficacy of drug holiday. Neurology. 31(4):473-6, 1981
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6. Package insert. Parlodel (bromocriptine). East Hanover, NJ: Novartis Pharmaceuticals Corporation, 1998.
7. Package insert. Requip (ropinirole). Philadelphia, PA: SmithKline Beecham Pharmaceuticals, 2001.
8. Package insert. Sinemet (levodopa/carbidopa). Wilmington, DE: DuPont Pharmaceuticals, 1998.
9. Package insert. Mirapex (pramipexole). Kalamazoo, MI: Pharmacia & Upjohn Company, 1999.
10. Package insert. Symmetrel (amantadine). Chadds Ford, PA: Endo Pharmaceuticals Inc., 1998.

Care Process:

34. Avoiding high-potency neuroleptics (eg. haloperidol, chlorpromazine), olanzapine, and risperidone to treat a PD patient with persistent medication-induced hallucinations or delirium not improved by PD medication adjustments (consisting of discontinuing or reducing anticholinergics, amantadine, dopa agonists, and/or levodopa)

Evidence Sources: one RCT for olanzapine (early termination), one RCT for risperidone, one meta-analysis comparing haloperidol to risperidone in schizophrenics, one review article

Level of Evidence: A1

Summary: Two, small randomized controlled trials favor clozapine over olanzapine and risperidone, respectively, for the treatment of drug-induced psychosis in Parkinson's disease patients. While no direct evidence was available with respect to the use of haloperidol, indirect evidence in the form of a meta-analysis of six RCTs comparing risperidone to haloperidol in schizophrenics found haloperidol to be associated with higher incidence of extrapyramidal symptoms. Therefore, combining the direct and indirect evidence, haloperidol would not be recommended for drug-induced psychosis in patients with Parkinson's disease.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: A randomized, double-blind, parallel comparison of olanzapine and clozapine in patients with PD with chronic hallucinations was conducted. After 15 patients had completed the study, safety stopping rules were invoked because of exacerbated parkinsonism in olanzapine-treated subjects. UPDRS motor impairment scores from baseline to study end significantly increased with olanzapine treatment, and change scores between the olanzapine and clozapine groups significantly differed.[1]

The authors compared efficacy and safety of risperidone and clozapine for the treatment of psychosis in a double-blind trial with 10 subjects with Parkinson's disease (PD) and psychosis. Mean improvement in the Brief Psychiatric Rating Scale psychosis score was similar in the clozapine and the risperidone groups (P=0.23). The mean motor Unified Parkinson's Disease Rating Scale score worsened in the risperidone group and improved in the clozapine group, although this difference did not reach statistical significance.[2]

In a random effects model meta-analysis of RCTs comparing trials of risperidone and haloperidol in patients with schizophrenia, results demonstrate greater treatment

efficacy associated with risperidone compared with haloperidol and suggest both a lower incidence of EPS and improved treatment compliance with risperidone[3].

References

1. Goetz CG, Blasucci LM, Leurgans S, Pappert EJ. Olanzapine and clozapine. Comparative effects on motor function in hallucinating PD patients. Neurology 2000; 55:789-794.
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3. Davies A, Adena MA, Keks NA, Catts SV, Lambert T, Schweitzer I. Risperidone versus haloperidol: I. meta-analysis of efficacy and safety. Clinical Therapeutics 1998; 20:58-71.

Care Process:

35. Prescribing quetiapine or clozapine for a PD patient with persistent medication-induced hallucinations or delirium not improved by PD medication adjustments (consisting of discontinuing or reducing anticholinergics, amantadine, dopamine agonists, and/or levodopa)

Evidence Sources: 2 systematic reviews, 2 RCTs, 1 open-label trial, 6 case series

Level of Evidence: A1

Summary: Clozapine has demonstrated efficacy at low doses for improvement of drug-induced hallicinosis/psychosis in patients with PD. Reported effective doses range from 6.25 to 150 mg/d, with most below 50 mg/d. Evidence for short-term efficacy (4 weeks) is stronger than for long-term; two RCTs were conducted for four-week trials, but long-term research is limited to case series and retrospective chart review. While clozapine requires close monitoring, it does not appear to induce deterioration in parkinsonism.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: "Based on two RCTs [see below], The Movement Disorder Society systematic review concluded that low dose clozapine (less than 50 mg/d) is EFFICACIOUS in short-term (4 weeks) improvement or clearing of drug-induced hallucinosis/psychosis in patients with PD. Additional case studies provide INSUFFICIENT EVIDENCE to conclude on the long-term efficacy of clozapine in patients with PD..... The available evidence suggests that under conditions of weekly blood count monitoring, clozapine treatment of drug-induced psychosis carries an ACCEPTABLE RISK WITH SPECIALIZED MONITORING. The addition of low-dose clozapine (less than 50 mg/d) is not usually associated with worsening of PD-related motor symptoms and may improve parkinsonian rest tremor."[1]

The AHRQ-sponsored evidence review (Metaworks) concludes, "Limited data suggests efficacy and safety of clozapine in the treatment of PD patients with dopamine-induced psychosis. Long-term RCTs (i.e., > 6 months) are needed to confirm these findings."[2]

Randomized Controlled Trials: Sixty patients with idiopathic PD and drug-induced psychosis were randomized in a placebo-controlled, double-blind, randomized trial by the Parkinson Study Group. The clozapine group experienced a highly significant improvement in all psychosis rating scores without evidence of motor decline as assessed by the Unified Parkinson's Disease Rating Scale. The clozapine doses necessary to produce the observed effects were less than 25 mg/d with individual cases responding at doses as low as 6.25 mg.[3] [Adapted from MDS]

The French Clozapine Parkinson Study Group also conducted a multicenter, four week, double-blind, placebo-controlled trial involving 60 patients with PD and drug-induced

psychosis. This study used clozapine doses titrated to a maximum of 50 mg/day. The trial used established scales to rate severity of psychotic function and motor disability and found significant changes in global clinical impression and PANSS positive subscore items in favor of clozapine at week four.[3] [Adapted from MDS]

An additional randomized controlled trial [4] compared clozapine to olanzapine but was prematurely discontinued because of unacceptable deterioration of parkinsonism in the olanzapine arm. At 9 weeks, patients in the clozapine arm showed statistically significant improvement from baseline score in total scale for Assessment of Positive Symptoms (SAPS) for psychotic symptoms as well as the visual hallucination item on the SAPS. Mean clozapine dose was 25.8 mg/dl. [Adapted from MDS]

Observational studies: MDS summarized three observational studies evaluating a total of 129 patients[5-7] and Metaworks summarized six studies with a total number of 314 patients. [6-11]Two of those studies [6, 7] were reviewed by both groups. These studies (case series, retrospective chart reviews and an open-label trial) provide follow-up data for 12 months or more for patients with idiopathic PD receiving clozapine treatment for drug-induced psychosis. MDS found antipsychotic effects maintained for up to 37 months in patients remaining in follow-up; in two chart reviews with a mean duration of 15.2 months follow-up, there was 20.8 percent non-compliance due to adverse effects. Common adverse reactions included sedation, increased drooling, amnesia, delirium, and orthostatic hypotension. MDS reported leukopenia in 5 cases, three of which resolved with temporary discontinuation of the drug; Metaworks reported 6 transient cases of leukopenia. No cases of agranulocytosis were reported.

References

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11. Rabey JM, Treves TA, Neufeld MY. Low-dose clozapine in the treatment of levodopa-induced mental disturbances in Parkinson's Disease. Neurology 1995; 45:432-4.

Care Process:
36. Performing blood monitoring for agranulocytosis weekly for the first six months of treatment, then every other week thereafter for a PD patient prescribed clozapine for hallucinations or other psychosis

Evidence Sources: FDA drug label/PDR, current as of 2002

Level of Evidence: C1
Summary: Patients receiving clozapine must have a baseline white blood cell (WBC) and differential count before initiation of treatment, and a WBC every week for the first six months thereafter. If acceptable WBC counts have been maintained through the first 6 months of continuous therapy, WBC counts can be monitored every other week.

Details of Literature Review

Practice Guidelines: none

Systematic Reviews: none

Randomized Controlled Trials: none

Other: Food and Drug Administration (FDA) guidelines stipulate that patients who are being treated with (clozapine) must have a baseline white blood cell (WBC) and differential count before initiation of treatment and a WBC every week for the first six months thereafter. If acceptable WBC counts (WBC greater than or equal to 3,000/mm3, ANC 1500/mm3) have been maintained during the first 6 months of continuous therapy, WBC counts can be monitored every other week. WBC counts must be monitored weekly for at least 4 weeks after the discontinuation of (clozapine)[1]. Based on Novartis registries, the risk of developing agranulocytosis during the initial 6 months is 860 cases per 100 000 person-years' exposure, and 70 cases per 100 000 person-years' exposure in months 7-24[2, p. 1013].

References

1. Package insert. Clozaril (clozapine). East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2002.
2. Patel NC, Dorson PG, Bettinger TL. Sudden late onset of clozapine-induced agranulocytosis. Annals of Pharmacotherapy 2002; 36:1012-5.

Education and Reporting

Guide to Level of Evidence*

A: Methods strong, results consistent – RCTs, no heterogeneity
1: Effect clear – Clear that benefits do (or do not) outweigh risks

A: Methods strong, results consistent – RCTs, no heterogeneity
2: Effect equivocal – Uncertainty whether benefits outweigh risks

B: Methods strong, results inconsistent – RCTs, heterogeneity present
1: Effect clear – Clear that benefits do (or do not) outweigh risks

B: Methods strong, results inconsistent – RCTs, heterogeneity present
2: Effect equivocal – Uncertainty whether benefits outweigh risks

C: Methods weak – Observational studies
1: Effect clear – Clear that benefits do (or do not) outweigh risks

C: Methods weak – Observational studies
2: Effect equivocal – Uncertainty whether benefits outweigh risks

* Guyatt GH, Cook DJ, Sackett DL, Eckman M, Pauker S. Grades of Recommendation for Antithrombotic Agents. Chest 1998;114:441S-444S.

Care Process:

37. Informing a PD patient with dementia and their caregivers about resources for information, education, and support regarding dementia

Evidence Sources: six clinical practice guidelines on dementia; the ACOVE project literature review; nine randomized controlled trials

Level of Evidence: A1

Summary: There is a substantial body of evidence, including at least nine randomized controlled trials, supporting the positive impact of education, information, access to respite care, and other resources on important patient and caregiver outcomes for persons with dementia. Practice guidelines from the Veterans Health Administration and from three professional organizations (AMA, American Academy of Neurology, American Psychiatric Association) and other groups (California Workgroup's Guidelines on AD Management; North of England Development Group's Evidence-Based Dementia Guideline) all endorse a similar recommendation regarding provision of information, education, and support.

Details of Literature Review

Practice Guidelines: Practice guidelines from the Veterans Health Administration (*Dementia: Guidelines for Diagnosis and Treatment*, 2nd ed., 1989) and from three professional organizations (AMA, Guttman and Seleski, 1999; American Academy of Neurology, Doody et al, 2001; American Psychiatric Association, 1997) and other groups (California Workgroup's Guidelines on AD Management, Cummings, 2002; North of England Development Group's Evidence-Based Dementia Guideline, Eccles et al, 1998) all endorse similar recommendations.

Systematic Reviews: Chow and MacLean (2001) conducted a systematic review of clinical trials on caregiver support and respite care. The text of this review is quoted in the following section, 'Randomized Controlled Trials.'

Randomized Controlled Trials: "Nine clinical trials reported significantly improved patient or caregiver outcomes when caregiver needs were assessed and education or counseling was provided. Educational interventions both delayed institutionalization and enhance caregivers' quality of life and satisfaction with nursing care (Mohide et al, 1990). Comprehensive support and counseling for spouse-caregivers delay nursing home placement of mildly and moderately demented patients with Alzheimer disease by 329 days (Mittelman et al, 1996). The relative risk for institutionalization among patients in the treatment group was 0.65 (95% CI, 0.45 to 0.94).

A third study showed that counseling by telephone assisted spouse-caregivers in feeling more competent and knowledgeable about Alzheimer disease and enabled them to make caregiving decisions with greater independence (Chiverton and Cain, 1989). Scores on the Zarit Burden Interview, which assesses caregiver burden, improved for

caregivers who received serial, extended telephone contact over 8 weeks, whereas scores for caregivers who only had one informational phone contact worsened. Use of community support services increased in the group with extended contact (Coyne et al, 1995). A more intensive caregiver education program, which provided 10 days of residential training for dementia caregivers, demonstrated marked differences in patient outcomes (Brodaty and Peters, 1991). At 39 months of follow-up, patients who were living at home with trained caregivers at the start of the study had higher adjusted rates of survival at home compared with controls (53% vs. 13%; *P* = 0.02) and fewer total deaths (20% vs. 41%; *P* = 0.02). Caregiver training did not affect institutionalized patients. The investigators calculated that caregiver training saved $5975 per patient in nursing home expenses over 39 months. Because delayed enrollment in caregiver training reduced the benefits accrued from the intervention, caregiver support and education should begin as soon as dementia is diagnosed.

Respite care also may benefit the caregiver and the patient. One pre- and post-intervention study on the effects of respite care on patients and caregivers observed improvements only in patient behavior (Burdz et al, 1988). In another study, respite care reduced subjective caregiver burden and depression, but the effect lasted only as long as the respite period (Grasel, 1997). Although the recurrence of burden and distress might seem likely to hasten institutionalization, even brief respite delayed institutionalization. Education of caregivers about the importance of their own well-being may enhance the perceived benefit of respite care. “ (from Chow and MacLean, *Annals of Internal Medicine* 2001, page 671-2).

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Care Process:
38. Assessing a PD patient for evidence of abuse (physical, sexual, financial, neglect, isolation, abandonment)

Evidence Sources: three practice guidelines on dementia; five physician surveys

Level of Evidence: C1

Summary: Three clinical practice guidelines (AMA Guide on diagnosis, management, and treatment of dementia; practice guidelines of the American Psychiatric Association; and the California Alzheimer's Disease Workgroup's guidelines) recommend assessment of people with dementia for evidence of abuse. Individuals with PD - particularly those with dementia or with advanced PD - are also likely to be at increased risk for abuse. While there are no randomized controlled trials of the impact of assessment and monitoring for elder abuse on outcome, indirect evidence provided by a number of surveys and observational studies support that there are very low rates of detection of abuse in health care settings. For example, in one study, only 2% of abuse cases in Michigan were reported by physicians. In addition, it is documented that abuse can lead to a variety of adverse health outcomes, including death.

Details of Literature Review

Practice Guidelines: While it appears that no guidelines specific to PD address this issue, three clinical practice guidelines (AMA Guide on diagnosis, management, and treatment of dementia, Guttman and Seleski, 1999; practice guidelines of the American Psychiatric Association, 1997; and the California Alzheimer's Disease Workgroup's guidelines, Cummings et al, 2002) recommend assessment of people with dementia for evidence of abuse. Individuals with PD - particularly those with dementia or with advanced PD - are also likely to be at increased risk for abuse. The APA guideline states that providers should be "vigilant regarding the possibility of elder abuse or neglect. Demented individuals are at particular risk for abuse because of their limited ability to protest and the added demands and emotional strain on caregivers, and those whose caregivers appear angry or frustrated may be at still higher risk." (APA, 1997, page 11). The AMA guideline also notes the potential for a higher risk of abuse in patients with dementia. The California AD Guidelines also include an explicit recommendation that health care providers monitor for evidence of abuse.

Systematic Reviews: none

Randomized Controlled Trials: none

Other Studies [adapted from Mittman et al, 1998]: A number of studies have found that physicians fail to recognize and report elder abuse. Michigan physicians reported only 2% of abuse cases reported in the state; no change in this figure was seen when the analysis was limited to substantiated cases (Rosenblatt, 1996). Among the reasons discussed in one study for failure to report were a lack of familiarity with reporting laws,

risk of offending patients, time pressure, and perceived lack of appropriate evaluation skills (Kleinschmidt, 1997). In another study, reasons included a perception by physicians that elders deny abuse or would be resistant to intervention, lack of knowledge about available resources, and lack of knowledge or protocols to define, assess and intervene against abuse (Krueger, 1997). Physicians report that the following would be helpful in improving detection and reporting of abuse: a single contact agency, a directory or list of services and resource people, educational materials, diagnostic and management guidelines, continuing medical education and changes in compensation (Krueger, 1997). Another study reported that physicians perceive that they lack the tools and resources for evaluating elder abuse. Approximately 69% of emergency physicians reported the absence of written protocols for the reporting of elder mistreatment. These physicians also reported a lack of familiarity with applicable state laws. Only a small percentage recalled any residency education related to elder mistreatment (25%); 74% expressed a lack of certainty that clear-cut medical definitions of elder abuse or neglect exist. Nearly all (92%) felt that their states lacked sufficient resources to meet the needs of victims (Jones, 1997). Results of another survey, conducted in Virginia, show that only 19% of medical schools responding to a survey reported that their curriculum included instruction related to detecting or addressing elder abuse (Hendricks-Mathews, 1997).

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Care Process:
39. Reporting a PD patient for whom there is a suspicion of abuse (physical, sexual, financial, neglect, isolation, abandonment) to Adult Protective Services, a local police department, or the appropriate state agency, as required by law

Evidence Sources: two practice guidelines on dementia

Level of Evidence: N/A (required by law in 43 states)

Summary: In 43 US states, it is mandatory that health care providers report instances of apparent elder abuse. In the remaining seven states, reporting is voluntary. Guidelines of the AMA and of the California Workgroup include recommendations to report suspected elder abuse cases.

Details of Literature Review

Practice Guidelines: "In all but seven states, health care and social service providers are required to report elder abuse. The states with voluntary reporting are Colorado, New Jersey, New York, North Dakota, Pennsylvania, and South Dakota. Laws about reporting and requirements concerning this reporting vary by state. The web site for the National Center on Elder Abuse (www.elderabusecenter.org) provides links to individuals states for specific information on reporting requirements and procedures." (Cummings, et al, American Family Physician, 2002,vol. 65, page 2533)

The AMA Guide (Guttman and Seleski, 1999) notes that "a number of jurisdictions have enacted laws requiring health care providers to report suspected cases of elder abuse," and recommends that suspected cases of abuse or neglect be reported to the appropriate protective service agency.

Systematic Reviews: None

Randomized Controlled Trials: None

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Care Process:
40. Reporting a PD patient with dementia to the local health officer in accordance with California law (Sections 2800-2812 of Title 17, California Code of Regulations)

Evidence Sources: An explicit recommendation of one practice guideline for dementia; indirectly supported by several other guidelines, one systematic review, and a half dozen observational studies

Level of Evidence: N/A (required by law)

Summary: The California Workgroup's Guidelines for Alzheimer's Disease Management include a recommendation to report the diagnosis of dementia to the local health officer, as required by California law (Sections 2800 and 2812 of Title 17 of the California Code of Regulations). A diagnosis of dementia (particularly with a Clinical Dementia Rating =1 or higher) is associated with an increased risk of traffic accidents, according to at least six studies and a systematic review for a practice parameter of the American Academy of Neurology. At least three clinical practice guidelines (including an American Academy of Neurology Practice Parameter) support the notion of restricting driving privileges in persons with dementia.

Details of Literature Review

Practice Guidelines: The California Workgroup's Guidelines for Alzheimer's Disease Management (Cummings, et al, 2002) includes a recommendation to report the diagnosis of dementia to the local health officer, as required by California law (Sections 2800 and 2812 of Title 17 of the California Code of Regulations). Several other guidelines support restriction of driving privileges for persons with dementia (Small et al, 1997; American Psychiatric Association, 1997).

Systematic Reviews: A systematic review conducted to develop a practice parameter of the American Academy of Neurology found that persons with dementia having a Clinical Dementia Rating Scale score =1 or more severe were a "significant traffic safety problem both from crashes and from driving performance measurements" (Dubinsky, et al, 2000).

Randomized Controlled Trials: none

Other Studies: At least six studies "have positively correlated dementia, even at mild stages, with hazardous driving and increased frequency of motor vehicle accidents...Three retrospective studies compared the driving records of demented patients with those of age-matched controls without dementia. In two of these studies, the number of accidents was higher among persons with even mild dementia (Friedland et al, 1988; Johansson et al, 1996). In the third study, the rate of motor vehicle accidents among demented patients increased yearly to a maximum of 70% (Drachman and Swearer, 1993) … The three prospective, controlled studies that compared

performance on a practical road test showed that up to 40% of patients with mild Alzheimer disease failed the test, whereas all nondemented older adult controls passed (Hunt et al, 1993; Kapust and Weintraub, 1992; Perryman and Fitten, 1996)." (from Chow and MacLean, page 673).

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Care Process:
41. If a PD patient or his/her family expresses concern about driving safely, doing one or more of the following (in accordance with state laws): (1) advising the patient not to drive a motor vehicle, (2) requesting that the DMV retest the patients' ability to drive, and/or (3) referring the patient to a driver's safety course that includes assessment of driving ability

Evidence Sources: multiple observational studies

Level of Evidence: C1

Summary: PD can impair the motor and cognitive skills necessary to operate a motor vehicle. Multiple observational studies have shown that patients with greater severity of PD are more likely to have their driving skills impaired. There may be an increased risk of falling asleep while driving, according to another observational study. At least two states (California and Pennsylvania) require that persons "with any condition that would impair driving ability" (Cummings et al, 2002, page 2529) be reported to the appropriate agency/official (in California, the local health officer). Some other states encourage but do not mandate such reporting.

Details of Literature Review

Practice Guidelines: None

Systematic Reviews: None

Randomized Controlled Trials: None

Other studies/Review/Issues: Madeley et al compared 10 PD drivers with 10 age, sex-matched drivers and with 4 PD patients who were not driving.[1] Patients underwent a computerized simulator study. On their tests, PD patients had slower reaction times, decreased accuracy of steering, and more missed red lights. Greater severity of PD was associated with worse test scores.

Dubinsky et al interviewed 150 PD patients and 100 controls about their driving habits.[2] They found that those patients with greater severity of PD (as measured on the Hoehn and Yahr stage) or with cognitive impairment (as measured by MMSE) had higher accident rates. However, they also note that since some Hoehn and Yahr stage III PD patients still drive safely, this scale is not sensitive enough to determine who should or should not drive.

Lings et al compared the driving ability of 28 PD patients with 109 healthy controls through the use of a driving simulator.[3] Fifteen of the 28 PD patients were currently not driving. Overall, the PD patients had slower pedal and steering wheel reaction times. 21% of the PD group committed two or more errors, compared to 6% in the control group ($p<0.01$).

Heikkila et al compared the driving ability of 20 consecutive drivers with PD with 20 age-matched patients with similar driving habits.[4] The patient's driving ability was estimated by a neurologist, by a psychologist through tests and an interview, and by a traffic instructor through a driving test. The same neurologist and driving instructor evaluated all the patients. PD patients had significantly worse scores on psychologic testing compared to controls, especially visual memory, choice reactions, and information processing ($p<0.01$). PD patients also had significantly more faults and offences on the driving test than controls ($p<0.05$). The neurologist's evaluation was consistently more optimistic than either the psychologist or the traffic instructor ($p<0.001$). The study did not assess sleepiness or the effect of anti-parkinsonian medication.

Hobson et al[5] studied 638 patients seen in 18 Canadian movement disorder clinics. The mean Epworth score was 7.4. They found that disease duration and use of medication were associated with higher Epworth and Inappropriate Sleep Composite scores. 49 (12%) of the 420 drivers experienced dozing while driving, including falling asleep when stopped for a few minutes in traffic. 16/420 (3/8%) had one episode of sudden onset of sleep while driving.

At least two states (California and Pennsylvania) require that persons "with any condition that would impair driving ability" (Cummings et al, 2002, page 2529)[6] be reported to the appropriate agency/official (in California, the local health officer). Some other states encourage but do not mandate such reporting.

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