Mini-CAT Final Name Arianne Diaz

Clinical Question: Brief description of patient problem/setting (summarize the case very briefly)
71 y/o M w/ PMHx schizophrenia and Parkinson's admitted to inpatient psych unit for aggressive behavior. During intake patient exhibited shuffling gait and tremor of the RT wrist and hand. States he no longer wants to take medications for any of his medical conditions.

PICO Search Question: Clearly state the question (including outcomes or criteria to be tracked)
In patients with Parkinson's disease, does Deep Brain Stimulation compared to medical management with levodopa/levodopa-carbidopa improve motor symptoms and ability to perform activities of daily living?

PICO Search terms:

Population	Intervention	Comparison	Outcome
Patients with Parkinson's Disease	Deep Brain Stimulation	Pharmacologic therapy	Quality of Life
	Surgical Intervention	Dopamine Agonist	Improved motor symptoms
		Levodopa	Decrease in motor symptoms
		Levodopa/Carbidopa	Ability to perform ADLs
		Sinemet	

Search tools and strategy used:
Please indicate what data bases/tools you used, provide a list of the terms you searched together in each tool, and how many articles were returned using those terms and filters.

Database	Terms	Filter	Articles
Wiley Online Library	Patients w/ Parkinson's Disease AND Deep Brain Stimulation AND Levodopa AND motor symptoms	Open access content and movement disorders published within the last 10 years	344
Cochrane Library (Wiley)	Parkinson Disease AND Deep Brain Stimulation AND Dopamine agonist	Randomized control trials published within the last 10 years	18
PubMed	Patients w/ Parkinson's Disease AND Deep Brain Stimulation AND Levodopa AND ADLs	Systematic review published within the last 10 years	1
UpToDate	Improvement of motor symptoms in Parkinson's patients taking Levodopa	Looked at the references section of *Medical Management of Motor Fluctuations and Dyskinesia in Parkinson Disease* and Selected "Systematic Review"	4
JAMA	Patients w/ Parkinson's Disease taking Levodopa for Mobility	Full Text Research Articles published within the last 10 years	28
TRIP Database	PICO Format: P → Patient w/ Parkinson's	Systematic Review published within the last 10 years	1

	I → Deep Brain Stimulation C → Levodopa O → Ability to perform ADLs		
ScienceDirect	Patients with Parkinson's taking levodopa for decrease in motor symptoms	Open access research articles published within the last 5 years	194

Results found: 590 results

Explain how you narrow your choices to the few selected articles.

I narrowed down my searches to focus on articles of the highest level of evidence that were published within the last ten years. I aimed to use systematic reviews, meta-analysis, and randomized control trials conducted in the United States. Systematic reviews compile all pertinent evidence that meets a particular set of inclusion criteria to address a specific research question while meta-analyses are a "numerical summary" of the results across a study. Furthermore, systematic reviews aim to answer a specific clinical question and use specific criteria to select relevant articles from various databases. Meta-analyses function similarly but they are also statistically significant which is important as these results may overturn the results of smaller clinical trials. Randomized control trials are considered the gold standard in trial design as they tend to be double blinded. Patients are randomly placed in two or more groups to test how a drug or treatment performs against a control group. Overall, I wanted to select the most relevant/informative articles and I knew that focusing on the level of evidence was imperative for me to do so.

Articles Chosen (3-5):

Article #1

CITATION	Sivanandy P, Leey TC, Xiang TC, et al. Systematic Review on Parkinson's Disease Medications, Emphasizing on Three Recently Approved Drugs to Control Parkinson's Symptoms. *Int J Environ Res Public Health*. 2021;19(1):364. Published 2021 Dec 30. doi:10.3390/ijerph19010364
ABSTRACT	**Parkinson's Disease** (PD) is a disease that involves neurodegeneration and is characterised by the motor symptoms which include muscle rigidity, tremor, and bradykinesia. Other non-motor symptoms include pain, depression, anxiety, and psychosis. This disease affects up to ten million people worldwide. The pathophysiology behind PD is due to the neurodegeneration of the nigrostriatal pathway. There are many conventional drugs used in the treatment of PD. However, there are limitations associated with conventional drugs. For instance, levodopa is associated with the on-off phenomenon, and it may induce wearing off as time progresses. Therefore, this review aimed to analyze the newly approved drugs by the United States-Food and Drug Administration (US-FDA) from 2016–2019 as the adjuvant therapy for the treatment of PD symptoms in terms of efficacy and safety. The new drugs include safinamide, istradefylline and pimavanserin. From this review, safinamide is considered to be more efficacious and safer as the adjunct therapy to levodopa as compared to istradefylline in controlling the motor symptoms. In Study 016, both safinamide 50 mg (p = 0.0138) and 100 mg (p = 0.0006) have improved the Unified Parkinson's Disease Rating Scale (UPDRS) part III score as compared to placebo. Improvement in Clinical Global Impression—Change (CGI-C), Clinical Global Impression—Severity of Illness (CGI-S) and off time were also seen in both groups of patients following the morning levodopa dose. Pimavanserin also

	showed favorable effects in ameliorating the symptoms of Parkinson's Disease Psychosis (PDP). A combination of conventional therapy and non-pharmacological treatment is warranted to enhance the well-being of PD patients.
LINK/PDF	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8744877/ **PDF POSTED ON BLACKBOARD**

Article #2

CITATION	Xu H, Zheng F, Krischek B, et al. Subthalamic nucleus and globus pallidus internus stimulation for the treatment of Parkinson's disease: A systematic review. J Int Med Res. 2017;45(5):1602-1612. doi:10.1177/0300060517708102
ABSTRACT	**Objective**: Deep brain stimulation (DBS) for treatment of advanced Parkinson's disease (PD) has two anatomical targets: the subthalamic nucleus (STN) and the globus pallidus internus (GPI). The clinical effectiveness of these two stimulation targets was compared in the present study. **Methods**: A systematic review and meta-analysis was performed to evaluated the postoperative changes in the United Parkinson's Disease Rating Scale (UPDRS) on- and off-phase, on-stimulation motor scores; activities of daily living score (ADLS); and levodopa equivalent dose (LED) after STN and GPI stimulation. Randomized and nonrandomized controlled trials of PD treated by STN and GPI stimulation were considered for inclusion. **Results**: Eight published reports of eligible studies involving 599 patients met the inclusion criteria. No significant differences were observed between the STN and GPI groups in the on-medication, on-stimulation UPDRS motor score [mean difference, 2.15; 95% confidence interval (CI), −0.96–5.27] or ADLS (mean difference, 3.40; 95% CI, 0.95–7.76). Significant differences in favor of STN stimulation were noted in the off-medication, on-stimulation UPDRS motor score (mean difference, 1.67; 95% CI, 0.98–2.37) and LED (mean difference, 130.24; 95% CI, 28.82–231.65). **Conclusion**: The STN may be the preferred target for DBS in consideration of medication reduction, economic efficiency, and motor function improvement in the off phase. However, treatment decisions should be made according to the individual patient's symptoms and expectations.
LINK/PDF	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5718722/ **PDF POSTED ON BLACKBOARD**

Article #3

CITATION	Hauser RA, Espay AJ, Ellenbogen AL, et al. IPX203 Vs Immediate-Release Carbidopa-Levodopa for the Treatment of Motor Fluctuations in Parkinson Disease: the RISE-PD Randomized Clinical Trial. *JAMA Neurology*. 2023;80(10):1062-1069. doi:https://doi.org/10.1001/jamaneurol.2023.2679

ABSTRACT	**Importance:** Levodopa has a short half-life and a limited window of opportunity for absorption in the proximal small intestine. IPX203 is an oral, extended-release formulation of carbidopa-levodopa developed to address these limitations. **Objective:** To assess the efficacy and safety of IPX203 vs immediate-release carbidopa-levodopa in patients with Parkinson disease who are experiencing motor fluctuations. **Design, Setting, and Participants:** RISE-PD was a 20-week, randomized, double-blind, double-dummy, active-controlled, phase 3 clinical trial. The study was conducted between November 6, 2018, and June 15, 2021, at 105 academic and clinical centers in the US and Europe. Patients with Parkinson disease taking a total daily dose of 400 mg or more of levodopa and experiencing an average of 2.5 hours or more daily off-time were included in the study. A total of 770 patients were screened, 140 were excluded (those taking controlled-release carbidopa-levodopa apart from a single daily bedtime dose, Rytary (Amneal Pharmaceuticals), additional carbidopa or benserazide, or catechol O-methyl transferase inhibitors or who had a history of psychosis within the past 10 years), and 630 were enrolled in the trial. **Interventions:** Following open-label immediate-release carbidopa-levodopa dose adjustment (3 weeks) and conversion to IPX203 (4 weeks), patients were randomized in a 1:1 ratio to double-blind, double-dummy treatment with immediate-release carbidopa-levodopa or IPX203 for 13 weeks. **Main Outcome and Measures:** The primary end point was mean change in daily good on-time (ie, on-time without troublesome dyskinesia) from baseline to the end of the double-blind treatment period. **Results:** A total of 630 patients (mean [SD] age, 66.5 [8.95] years; 396 [62.9%] men) were enrolled, and 506 patients were randomly assigned to receive IPX203 (n = 256) or immediate-release carbidopa-levodopa (n = 250). The study met its primary end point, demonstrating statistically significant improvement in daily good on-time for IPX203 compared to immediate-release carbidopa-levodopa (least squares mean, 0.53 hours; 95% CI, 0.09-0.97; *P* = .02), with IPX203 dosed a mean 3 times per day vs 5 times per day for immediate-release carbidopa-levodopa. Good on-time per dose increased by 1.55 hours with IPX203 compared to immediate-release carbidopa-levodopa (95% CI, 1.37-1.73; *P* < .001). IPX203 was well tolerated. The most common adverse events in the double-blind phase (IPX203 vs immediate-release carbidopa-levodopa) were nausea (4.3% vs 0.8%) and anxiety (2.7% vs 0.0%). **Conclusions and Relevance** In this study, IPX203 provided more hours of good on-time per day than immediate-release carbidopa-levodopa, even as IPX203 was dosed less frequently.
LINK/PDF	https://jamanetwork-com.york.ezproxy.cuny.edu/journals/jamaneurology/fullarticle/2808496 **PDF POSTED ON BLACKBOARD**

Article #4

CITATION AMA FORMAT	Lin Z, Zhang C, Li D, Sun B. Preoperative Levodopa Response and Deep Brain Stimulation Effects on Motor Outcomes in Parkinson's Disease: A Systematic Review. *Mov Disord Clin Pract*. 2021;9(2):140-155. Published 2021 Dec 9. doi:10.1002/mdc3.13379

ABSTRACT	**Background:** The up-to-date literature systematically reviewing the predictive value of preoperative levodopa responsiveness after deep brain stimulation (DBS) surgery in motor outcomes in Parkinson's disease (PD) is lacking. **Objective:** To address this issue in patients with PD undergoing bilateral subthalamic nucleus (STN) or globus pallidus interna (GPi) DBS. **Methods:** We used the existing PRISMA consensus statement. A comprehensive review of literature from 1993 to May 2021 retrieved from PubMed was conducted. **Results:** The STN-DBS responsiveness was significantly correlated with the preoperative levodopa responsiveness for the total score of UPDRS-III at both 6- and 12-month follow-ups ($P < 0.001$). Such correlations were significant after controlling for age at time of surgery and disease duration. The significance of correlation disappeared for longer follow-up times. For the sub-scores of UPDRS-III, a significant correlation between the preoperative levodopa responsiveness and STN DBS responsiveness was observed for rigidity, bradykinesia, and axial symptoms, but not for tremor ($P = 0.002$, 0.010, 0.007, and 0.542, respectively). The preoperative levodopa responsiveness was significantly correlated with GPi DBS responsiveness for the UPDRS-III total score at a median follow-up of 12 months ($P = 0.030$). **Conclusion:** The current study confirmed the value of preoperative levodopa responsiveness for prediction of the short-term motor outcome after DBS (for both STN and GPi). The predictive value of levodopa responsiveness in short-term outcomes for respective cardinal motor disabilities and the loss of its predictive value after STN DBS for long-term motor outcomes were highlighted by this study.
LINK/PDF	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8810442/ **PDF POSTED ON BLACKBOARD**

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
Palanisamy Sivanandy, Tan Choo Leey, Tan Chi Xiang, Tan Chi Ling, Sean Ang Wey Han, Samantha Lia Anak Semilan, Phoon Kok Hong	Systematic Review	Authors searched Science direct, PubMed, and Google Scholar using terms such as "Parkinson Disease, Parkinson, Parkinsonism... safety, and efficacy" Drugs included in the study were approved by the US-FDA between 2016 and 2019	Safety and efficacy of levodopa/ carbidopa in management of dyskinesia associated with Parkinson's Disease compared to US-FDA approved drugs released between 2016-2019 Outcomes studied were dependent on	- Levodopa must be admin. multiple times a day s/t its short half life (36-96 minutes). Chronic use of levodopa is associated with motor fluctuations and dyskinesia which severely impair quality of life. - the **clinical global impression scale** was used to measure psychosis intensity and the **brief psychiatric rating scale** was used to rate	Authors do not explicitly state there are any limitations but based on article: - some publication bias may be present, particularly as it concerns the efficacy of US-FDA approved drugs released between 2016-2019. It is possible that researchers may have

		Of 1210 article selected for topic review, 47 articles were selected for final review Inclusion criteria: RCT and studies on human subjects Exclusion criteria: studies performed on animals	drug used for tx of Parkinson's: Safinamide: change in daily "on" time with no or non-troublesome dyskinesia. Istradefylline: change in daily "off" time Pimavanserin: change in the scale for the assessment of positive symptoms-PD	positive and negative symptoms associated with PD psychosis in patients taking clozapine; this intervention was effective in mitigating hallucinations; ultimately participants had to be withdrawn d/t neutropenia - there was no statistically significant improvement in PD psychosis in participants taking olanzapine or quetiapine - risperidone caused aggravation of EPS which worsened motor symptoms in patients with PD psychosis - participants taking safinamide 100 mg as adjunct therapy to levodopa had significant improvement in controlling motor fluctuations as opposed to levodopa/carbidopa - Istradefylline is effective in reducing motor fluctuation without increasing troublesome dyskinesia - Pimanvanserin 34 mg is effective at treating delusions, hallucinations, and motor function in patients with PD psychosis	unintentionally included more studies that show positive outcomes associated with levodopa/ safinamide therapy since this is a relatively new pharmacologic intervention
Hao Xu, Feng Zheng, Boris Krischek, Wanhai Ding, Chi	Systematic Review	- Authors searched Medline, Embase, Cochrane Library, Ovid, and CBM databases for articles publish	Changes in the on-phase **and** off-phase United Parkinson's Disease Rating Scale motor	- Four studies in which patients followed up within the year indicated no significant difference in motor function	Authors acknowledge: Bias may be introduced in retrospective studies if they

Xiong, Xin Wang, Chaoshi Niu		from September 1993 to September 2013. Prespecified search times included ‘‘Parkinson’s disease,’’ ‘‘deep brain stimulation,’’ ‘‘sub- thalamic nucleus,’’ ‘‘globus pallidum,’’ ‘‘randomized controlled trials,’’ ‘‘random,’’ ‘‘control,’’ and ‘‘trials.’ - Eight reports with eligible studies involving 599 patients were included in this systematic review Inclusion Criteria: Randomized and non-randomized control trials of PD treated by STN and GPI stimulation Exclusion Criteria: Case reports containing fewer than five patients, comments, letters, editorials, protocols, guidelines, animal studies, and cadaver articles	score, ability to perform ADLs, and Levodopa equivalent dose from preoperatively to >3 months postoperatively. The motor subscale is comprised of 14 items, scores range from 0 to 104; ability to perform ADLs is self-reported by patients and focuses on activities such as being able to walk, write, dress oneself, and speak, score ranges from 0 to 52.	between patients who had undergone deep brain stimulation targeted at the subthalamic nucleus vs the globus pallidus internus. - A meta-analysis of six studies, however, indicated a change in the United Parkinson’s Disease Rating Scale motor score during the “off phase” indicative of improvement in patients who received subthalamic nucleus stimulation - Four studies comparing subthalamic nucleus vs the globus pallidus internus stimulation found no difference in ability to form ADLs within the year - Five studies showed a reduction in levodopa dose in patients who received subthalamic nucleus stimulation	are not randomized properly. Reported infection rates were bias as different types of infections developed over time. Studies with short follow-p (within 3-6 months) showed the lowest infection rates and studies that were longer (within the year) had higher infection rates Interventionists and assessors were poorly blinded to surgical interventions performed as they were the surgeons performing the procedure
Robert A. Hauser, Alberto J. Espay, Aaron L. Ellenbogen, Hubert H. Fernandez, Stuart H. Isaacson, Peter A. LeWitt, William G. Ondo, Rajesh	Randomized Control Trial	Study consisted of 506 participants: 4-week screening period, 3-week open label instant release dose-adjustment period of levodopa-carbidopa—Sinemet), 4-week open label extended-release dose-conversion period of IPX203 (extended-release	Mean change in daily good “on” time from baseline to the end of the double-blind treatment period – good “on” time was defined as “the sum of “on” time without dyskinesia and “on” time without	- 770 patients were selected to be screened between November 06, 2018 and June 15, 2021. Participants were selected from 1-5 academic and clinical centers in the United States and Europe. - 589 patients were eligible for the extended-release conversion period, and 506 completed	Authors acknowledge: Patients were experiencing motor fluctuations while taking instant release levodopa-carbidopa. It did not evaluate the extended-release version in patients with early PD vs

Pahwa, Johannes Schwarz, Fabrizio Stocchi, Leonid Zeitlin, PhD; Ghazal Banisadr, PhD; Stanley Fisher, MD; Hester Visser, MD, PhD; Richard D'Souza, PhD		formulation of Sinemet), 13- week double-blind treatment period. Inclusion Criteria: Established Dx of PD, ≥ 40 y/o at time of Dx, Hoehn-Yahr stage I to IV in the on-state, MOCA score 24 or greater, treatment with a stable regimen of levodopa/carbidopa for 4 weeks or longer before screening ... Concomitant therapy with dopamine agonists, monoamine oxidase type B inhibitors, amantadine, and anticholinergic drugs at stable doses was permitted. Exclusion Criteria: Atypical or secondary parkinsonism, previous neurosurgical treatment for PD, lack of response to levodopa, patients taking controlled-release Sinemet apart from a single daily bedtime dose, patients taking Rytary, patients taking additional carbidopa or benserazide, patients taking catechol O- methyl transferase inhibitors, or a history of psychosis	troublesome dyskinesia.	the open-label conversion and were able to enter the randomized treatment period. - During the extended-release dose conversion period 229 patients reported treatment emergent adverse effects ; six were unable to continue the study. The most frequent complaints were dyskinesia, nausea, and dry mouth. - During the double-blind period, 108 patients (42.4%) treated with the extended-release formulation experienced treatment emergent adverse effects compared with 79 patients who received the instant release formulation - IPX203 (extended-release formulation of Sinemet) demonstrated increased daily good "on" time when administered 3 times a day as opposed to the instant-release formulation when administered 5 times a day.	placebo or to delay motor fluctuations and dyskinesia. Only 25-100 instant release tablets and 35-140 extended capsules were used in the study Extended-release tablets could not be administered more every 6 hours.

		within the past 10 years			
Zhengyu Lin, Chencheng Zhang, Dianyou Li, Bomin Sun	Systematic Review	Authors selected 76 articles from 1993 to May 2021 using the PubMed database with the combination of these search terms: "deep brain stimulation", "neurostimulation", "Parkinson's disease", "subthalamic", "pallidal", and "globus pallidus interna" <u>Inclusion Critera:</u> the effective sample size was no less than ten and five subjects for subthalamic nucleus or the globus pallidus internus deep brain stimulation, respectively, the follow-up time was at least for 6-months, the outcome data of preoperative and postoperative off- and on-medication UPDRS-III scores were available, patients did not undergo any neurosurgical treatments (e.g., pallidotomy, thalamotomy, stem cell transplant, etc.) other than DBS for PD.	Predictive value of pre-operative levodopa responsiveness for motor outcomes Required use of the United Parkinson's Disease Rating Scale III to measure change in motor outcome	As seen in other studies, authors of this systemic review concluded that pre-operative levodopa responsiveness may be a predictive outcome for improvement of motor symptoms **after** subthalamic nucleus deep brain stimulation. In other words, patients who respond well to levodopa before surgery are likely to have improvement in stiffness/rigid movement shortly after their procedure. There is still not enough research to demonstrate long-term results in patients who responded well to Levodopa prior to deep brain stimulation Subthalamic nucleus deep brain stimulation may be more effective in treating Parkinson symptoms that respond well to Levodopa versus symptoms that may respond poorly or be refractory to Levodopa.	Authors acknowledge: Heterogeneity I included studies is considered a drawback. Example provided includes pharmacological tests used for the evaluation of preoperative levodopa response. These tests varied across studies. Lack of data prevented authors from performing a study-level correlation analysis between levodopa and globus pallidus internus deep brain stimulation.

		Articles must have been originally pubslihed in the English language Exclusion Criteria: Non-human studies, reviews, and meta-analyses			

Conclusion(s):

Briefly summarize the conclusions of each article, then provide an overarching conclusion.

Article #1:

Istradefylline, Pimanvanserin, and Safinamide are three US-FDA approved drugs released between 2016 and 2019. Authors compared the efficacy of these three drugs and other antipsychotics against levodopa/levodopa-carbidopa to determine which drug was more effective in controlling PD symptoms such as motor performance. Among the new medications approved from 2016 to 2019, safinamide is the most effective as indicated by improvement in the United Parkinson's Disease Rating Scale III, and the clinical global impression scale (includes two separate scales which account for change in symptoms and severity of illness). "Off" time was reported in both group of patients treated with safinamide 50mg and 100mg following the morning levodopa use. Authors concluded that safinamide is superior to levodopa/carbidopa at increasing "on" time with non-troublesome or no dyskinesia.

Article #2

Deep brain stimulation is a surgical intervention used in patients with severe symptoms of Parkinson's disease. Stimulation may be performed either at the subthalamic nucleus or the globus pallidus internus. The aim of the study was to compare motor function and ability to perform ADLs according to the United Parkinson's Disease Rating Scale status post deep brains stimulation at either anatomical site. Authors concluded that mortality for this procedure is "extremely rare but has been reported". Risks of this procedure include spontaneous intracerebral hemorrhage, infection, and acute postoperative confusional state . It was found that subthalamic nucleus stimulation was more effective at improving motor function compared to the other anatomical site. Patients who underwent the former procedure also experienced a reduction in medication which is associated with improvements in medication side effects including cognitive slowing, sleepiness, mania/hypomania, and dyskinesia. Less of these medication side effects allow for improved quality of life.

Article #3

IPX203 is an extended-release version of Sinemet that can be used for management of motor fluctuations associated with Parkinson's Disease. According to the study, patients taking IPX203 have "statistically significant improvement in daily good "on " time by taking this medication three times a day compared to those taking tradition instant release Sinemet which participants took five times a day. Based on the results of this study, IPX203 required less daily dosing and provided more consistent relief throughout the day, even when administered fewer times a day.

Article #4

As mentioned in my second article, there are two anatomical locations where deep brain stimulation can be performed. Because subthalamic nucleus deep brain stimulation has yielded better outcomes in terms of motor function, it is the most common surgical intervention for patients with Parkinson Disease. As a result, this study focused on the relationship between patient response to pre-operative Levodopa and post-operative Levodopa in patients who underwent subthalamic nucleus DBS. It was found that patients who responded well on pre-operative Levodopa were more likely to experience improvement in motor symptoms immediately after the surgery compared to patients who had poor or refractory response to the medication. Despite this, studies are still required to determine the long-term response in patients taking post-operative Levodopa.

Overarching Conclusion

There are a wide variety of interventions that can be implemented to treat motor symptoms associated with Parkinson's Disease. Studies using the United Parkinson's Disease Rating Scale III and the clinical global impression scale indicate that improvement in motor symptoms allow patients to regain some functional capacity which overall improves quality of life. As far as deep brain stimulation is concerned, there is evidence demonstrating that stimulation performed

at the subthalamic nucleus is associated with reduction in motor symptoms and increased ability to perform ADLs when compared to globus pallidus internus stimulation. Levodopa monotherapy or levodopa-carbidopa (MC) is also frequently used to treat symptoms of Parkinson's Disease but there are now alternate medications on the market which can be prescribed for patients who cannot undergo surgical treatment or who cannot tolerate the adverse effects associated with levodopa or Sinemet.

PICO Question:
In patients with Parkinson's disease, does Deep Brain Stimulation compared to medical management with levodopa improve motor symptoms and ability to perform activities of daily living?

Clinical Bottom Line:

Deep Brain Stimulation is effective at reducing motor symptoms associated with Parkinson Disease. Studies have demonstrated that patients who underwent subthalamic nucleus deep brain stimulation specifically have experienced improved outcomes compared to globus pallidus internus deep brain stimulation. These patients were more likely to experience improved quality of life where motor symptoms and pharmacologic management was concerned. Namely, these patients experienced fewer motor symptoms which allowed them to perform their ADLs more easily. Additionally, patients who performed well on pharmacological management (levodopa-carbidopa) prior to surgery required less medication in the post-op phase which is associated with reduction in medication side effects. Although surgical intervention is an excellent option for the PICO question proposed, certain factors must be taken into consideration to determine eligibility such as risk of bleeding, infection, and other comorbidities that may affect the healing process. According to the articles I've selected, alternatives to levodopa-carbidopa such as levodopa-safinamide can be used in patients who are not eligible for deep brain stimulation. Studies show that adjunct safinamide therapy is associated with improvement in bradykinesia, tremor, rigidity, and gait and while antipsychotics have been used to mitigate psychotic symptoms seen in severe/late Parkinson's Disease, these medications are associated with their own adverse effect profile. Overall, both deep brain stimulation and pharmacologic treatment can be used to manage motor symptoms associated with PD. Improving motor symptoms and managing other aspects of PD will allow patients to retain ability to perform ADLs amongst other measures determine good quality of life.

Weight of the Evidence (With Rank and Explanation)

1 Zhengyu Lin, Chencheng Zhang, Dianyou Li, Bomin Sun →

This article is ranked #1 because it is a systematic review published within the last 10 years. It directly compares my intervention and comparison and clearly delineates the inclusion and exclusion criteria for article selection. Seventy-six articles were selected over the course of 18 years. The authors used the United Parkinson's Disease Rating Scale III to effectively measure change in motor outcome after deep brain stimulation which measures severity and progression of symptoms associated with Parkinson's Disease. This article demonstrated that pre-operative levodopa responsiveness was a predictive outcome for improvement of motor symptoms after subthalamic nucleus deep brain stimulation. Finally, the limitations and biases of the study are mentioned which include important considerations for future research.

2 Robert A. Hauser, Alberto J. Espay, Aaron L. Ellenbogen, Hubert H. Fernandez, Stuart H. Isaacson, Peter A. LeWitt, William G. Ondo, Rajesh Pahwa, Johannes Schwarz, Fabrizio Stocchi, Leonid Zeitlin, PhD; Ghazal Banisadr, PhD; Stanley Fisher, MD; Hester Visser, MD, PhD; Richard D'Souza, PhD →

This article is ranked #2 because it is a randomized control trial published in the United States within the last 5 years. The study consisted of 506 participants monitored over 20 weeks to determine the efficacy and safety of an extended-release formulation of levodopa-carbidopa (IPX203). The authors had specific inclusion/exclusion criteria and documented all instances in which participants were withdrawn from the study and why they were withdrawn from the study.

3 Hao Xu, Feng Zheng, Boris Krischek, Wanhai Ding, Chi Xiong, Xin Wang, Chaoshi Niu →

I ranked this article #3 because although it is a systematic review published within the last 10 years that directly compares the intervention and comparison in my PICO, the authors incorporated non-randomized control trials in their inclusion criteria. As explained in my "results found" section, randomized control trials are effective at eliminating bias

because they tend to be double or triple blinded. Although non-randomized control studies are not necessarily bad, they do possess a greater likelihood for bias when compared to randomized control trials.

4 Palanisamy Sivanandy, Tan Choo Leey, Tan Chi Xiang, Tan Chi Ling, Sean Ang Wey Han, Samantha Lia Anak Semilan, Phoon Kok Hong →

I ranked this article as #4 because the authors made no mention of any limitations or biases in their study. The inclusion and exclusion criteria were clear and the article itself went over the safety and efficacy of various drugs that can be used to managed symptoms associated with Parkinson's Disease, including levodopa-carbidopa, antipsychotics, and US-FDA approved drugs released between 2016 and 2019. The authors used various rating scales to determine the efficacy of each drug and included dosing and frequency for symptom management, which is helpful for clinicians.

Magnitude of Effects:

1 Zhengyu Lin, Chencheng Zhang, Dianyou Li, Bomin Sun →

A statistically significant positive correlation between preoperative levodopa responsiveness and deep brain stimulation responsiveness was obtained (r2 = 0.389, P = 0.030) with a median follow-up of 12 months. Patients experienced improvement in stiffness/rigid movement shortly after the procedure.

2 Robert A. Hauser, Alberto J. Espay, Aaron L. Ellenbogen, Hubert H. Fernandez, Stuart H. Isaacson, Peter A. LeWitt, William G. Ondo, Rajesh Pahwa, Johannes Schwarz, Fabrizio Stocchi, Leonid Zeitlin, PhD; Ghazal Banisadr, PhD; Stanley Fisher, MD; Hester Visser, MD, PhD; Richard D'Souza, PhD →

The study demonstrated improvement in good "on-time" hours per day for the extended-release formulation of levodopa-carbidopa, IPX203. IPX203 was drosed three times compared to instant release levodopa-carbidopa which was administered approximately 5 times a day on average. (LS mean change for IPX203, −0.50; LS mean change for IR CD-LD, −1.03; difference in LS means, 0.53; 95% CI, 0.09-0.97; *P* = .02) Treatment with IPX203 resulted in less off-time compared with IR CD-LD (difference in LS means, −0.48; 95% CI, −0.90 to −0.06; *P* = .03)

3 Hao Xu, Feng Zheng, Boris Krischek, Wanhai Ding, Chi Xiong, Xin Wang, Chaoshi Niu →

No differences in the United Parkinson's Disease Rating Scale(UPDRS) motor scores were observed between patients who underwent subthalamic nucleus vs globus pallidus internus deep brain stimulation for the on-medication, on-stimulation groups: [mean difference, 2.15; 95% confidence interval (CI), 0.96– 5.27] or ADLS (mean difference, 3.40; 95% CI, 0.95–7.76). Significant differences were noted in the subthalamic nucleus deep brain stimulation in the off-medication, on-stimulation UPDRS motor score (mean difference, 1.67; 95% CI, 0.98–2.37) and LED (mean difference, 130.24; 95% CI, 28.82–231.65).

4 Palanisamy Sivanandy, Tan Choo Leey, Tan Chi Xiang, Tan Chi Ling, Sean Ang Wey Han, Samantha Lia Anak Semilan, Phoon Kok Hong →

Compared to older drugs indicated for the management of symptoms associated with Parkinson's Disease, the newer drugs approved between 2016 and 2019 have improved safety and efficacy. Safinamide was found to be superior in controlling PD symptoms.

Clinical Significance:

In conclusion, management of Parkinson Disease depends on a variety of elements: risk factors, comorbid conditions, ability to adhere to pharmacologic regimen, age of onset, and severity, are just some considerations that must be taken into account before deciding whether deep brain stimulation or pharmacologic intervention is a better intervention. The clinical significance lies in the ability to improve motor symptoms and therefore quality of life in patients with Parkinson's Disease: while some patients may be great candidates for surgery, others may benefit from a more conservative approach with decreased frequency such as that offered in extended-release formulations of levodopa carbidopa (IPX203), and yet others may benefit from a completely different medication to manage their symptoms such as levodopa-safinamide.

Other Considerations:

- Authors in future studies should focus on specific comorbidities that prevent patients with Parkinson's from undergoing deep brain stimulation procedures.

- Adverse effect profiles should be discussed as part of research for medications used in the management of Parkinson's Disease associated symptoms.

Replies:
Hi Racheli! While on my Internal Medicine rotation I was introduced to Lokelma as a potassium binder indicated for hyperkalemia. I think that the way you narrowed down your searches was effective, and I'm impressed that you were able to find articles that contrast your intervention and comparison. This is something I tend to struggle with when I perform my article search for my PICOs, so I wind up selecting articles that look at my intervention and comparison separately and draw conclusions based on the information collected for my clinical bottom line. Your second article possesses interesting findings regarding the correlation between Lokelma and the development/worsening of hypertension in patients treated with this potassium binder. I agree with your clinical bottom line and I especially like that you mentioned monitoring for hypertension in patients taking Lokelma. Great job!

Hey Martin!
I read your Mini-CAT draft a couple of weeks back and was really interested in the topic you selected. As I mentioned previously, ulcer formation was one of the more fascinating topics we learned about during our didactic year, so I wanted to read over your final Mini-CAT to see what your final verdict is. I think the methods you employed to weigh your articles was great! I agree that Article 1 should be ranked first based on the selection criteria you described. Additionally, it includes many participants (945 elderly patients > 50 years old) . Although the sample size is small, the authors still determined that NPWT can be implemented to promote improved wound healing compared to "moist wound therapy". This first article directly focused on your intervention and comparison which, in my opinion, is most useful for answering PICO questions. I agree with the clinical significance you mentioned and believe that NPWT can improve quality of life by accelerating wound healing without increasing risk of adverse events. Great work!

Hi Emmanuel!
Your Mini-CAT final was very interesting to read! Your presentation is the first thing that stood out to me. I think it's interesting that this patient was not placed on any medications to manage his lupus. Although steroids can be used to mitigate symptoms associated with acute flair, it is best to treat the patient with a DMARD or immunosuppressive agent if the patient has recurrent flares (which seems to be the case in this patient). The agent you chose, hydroxychloroquine is an antimalarial and "antirheumatic drug" which can decrease the activity of the immune system to help patients better manage their lupus symptoms. Your articles support what we were taught during didactic year, namely that hydroxychloroquine use is "protective against mortality risk across different regions". I like that your second article differentiates between the efficacy of hydroxychloroquine in acute lupus erythematosus and discoid lupus. I think this is important since it dictates the best course of management for the disease. Overall, you did a great job!
Source:
https://medlineplus.gov/druginfo/meds/a601240.html#:~:text=Hydroxychloroquine%20is%20in%20a%20class,the%20organisms%20that%20cause%20malaria.