

R E V I E W

The Parkinson's disease nurse specialist and subcutaneous apomorphine infusion. A scoping review of the literature

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Abstract. *Objective:* The aim of this scoping review is to outline the scientific evidence concerning the role of Parkinson's disease nurse specialists (PDNS) to provide education and guidance to patients with Parkinson's disease (PD) undergoing subcutaneous apomorphine therapy (CSAI). *Introduction:* PD affects approximately 1% of both men and women on a global scale, especially those aged 60 and above. Working within a multi-disciplinary team, the PDNS enhances adherence to the treatment regimen, even in a home-based setting. *Inclusion criteria:* Included studies involved participants over 18 years old, with texts in English or Italian. Exclusions covered research on alternative apomorphine administrations, brain stimulation, comparisons with other treatments, mood changes from apomorphine, or unrelated to PDNS training. *Methods:* We conducted a comprehensive literature review across databases such as Medline (via PubMed), The Cochrane Library, Scopus, Web of Science (WOS), and Google Scholar, sourcing relevant articles to identify primary indexed studies examining the interaction between nurse practitioners and PD patients undergoing subcutaneous apomorphine treatment; *Results:* The review encompasses twenty studies, revealing that specialized nursing education and training during the subcutaneous apomorphine therapy phase can effectively mitigate the considerable risks associated with treatment nonadherence. *Conclusions:* The collaboration of proficient and specialized nursing personnel, working alongside a multidisciplinary team, to deliver suitable training and education during CSAI, is instrumental in averting adverse outcomes and potential nonadherence issues, thereby enhancing the quality of life for both PD patients and their caregivers.

Key words: Parkinson's disease, subcutaneous apomorphine infusion therapy, Parkinson's disease nurse specialists (PDNS)

Introduction

Parkinson's disease (PD) affects about 1% of people worldwide, mainly those aged 60 and above. It is the second most common neurodegenerative disorder after Alzheimer's disease. PD is characterized by the loss of

dopamine-producing neurons in the substantia nigra region of the midbrain, along with the presence of abnormal protein clumps called Lewy bodies in the brainstem and cortex (1). PD is classified as an idiopathic neurological disorder characterized by the slow onset of symptoms such as tremors, slowness of movement

(bradykinesia), stiffness (rigidity), and problems with balance and posture (2). Responses to treatment can vary greatly among individuals (3,4). Levodopa remains the gold standard for treating PD and retains its efficacy even during the advanced stages of the condition. However, alternative therapies may be considered based on individual patient characteristics (5). Other therapeutic management include deep brain stimulation (DBS), levodopa-carbidopa intestinal gel (LCIG), and subcutaneous apomorphine infusion (CSAI). Apomorphine is administered subcutaneously, either as an intermittent injection or as a CSAI (6,7). Notably, within Europe, a significant 44% of individuals newly diagnosed with PD lack the opportunity for treatment and ongoing clinical oversight by neurologists specializing in PD. Additionally, limited economic resources and inadequate training of personnel contribute to restricted access to skilled nursing care (8). A multidisciplinary care team (MDT) is considered the best approach for managing advanced PD, with the Parkinson's disease nurse specialist (PDNS) playing a crucial role. The PDNS helps patients adapt to various treatment options, including oral medications and infusion therapies like apomorphine and LCIG, as well as DBS (9). Apomorphine is an effective treatment option for PD that works well regardless of age. It is particularly useful for managing both "off" periods and dyskinesias (abnormal involuntary movements) associated with PD. This is achieved through either intermittent injections or continuous infusion to regulate motor complications (10). For patients experiencing persistent motor fluctuations (on-off effects) that cannot be controlled with oral medications or fewer than six intermittent subcutaneous apomorphine injections, CSAI throughout the waking hours is recommended (2). Subcutaneous injection results in rapid absorption, almost complete bioavailability, and a short half-life of about 43 minutes. Its high lipid solubility allows it to quickly enter the central nervous system, leading to rapid clinical effects. The impact on dyskinesias can be seen within 5 to 15 minutes after administration, with the timing influenced by factors like injection site (preferably the abdominal wall over the thigh), skin temperature, and subcutaneous tissue thickness (11). During the maintenance phase of CSAI therapy, the primary objective is to empower patients to manage their treatment

independently or with assistance from caregivers, along with the support of a PDNS or a trained community nurse (9). The success of apomorphine therapy extends beyond its pharmacological effects to include patient understanding of their condition and ability to manage the treatment regimen. In this context, the PDNS, as a key member of the MDT, plays a crucial role. PDNS ensure treatment adherence, provide education, deliver training, offer ongoing support, and are available for consultations regarding nursing-related aspects of the treatment (9). The effectiveness of CSAI depends on diligent patient compliance, sustained caregiver involvement, regular nursing assessments (including home visits), and ongoing medical/nursing follow-up (11). Starting apomorphine pump therapy is ideally done in a hospital setting. The normally adopted syringe driver is specifically designed for delivering apomorphine. Its small size allows for discreet concealment in a pocket or under clothing, enabling longer treatment periods without frequent syringe changes. The pump includes a time display, providing patients with precise information about infusion duration for better at-home management. An illuminated sensor visually indicates when the continuous infusion is active. The PDNS plays a critical role in easing the burden on healthcare providers and reducing workload pressure on physicians by providing consistent daily management of PD patients. Of particular importance is the PDNS invaluable contribution throughout the spectrum of apomorphine therapy, including candidate selection, dosage adjustment, treatment maintenance, and management of adverse effects (9). Despite advancements, this area remains controversial and certain aspects are inadequately addressed in the literature. Therefore, there is a compelling need for a systematic review of existing literature. The purpose of this scoping review would be to comprehensively evaluate the relationship between the presence of a skilled PDNS involved in guiding patients through subcutaneous apomorphine administration and its impact on treatment adherence and continuation of therapy among patients.

Review question

What is the role of Parkinson's disease nurse specialists (PDNS) in providing education and guidance

to patients with Parkinson's disease undergoing subcutaneous apomorphine infusion (CSAI) in various healthcare settings?

- Centered on mood changes in patients receiving subcutaneous apomorphine.
- Were not directly related to the instructional or training phase involving PDNS.

Methods

Eligibility criteria

POPULATION

Studies were included if they involved adult participants (≥ 18 years old) with PD undergoing CSAI therapy.

CONCEPT

Studies needed to focus on the involvement of PDNS in the administration and management of CSAI therapy, particularly examining the role of PDNS in the instructional phase for patients and/or caregivers.

CONTEXT

Included studies were available as full-text articles in either English or Italian. Quantitative, qualitative, and mixed-method studies were included to encompass various aspects of the PDNS role in CSAI therapy. Studies were excluded if they:

- Investigated alternative modes of administration for apomorphine therapy.
- Focused on brain stimulation therapies.
- Compared CSAI therapy with other alternative treatments.

Informational sources

This scoping review included a variety of study designs, encompassing both experimental and quasi-experimental approaches such as randomized controlled trials, non-randomized controlled trials, before-and-after studies, and interrupted time-series studies. It also incorporated analytical observational studies, like prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies. Descriptive observational study designs, such as case series, individual case reports, and descriptive cross-sectional studies, were also eligible for inclusion. Secondary literature, qualitative research, and grey literature were not included in this review to maintain a focus on primary studies directly related to the role of PDNS in CSAI therapy.

Search strategy

To initiate the literature review, a research inquiry was formulated utilizing the Population, Concept, Context (PCC) approach (Table 1). Subsequently, a comprehensive exploration of the literature was conducted by querying databases such as MEDLINE (via PubMed), The Cochrane Library, Scopus, Web of Science (WOS), CINAHL (via EBSCO), and Google Scholar. This search yielded articles relevant to the designated topic.

The search methodology involved the utilization of specific terms, combining open searches and MeSH

Table 1. The PCC tool for the conduction of the literature review.

Population	Adult patients (≥ 18 years old) with Parkinson's disease undergoing CSAI
Concept	The role of PDNS in providing education and guidance, particularly in the instructional phase for patients and/or caregivers
Context	Various healthcare settings, including hospitals, outpatient clinics, and home-based care

Abbreviations: PCC: Population, Concept, Context; CSAI: continuous subcutaneous apomorphine infusion PDNS: Parkinson's disease nurse specialist; PD: Parkinson's disease.

Table 2. Combination of keywords used with the Boolean operator.

Database	Search String
<i>MEDLINE</i> (<i>Pubmed</i>)	("apomorphine"[MeSH Terms] OR "apomorphine"[All Fields] OR "apomorphin"[All Fields] OR "apomorphine s"[All Fields] OR "apomorphines"[All Fields]) AND ("nurses"[MeSH Terms] OR "nurses"[All Fields] OR "nurse"[All Fields]) AND ("subcutaneous"[All Fields] OR "subcutaneously"[All Fields] OR "subcutanous"[All Fields]) AND ("Parkinson's"[All Fields] OR "Parkinson"[All Fields]) AND ("education"[MeSH Subheading] OR "education"[All Fields]) AND ("training"[All Fields] OR "train"[All Fields] OR "trains"[All Fields] OR "trained"[All Fields])
<i>Scopus</i>	("apomorphine" AND "nurse" AND "subcutaneous" AND "Parkinson's" AND ("education" OR "training"))
<i>Google Scholar</i>	("apomorphine" AND "nurse" AND "subcutaneous" AND "Parkinson's" AND ("education" OR "training"))
<i>CINAHL</i> (<i>EBSCO</i>)	("apomorphine" AND "nurse" AND "subcutaneous" AND "Parkinson's" AND ("education" OR "training"))
<i>Web of science</i> (<i>WOS</i>)	("apomorphine" AND "nurse" AND "subcutaneous" AND "Parkinson's" AND ("education" OR "training"))
<i>Cochrane Library</i>	"apomorphine" AND "Parkinson's disease"

terms with Boolean operators AND and OR. The terms employed included "apomorphine," "nurse," "subcutaneous," "Parkinson's," "education," and "training". A comprehensive search was conducted across multiple databases including MEDLINE (via PubMed), Scopus, Google Scholar, CINAHL (via EBSCO), Web of Science, and The Cochrane Library. The detailed search strategy for MEDLINE (via PubMed) is provided below as an example, and similar strategies were applied to the other databases. Table 2 shows the combination of keywords used with the Boolean operator.

MEDLINE search strategy

1. "apomorphine"[MeSH Terms] OR "apomorphine" [All Fields] OR "apomorphin"[All Fields] OR "apomorphine s"[All Fields] OR "apomorphines"[All Fields]
2. "nurse s"[All Fields] OR "nurses"[MeSH Terms] OR "nurses"[All Fields] OR "nurse" [All Fields] OR "nurses s"[All Fields]
3. "subcutaneous"[All Fields] OR "subcutaneously" [All Fields] OR "subcutanous" [All Fields]
4. "Parkinson's"[All Fields] OR "Parkinson" [All Fields]
5. "education"[MeSH Subheading] OR "education" [All Fields] OR "educability"[All Fields] OR "educable"[All Fields] OR "educates" [All Fields]

6. "training"[All Fields] OR "education"[MeSH Terms] OR "train"[All Fields] OR "trains"[All Fields] OR "trained"[All Fields]

Similar search strategies were applied to the other databases, adjusting the terms and Boolean operators as necessary to fit the specific database syntax and search capabilities.

Following an initial electronic exploration of bibliographic databases, articles deemed pertinent were identified for the purpose of this review. Duplicate entries were eliminated, subsequently isolating suitable articles. Specifically, two authors assessed studies that potentially aligned with the primary search objective and evaluated the feasibility of obtaining full-text access (12).

Data charting strategy

The data charting process involved systematically extracting and organizing key information from each included study. A standardized data charting form was developed and piloted on a subset of studies to ensure consistency and comprehensiveness. The data charting form included fields for study characteristics (e.g., author and year), population details (e.g., number of participants setting of the studies), and key findings. Two reviewers independently charted the data from each study, and discrepancies were resolved through discussion or consultation with a third reviewer.

Data items

We abstracted data on article characteristics (e.g., author, year of publication, country of origin), study design (e.g., randomized controlled trial, cohort study), and specific details related to the intervention (e.g., role of PDNS, type of CSAI therapy). Additionally, we extracted information on the population (e.g., number of participants, age range), outcomes measured (e.g., treatment adherence, patient education), and key findings. The data synthesis was conducted using a narrative approach to summarize the findings from the included studies. This approach allowed us to integrate quantitative, qualitative, and mixed-methods data, focusing on identifying common themes and patterns. The synthesis was organized thematically to highlight the various dimensions of PDNS involvement and their impact on treatment adherence and patient outcomes. We also examined barriers and facilitators to the implementation of PDNS roles in CSAI therapy, as well as any reported outcomes related to patient and caregiver education. The narrative synthesis enabled us to present a comprehensive overview of the evidence, highlighting both the benefits and challenges associated with PDNS involvement in CSAI therapy.

Critical appraisal method

Although critical appraisal is not a mandatory component of scoping reviews, we conducted a quality assessment of the included studies to provide context for interpreting the findings. The Joanna Briggs Institute (JBI) critical appraisal checklists for various study designs were used to evaluate the methodological quality of the included studies. The assessment focused on aspects such as study design, sample size, intervention details, outcome measurement, and potential biases. The JBI critical appraisal tools measure overall quality, categorizing studies as high, moderate, or low quality based on their scores. Information for quality assessment was incorporated into the data extraction form, which was pilot tested on a random sample of included articles that ranged from low to high quality. Two reviewers independently assessed the quality of each study, and discrepancies were resolved through discussion or adjudication by a third reviewer. The results of the critical appraisal were used to inform the

discussion of the strengths and limitations of the evidence base, ensuring a comprehensive understanding of the quality and reliability of the included studies.

Results

In total, 5407 records were identified, of which 182 were duplicates. Of the 5225 unique records, 5184 were excluded based on the content of their titles and abstracts. After retrieving and reading the full text of the remaining 41 articles, the inclusion criteria were applied. Twenty-one articles were excluded, resulting in 20 studies being included in the final analysis (Figure 1).

Table 3 shows the 20 articles included in the review, including authors, year of publication, quantity and type of patients, evaluation of parameters studied, objectives and results.

The results of the critical appraisal allowed us to assess the methodological quality of the included studies, providing a foundation for interpreting the findings with greater confidence (data not shown). Research indicates that despite the availability of various oral medications, controlling PD dyskinesias can be challenging, often requiring alternative treatment options. Motor complications and other disabling symptoms can significantly impact the quality of life and independence of patients, as well as affecting the lives of their families and caregivers (6,7). Clinical experience with apomorphine for treating PD dates back to 1951, when early clinical trials demonstrated its potential to alleviate symptoms such as tremor and rigidity. Although apomorphine had been used for many years as an emetic (to induce vomiting) and for various neuropsychiatric conditions like insomnia, neurosis, mania, or schizophrenia, its therapeutic rationale was not understood until its dopaminergic properties were discovered (10). The choice of therapy and its method of administration for PD depends on various factors specific to each patient. Some studies highlight the lack of international guidelines for selecting the appropriate candidate for therapies such as LCIG, brain stimulation, sublingual apomorphine, or CSAI (1,21). A study analyzing 101 patient records with apomorphine infusion at the Department of Neurology, Bispebjerg University Hospital, aimed to understand

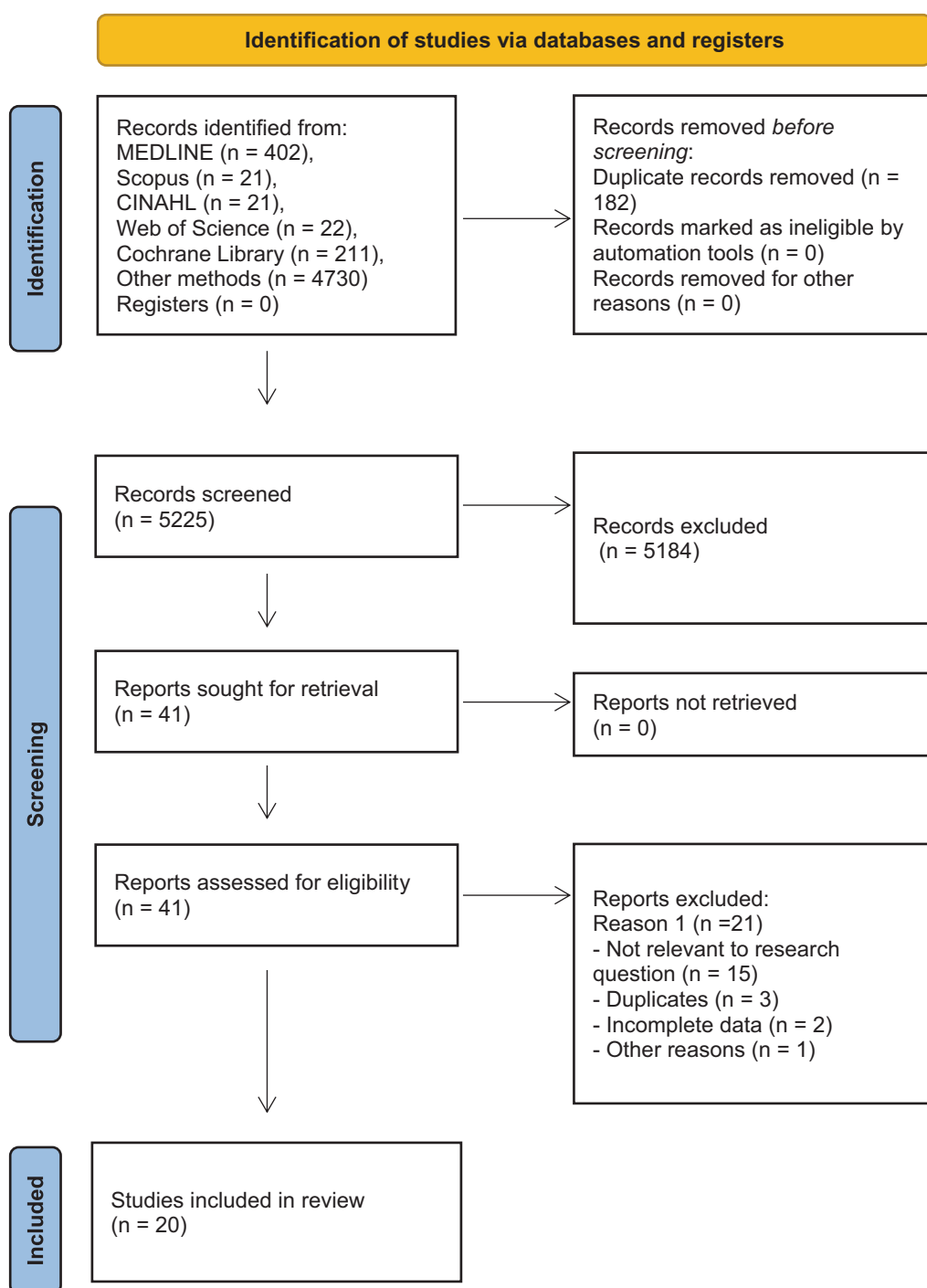


Figure 1. PRISMA 2020 flow diagram (13) of the research.

the reasons for treatment nonadherence with CSAI. It concluded that nonadherence could be attributed to insufficient communication with patients, the MDT, and caregivers, as well as inadequate monitoring of

treatment effects and timely management of adverse events (18). The appropriate dosage of apomorphine for each patient is determined through incremental dosing. Apomorphine infusion typically begins at

Table 3. Key characteristics of the included studies

Database Author year	Objective	Setting	Sample Setting study	Key findings
<i>Nijhuis et al. 2016 (6)</i>	The aim of this study was to explore the current decision-making process in advanced PD.	Observational Qualitative focus group	36 patients undergoing treatment	In this study, we found several factors that explain why in current practice, evidence-based decision making in PD advanced is not optimal. An important first step would be to develop objective information on all treatment options.
<i>Tyne et al. 2004 (7)</i>	Apomorphine is a potent dopamine agonist useful in the treatment of patients with disease Parkinson's disease with motor fluctuations disabling and "off" periods, which do not respond to oral medications.	Qualitative observational	107 patients treated with apomorphine	Subcutaneous apomorphine is easy for patients to use, is well tolerated, and has a low Incidence of side effects, particularly confusion.
<i>Bhidayasiri et al. 2016 (9)</i>	The role of a PDNS is particularly important in the Treatment of patients with advanced PD suitable for apomorphine	Observational, descriptive	27 patients on continuous subcutaneous apomorphine therapy	There is strong clinical evidence that the impact of PDNS on the management of apomorphine therapy is vital and indispensable for the success of this treatment
<i>Liberati A. et al., 2009 (14)</i>	Published systematic reviews have found that key information about these studies is often misreported.	Observational, descriptive	PRISMA consists of a 27-item checklist and a four-step flowchart; this document describes the items	PRISMA: This document and associated Web site (www.prisma-statement.org/) should be useful resources for improving the reporting of systematic reviews and meta- analyses.
<i>Lezzi et al. 2022 (1)</i>	Identify the role of the nurse in the selection phase of the patient candidate for LCIG therapy.	Observational	Literature Review	The stage of choosing a patient candidate for LCIG therapy is critical to improving adherence to LCIG therapy.
<i>De Rosa et al. 2016 (11)</i>	The purpose of this review is to focus on these complex therapies, highlighting rules of implementation, effectiveness, indications, contraindications.	Observational descriptive	Description of therapies of LCIG, DBS, CSAI.	All three procedures require careful selection and good compliance of the candidate patients.
<i>van den Heuvel et al. 2022 (15)</i>	Clinical decision making is a complex process, influenced by many different factors that differ for each decision and for each individual.	Observational, qualitative	There were 52 consultations with PD patients and their PD neurologist or nurse specialist in 6 outpatient clinics.	In daily practice, it is difficult to tailor decisions to individual characteristics (diseases) because there is a lack of sufficient evidence on the impact of these individual characteristics on outcomes.

Database Author year	Objective	Setting	Sample Setting study	Key findings
<i>Özkan et al. 2021 (10)</i>	The goal is to create a “treatment management guideline” that includes recommendations for the use of apomorphine in clinical practice	Observational	Literature Review	Scientific evidence related to the discussion of complications on subcutaneous apomorphine administration in patients with PD.
<i>Karni et al. 2022 (8)</i>	The main goal was to develop a new home monitoring system (called EMPARK) with patient and physician interface to improve patient empowerment and clinical care in PD.	Observational, qualitative	Patient interface on a sample of 80 patients included in the study	EMPARK would empower patients and could be used for future applications in daily care and research.
<i>Tsai et al. 2019 (3)</i>	With a unilateral injection of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle, it was applied to evaluate neuroprotective effects and motor behaviors by PD.	Observational pre- post	The experimental rats, assigned to the exercise group, spent 2 weeks in their exercise cages before 6-OHDA administration and 2 weeks after 6-OHDA administration.	The present results suggest that voluntary exercise can provide long-term improvements in functional motor behavior in patients with PD.
<i>Kaiyrzhanov et al. 2019 (16)</i>	The clinical characteristics, treatments used, epidemiology, and genetics of PD in CA and CT countries were examined.	Observational	Literature Review	Health professionals, local and national institutions, and stakeholders must come together to address deficiencies in PD health systems.
<i>Verzwyvelt et al. 2021 (17)</i>	A well-established approach for treating patients with rest periods and controlling the motor fluctuations refractory to conventional oral drug therapy is subcutaneous administration of the dopamine agonist apomorphine.	Observational, descriptive	3 main approaches in which is used: intermittent subcutaneous injection of apomorphine as “rescue” therapy for off states, continuous subcutaneous infusion of apomorphine for PD patients with intractable motor fluctuations as an alternative to other dopaminergic treatments, and in the apomorphine response (or challenge) test.	The management of potential adverse events with subcutaneous administration of apomorphine.

Database Author year	Objective	Setting	Sample Setting study	Key findings
<i>Henriksen et al. 2021 (18)</i>	CSAI adherence is generally considered low because of adverse events and because it is perceived as a treatment option to be used only for a limited period.	Observational, descriptive	101 patients who discontinued treatment with CSAI.	CSAI requires careful patient selection, a high level of communication with the patient and caregiver, and rigorous monitoring of treatment effects and for any adverse events so that they can be managed promptly.
<i>Lees et al. 2002 (2)</i>	Through follow-up measure adherence to subcutaneous apomorphine therapy in patients with PD	Observational, double-blind	A 3-year follow-up of 64 patients on apomorphine therapy at Middlesex-Hospital	Twenty-five percent of patients managed their apomorphine independently, 50 percent with the help of their caregiver, and only 25 percent required outside help from district nurses.
<i>Bhidayasiri et al. 2016 (19)</i>	Proactive management, most adverse effects are manageable if reported and addressed early enough.	Observational	Literature Review	Proactive management, most adverse events are manageable, and the benefits of apomorphine can be life-changing in reducing PD symptoms and improving quality of life.
<i>Caughman et al. 2021 (25)</i>	Description of sublingual apomorphine offers a new, novel and effective therapy developed for the treatment of “off” episodes.	Observational	Literature Review	The new sublingual apomorphine is safe and effective for the relief of “off” periods that affect quality of life.
<i>Katzenschlager et al. 2020 (20)</i>	The main objective was to evaluate the long-term safety of APO.	Observational, cohort	Eighty-four patients entered the PLO (40 previously treated with APO, 44 with placebo) and 59 patients (70.2%) completed the study.	The safety and efficacy of APO infusion have been demonstrated with long-term use for persistent motor fluctuations, allowing substantial reductions in oral PD medications.
<i>Marsili et al. 2021 (21)</i>	International survey of forty-four experienced movement disorder specialists regarding the management of device- assisted therapies in advanced PD.	Observational, qualitative	44 specialists in PD disease	Guidelines are needed to assist physicians and patients in choosing device-assisted therapies.
<i>Agbo et al. 2021 (22)</i>	The aim of this study was to evaluate these parameters in patients with PD and “OFF” episodes through the effective dosing range for these treatments.	Observational	Literature Review	Sublingual apomorphine film has a lower bioavailability than subcutaneous film.

Table 3 (Continued)

Database Author year	Objective	Setting	Sample Setting study	Key findings
<i>Nigro et al.</i> 2019 (23)	To examine the effects of apomorphine on the topological characteristics of functional connectivity networks in the resting state in patients with PD and tdPD .	Observational, pre- post	Sixteen patients with tdPD were examined using a combined approach of functional MRI with electromyography.	Patients were scanned twice after placebo (subcutaneous injection of 1 ml saline) or 1 mg apomorphine injection, demonstrating that drug treatment changes the functional brain organization of tdPD

Abbreviations: PD: Parkinson's disease; CSAI: subcutaneous infusion of continuous apomorphine; PDNS: Parkinson's disease specialist nurse; DBS: deep brain stimulation; LCIG: levodopa-carbidopa intestinal gel; APO: apomorphine; tdPD: tremor-dominant; 6-OHDA: 6-hydroxydopamine; CA: Central Asia; TC: Transcaucasian countries; OLP: open phase study; EMPARK: home monitoring system.

a dose of 1 mg/h during waking hours. The infusion dose is then gradually increased by 1 to 1.5 mg/h per day based on the patient clinical response and the discontinuation of other treatments (such as catechol-o-methyltransferase inhibitors, oral or transdermal dopamine agonists, monoamine oxidase-B inhibitors, and levodopa) (2,6). The target is to titrate the apomorphine dose to at least 3 mg/h (24). The "TOLEDO" study confirmed the effectiveness of apomorphine infusion in reducing "off" time in PD patients with persistent motor fluctuations compared to optimized oral/transdermal levodopa therapy (20,22). Additionally, a study involving sixteen patients with tremor-dominant PD (tdPD) used a combined approach of functional MRI and electromyography to examine the effects of subcutaneous apomorphine injection. This study demonstrated a significant reduction in tremor symptoms, reflected by increased overall connectivity strength compared to a control group receiving placebo subcutaneously (23). PDNS typically play a key role in educating patients, healthcare providers, district nurses, or community nurses on how to use apomorphine infusion pumps (9,11). For example, a center in Thailand provided a helpful video and step-by-step guide to offer practical information on using apomorphine infusion (9). The level and quality of education provided to patients about CSAI can significantly influence treatment compliance and success. Several studies indicate that patients with insufficient education and support,

especially in the absence of a PDNS, often discontinue apomorphine therapy within a few weeks (8,18). Optimal care for PD now recognizes the need for a multidisciplinary approach beyond traditional one-on-one physician-patient relationships. Given the complexity and variability of motor and nonmotor symptoms, comorbidities, and multiple medications involved in PD, it seems evident that a single physician cannot provide comprehensive management alone (9,16). Nurses play a critical role in establishing effective communication with patients, family members, and within the multidisciplinary team (19). They are pivotal in patient education, addressing fears and doubts related to therapy (25). The management of infusion devices, such as those used in CSAI, requires a team of trained nurses, particularly PDNS who are essential for managing technical issues like device malfunction or occlusion, as well as detecting and addressing local skin complications (11). They analyze factors such as skin health, home management of CSAI, family dynamics, and other aspects influencing therapeutic adherence, making PDNS involvement crucial at every stage of the treatment process (10).

Conclusion

The results of this scoping review highlight the critical role of PDNS in managing CSAI therapy for

patients with PD. Our findings indicate a significant deficiency in professional expertise and awareness about the range of potential therapies for PD, compounded by the lack of PDNS in many hospital settings and limited patient awareness of available treatment options. This lack of education and knowledge about PD impedes efforts to enhance individual quality of life (3,6). CSAI therapy has emerged over time as a valuable treatment option for reducing PD-related dyskinesias, showing superior efficacy compared to optimized oral treatments, and with no age-based exclusion criteria (20,23). The PDNS provide comprehensive care by offering professional expertise, technical nursing assistance, continuous support, and emotional guidance. They possess the necessary nursing skills for PD management and act as a crucial link connecting PD patients with the MDT. This involvement includes seamless collaboration, interaction, and coordination with other care providers to ensure a holistic care approach (9). Specialized nursing education focused on PD has been proposed for over two decades to enable the delivery of specialized nursing services covering all aspects of PD care, including clinical, educational, and professional aspects (9). In a holistic healthcare approach for PD, the focus remains on patient-centered outcomes, supported by the expertise of multidisciplinary professionals. The PDNS plays a crucial role across all aspects of PD care – from diagnosis and guiding patients through various treatment options to addressing non-motor symptoms (NMS), initiating palliative care, and providing support to caregivers and bereaved families even after death (9). In certain situations, PDNS should be available for home visits to reduce stress on the patient family and hospital healthcare services. Home-based administration of CSAI can be anxiety-inducing, as neither the patient nor the caregiver may have prior experience with this treatment. The controlled environment of a hospital, where proper training is provided, offers a sense of safety that may be lacking at home (9). Concerns often arise due to anxiety about a therapy involving subcutaneous needle insertion, leading to agitation and discouragement, especially regarding potential risks from insufficient technical knowledge to manage adverse events (25). An innovative home monitoring system

called EMPARK, equipped with patient and physician/nurse interfaces, has been used to empower patients and improve clinical care in PD. This approach highlights the importance of personalized attention to the patient care journey, promoting medication adherence (8). Local skin reactions associated with CSAI can range from transient redness and itching on the abdominal wall to the development of skin nodules, infections, abscesses, or, in severe cases, necrotic ulcers (9). Skin nodules are the most common consequence, often accompanied by skin discoloration or scarring. The duration, severity, and appearance of these nodules can vary significantly among individuals, influenced by factors such as apomorphine dosage, skin type, body mass index, needle type, and accurate insertion techniques (9). To address these complications and prevent therapy discontinuation, precise instructions on needle insertion techniques are essential. Additionally, maintaining a detailed recording chart by patients, healthcare providers, or nurses is crucial in preventing or mitigating nodule formation and associated issues (9). This proactive approach aims to manage skin reactions effectively and ensure the continuity of CSAI. During the hospitalization phase, a PDNS involvement is crucial in assisting patients with CSAI to monitor drug efficacy and potential side effects, which may include hypotension, vomiting, and hallucinations (25). Before hospital discharge, PDNS should educate patients and/or their family members, providing guidance on proper skin disinfection and timely identification of potential side effects (9). It is imperative that PDNS ascertain the patient or caregiver proficiency in independently performing these tasks. Nurses can recommend several strategies to prevent or mitigate skin reactions, such as daily rotation of the injection site with around-the-clock administration, avoiding the periumbilical area, adhering to aseptic protocols and skin hygiene, opting for gentle and slender 29-gauge needles equipped with a 30-cm Teflon cannula and a luer-lock connector, executing deep injections, using silicone patches to shield the needle, and massaging the insertion site after each infusion. The management approach for subcutaneous nodules varies based on their type and severity (11). For mild or fibrous nodules, treatment options may include topical application

of corticosteroids and fibrinolytics, along with low-frequency ultrasound therapy (11). These interventions aim to alleviate discomfort and reduce the impact of skin reactions associated with CSAI therapy. A study (18) emphasized that inadequate training and education by a PDNS, failing to guide patients through the treatment process, often leads to premature discontinuation of therapy within a few weeks. Conversely, a PDNS who educates the patient, particularly regarding strategies to manage early complications like nodules and hallucinations from subcutaneous infusion, contributes to successful therapy continuation. Therefore, vigilant monitoring of adverse events and prompt management are crucial. For instance, hallucinations associated with CSAI can be managed using medications like cholinesterase inhibitors or clozapine, preventing unnecessary discontinuation of CSAI. It is essential for patients to be well-informed about these management options (8,10).

To improve patient adherence to treatment, a contact number should be provided upon discharge, allowing patients to seek clarification and guidance as needed. This facilitates ongoing communication with the PDNS to ensure continuous therapy support (10). This proactive approach helps to address concerns and challenges that may arise during the course of CSAI therapy, promoting treatment adherence and patient well-being. Future research should focus on developing standardized guidelines for PDNS roles in CSAI therapy and investigating long-term outcomes. High-quality, large-scale studies are needed to further explore the impact of PDNS on treatment adherence and patient outcomes. In conclusion, the involvement of PDNS in CSAI therapy is crucial for managing PD effectively. PDNS play a key role in patient education, technical support, and continuous monitoring, which significantly contributes to the success of the therapy. Ensuring proper training and education for both PDNS and patients can prevent therapy discontinuation and improve overall patient outcomes. The limitation of the review relates to the paucity of scientific literature, particularly a small number of large, randomized, blinded studies related to the nursing figure who relates to the PD patient who is administered CSAI. Indeed, few studies describe what

happens during such a scenario and whether education plays a decisive role in ensuring adherence to therapy. Long-term patient outcomes were not reported in any of the studies included in this review. However, the impact of nurse education and the role of PDNS with MDT, is a significant topic for future research.

The use of CSAI in patients has proven to be an effective therapy for managing motor symptoms of PD, with no age restrictions on its use. PDNS play a critical role, particularly in the training phase of individuals involved in the treatment plan, ensuring adherence to drug therapy. The results of the review highlight the necessity for further research using larger sample sizes to gain a deeper understanding of how the nursing role can enhance the treatment process. This includes exploring how PDNS can help prevent complications associated with subcutaneous apomorphine infusion and improve therapeutic compliance among patients. More extensive studies are needed to assess the specific impact and effectiveness of nursing interventions in optimizing CSAI therapy for PD patients. This research would contribute valuable insights into maximizing treatment outcomes and patient satisfaction in PD management.

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References

- Lezzi P, Lupo R, Lezzi T, Vitale E. The Prephase Nursing in Levodopa Carbidopa Intestinal Gel Therapy. *J Neurosci Nurs*. 2022 Oct 1;54(5):215-219. doi: 10.1097/JNN.0000000000000671.
- Lees A, Turner K. Apomorphine for Parkinson's Disease. *Pract Neurol* 2002;2(5):280-287; doi: 10.1046/j.1474-7766.2002.00086.x.
- Tsai W-L, Chen H-Y, Huang Y-Z, et al. Long-Term Voluntary Physical Exercise Exerts Neuroprotective Effects and Motor Disturbance Alleviation in a Rat Model of Parkinson's Disease. *Behav Neurol* 2019;2019:1-10; doi: 10.1155/2019/4829572.
- Vitale E, Conte L, Pasquadibisceglie R, et al. Perceptions of workload in caregivers involved in the care of patients with Parkinson's disease: an exploratory - correlational study. *J Gerontol Geriatr* 2024; doi: 10.36150/2499-6564-N582.
- Conte L, Lupo R, Lezzi P, et al. Statistical analysis and generative Artificial Intelligence (AI) for assessing pain experience, pain-induced disability, and quality of life in Parkinson's disease patients. *Brain Res Bull* 2024;208:110893; doi: 10.1016/j.brainresbull.2024.110893.
- Nijhuis FA, van Heek J, Bloem BR, Post B, Faber MJ. Choosing an Advanced Therapy in Parkinson's Disease; is it an Evidence-Based Decision in Current Practice? *J Parkinsons Dis*. 2016 Jul 25;6(3):533-43. doi: 10.3233/JPD-160816.
- Tyne HL, Parsons J, Sinnott A, Fox SH, Fletcher NA, Steiger MJ. A 10 year retrospective audit of long-term apomorphine use in Parkinson's disease. *J Neurol*. 2004 Nov;251(11):1370-4. doi: 10.1007/s00415-004-0547-4.
- Karni L, Jusufi I, Nyholm D, Klein GO, Memedi M. Toward Improved Treatment and Empowerment of Individuals With Parkinson Disease: Design and Evaluation of an Internet of Things System. *JMIR Form Res*. 2022 Jun 9;6(6):e31485. doi: 10.2196/31485.
- Bhidayasiri R, Boonpang K, Jitkritsadakul O, et al. Understanding the role of the Parkinson's disease nurse specialist in the delivery of apomorphine therapy. *Parkinsonism Relat Disord* 2016;33:S49-S55; doi: 10.1016/j.parkreldis.2016.11.014.
- Özkan S, Erer S, Elibol B, et al. Apomorphine in the Treatment of Parkinson's Disease. *Turkish J Neurol* 2021;27(4):358-365; doi: 10.4274/tnd.2021.06706.
- De Rosa A, Tessitore A, Bilo L, et al. Infusion treatments and deep brain stimulation in Parkinson's Disease: The role of nursing. *Geriatr Nurs (Minneap)* 2016;37(6):434-439; doi: 10.1016/j.gerinurse.2016.06.012.
- Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018;169(7):467-473; doi: 10.7326/M18-0850.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;n71; doi: 10.1136/bmj.n71.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6(7):e1000100; doi: 10.1371/journal.pmed.1000100.
- van den Heuvel L, Meinders MJ, Post B, Bloem BR, Stiggelbout AM. Personalizing decision-making for persons with Parkinson's disease: where do we stand and what to improve? *J Neurol*. 2022 Jul;269(7):3569-3578. doi: 10.1007/s00415-022-10969-4.
- Kaiyrzhanov R, Rizig M, Aitkulova A, et al. Parkinson's Disease in Central Asian and Transcaucasian Countries: A Review of Epidemiology, Genetics, Clinical Characteristics, and Access to Care. *Parkinsons Dis* 2019;2019:1-7; doi: 10.1155/2019/2905739.
- Ashley Verzwylvelt L, McNamara A, Xu X, et al. Effects of virtual reality v. biophilic environments on pain and distress in oncology patients: a case-crossover pilot study. *Sci Rep* 2021;11(1):20196; doi: 10.1038/s41598-021-99763-2.
- Henriksen T, Staines H. Continuous Subcutaneous Apomorphine Infusion in Parkinson's Disease: A Single-Center, Long-Term Follow-Up Study of the Causes for Discontinuation. *J Pers Med* 2021;11(6):525; doi: 10.3390/jpm11060525.
- Bhidayasiri R, Garcia Ruiz PJ, Henriksen T. Practical management of adverse events related to apomorphine therapy. *Parkinsonism Relat Disord* 2016;33:S42-S48; doi: 10.1016/j.parkreldis.2016.11.017.
- Katzenschlager R, Poewe W, Rascol O, et al. Long-term safety and efficacy of apomorphine infusion in Parkinson's disease patients with persistent motor fluctuations: Results of the open-label phase of the TOLEDO study. *Parkinsonism Relat Disord* 2021;83:79-85; doi: 10.1016/j.parkreldis.2020.12.024.
- Marsili L, Bologna M, Miyasaki JM, Colosimo C. Device-aided therapies for advanced Parkinson disease: insights from an international survey. *Neurol Sci*. 2021 Jul;42(7):2961-2964. doi: 10.1007/s10072-021-05106-4.
- Agbo F, Isaacson SH, Gil R, et al. Pharmacokinetics and Comparative Bioavailability of Apomorphine Sublingual Film and Subcutaneous Apomorphine Formulations in Patients with Parkinson's Disease and "OFF" Episodes: Results of a Randomized, Three-Way Crossover, Open-Label Study. *Neurol Ther* 2021;10(2):693-709; doi: 10.1007/s40120-021-00251-6.
- Nigro S, Bordier C, Cerasa A, et al. Apomorphine-induced reorganization of striato-frontal connectivity in patients

- with tremor-dominant Parkinson's disease. *Parkinsonism Relat Disord.* 2019 Oct;67:14-20. doi: 10.1016/j.parkreldis.2019.09.006.
24. Bhidayasiri R, Chaudhuri KR, LeWitt P, et al. Effective Delivery of Apomorphine in the Management of Parkinson Disease. *Clin Neuropharmacol* 2015;38(3):89-103; doi: 10.1097/WNF.000000000000082.
25. yne HL, Parsons J, Sinnott A, Fox SH, Fletcher NA, Steiger MJ. A 10 year retrospective audit of long-term apomorphine use in Parkinson's disease. *J Neurol.* 2004 Nov;251(11):1370-4. doi: 10.1007/s00415-004-0547-4.n
- CY, Factor S. A critical review of apomorphine hydrochloride sublingual film for the treatment of Parkinson's disease 'OFF' episodes. *Expert Rev Neurother* 2021;21(2): 169-177; doi: 10.1080/14737175.2020.1855145.

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