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Long-term effect and reasons for switching and combining device-aided therapies in Parkinson's Disease

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ABSTRACT

Introduction. In the advanced stages of Parkinson's disease (PD), when standard drug adjustments fail to sufficiently improve patients' quality of life, device-aided therapies (DATs) such as deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion (CSAI), levodopa-carbidopa intestinal gel infusion (LCIG), levodopa-carbidopa-entacapone intestinal gel infusion, or continuous subcutaneous foslevodoa-foscarbidopa infusion are beneficial in the long run. However, sometimes patients need to switch or combine DATs due to either adverse events or loss of efficacy.

Aim of study. The aim of this article was to summarise the existing data on the long-term efficacy and adverse events of DATs, and to review the data on the rationale and efficacy for switching or combining DATs in advanced PD.

State of the art. A total of 50 studies on the long-term efficacy of DBS (N = 28), LCIG (N = 12), CSAI (N = 10) and 13 studies on switching and combining DATs were included in this review. Although the DATs show a favourable long-term effect on the main motor and non-motor symptoms of PD they all feature specific adverse events that need to be considered when deciding which DAT to offer to a particular patient. Occasionally, switching or combining DATs is recommended, e.g. if the first DAT shows inadequate symptom control, or due to adverse events. The choice of the second DAT depends above all on the main problems of the first DAT being correctly recognised.

Clinical implications. DATs are a safe and long-term effective option for the treatment of advanced PD. Switching and/or combining DATs is recommended for patients in whom the first treatment option is not optimal.

Future directions. Future studies are warranted to address the unresolved issues related to long-term efficacy, side effect profile and switching and combination of DATs in multicentric studies and using advanced analytical approaches such as machine learning.

Keywords: advanced Parkinson's Disease, device-aided therapies, long-term effect of device-aided therapies, switches and combinations of device-aided therapies

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Introduction

Parkinson's Disease (PD) is a chronic, neurodegenerative disorder characterised by the loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to the bradykinesia, rigidity, tremor and, later during the disease progression, postural instability [1]. The disease progresses through the prodromal, motor, and advanced stages [2]. In parallel with increasing neurodegeneration and increasing doses of dopaminergic drugs, especially levodopa, motor (i.e. motor fluctuations and dyskinesias) and non-motor complications occur [2]. In routine clinical practice, advanced stage PD can be detected by applying the '5-2-1' rule, which characterises a patient who takes at least 5 doses of levodopa

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per day, spends at least 2 hours in 'OFF' state, and experiences disruptive dyskinesias for at least 1 hour [3]. In advanced PD, the dosages of levodopa and other dopaminergic medication are being adjusted (e.g. increasing the frequency of levodopa intake to reduce 'OFF' periods, adjusting single levodopa doses to improve pick-dose or biphasic dyskinesias) and new drugs are constantly being added to the existing therapy (e.g. COMT inhibitors such as entacapone and opicapone, MAO-B inhibitors such as safinamide to reduce wearing off symptoms, or amantadine to improve dyskinesias). Ultimately, however, it is often not possible to control the symptoms of advanced PD with these medication adjustments.

At that point, device-aided therapies (DATs) — deep brain stimulation (DBS) [4], continuous subcutaneous apomorphine infusion (CSAI) [5], levodopa-carbidopa intestinal gel infusion (LCIG) [6], levodopa-carbidopa-entacapone intestinal gel infusion (LCEIG) [7], and continuous subcutaneous foslevodopa-foscarbidopa infusion (CSFFI) [8] — are usually the only effective treatment option left for patients. The subthalamic nucleus (STN), the most common target [4], and the globus palidus pars interna (GPi) DBS [4, 9] are effective treatment options for advanced PD. Together with CSAI and LCIG, DBS has been an available treatment option for advanced PD for longer than any other [10]. In contrast to the recently introduced LECIG and CSFFI, the long-term efficacy of all three DATs has been proven in many studies so far. However, in certain cases, the efficacy of DATs can decrease, and adverse events can occur that require withdrawal and/or change of treatment strategy, including the addition of an additional DAT or switching and combining DATs. To date, several reviews have been published on the long-term effects of DATs [4, 6, 10–13].

The aim of this review article was to summarise existing data on the long-term efficacy and adverse events of the DATs that have been available the longest (DBS, LCIG, CSAI), as well as data on the efficacy of, and rationale for switching or combining DATs in PD.

State of the art

Long term effect of deep brain stimulation for Parkinson's Disease

Twenty-eight studies on the long-term effects of DBS were included in our review (Tab. 1). In addition to the target nucleus, information on the main findings, adverse events, study type, number of patients included, and median/mean and maximum years of follow-up was extracted and analysed. A detailed description of the search process and the selection of studies can be found in the Supplementary Material (A).

Twenty-one studies [9, 14–33] were prospective while the other seven [34–40] were retrospective. In total, data from 1,507 PD patients was reviewed and analysed. The average follow-up time for PD patients treated with DBS was 6.79 ± 3.55 years, which was longer than the follow-up time for PD patients treated with LCIG and CSAI. The maximum follow-up time for PD patients treated with DBS from the reviewed articles was 24 years, which was again the longest maximum follow-up time compared to either LCIG or CSAI. Apart from four studies [9, 29, 33, 36] that reported the outcomes of GPi-DBS-treated PD patients, the remaining studies reported the outcomes of STN-DBS patients. All studies reported a very good long-term effect of DBS not only on motor symptoms [14, 19], but also on non-motor symptoms [18, 21, 22]. For example, in the study [38] with the longest mean follow-up time of 17.06 years after STN-DBS, the time spent with dyskinesia was reduced by 75% and the 'OFF' time was reduced by 58.7%. Dopaminergic drugs were reduced by 50.6%. In addition, health-related quality of life (HQoL) remained improved by 13.8%. Nevertheless, a worsening of certain motor symptoms, such as axial symptoms including postural instability and gait, has been observed in patients receiving long-term STN-DBS [14, 35]. Some studies have also reported a long-term general cognitive decline (higher than expected) after the introduction of STN-DBS [14, 35, 37], such as an increase in dementia prevalence from 2.3% one year after STN-DBS to 29.8% 10 years after STN-DBS [37]. It is worth noting that these studies were not controlled, so it is difficult to draw conclusions about whether there was a specific effect of STN-DBS on cognitive decline, or whether instead cognitive decline was simply a reflection of the expected, natural disease progression unrelated to STN-DBS. Some studies have reported domain-specific deterioration in cognitive abilities such as verbal fluency and frontal lobe functions [17]. Even though GPi-DBS is mostly used in elderly patients in whom dyskinesias is the leading symptom of advanced PD, several studies [9, 29, 33, 36] have shown good long-term effects on motor and non-motor symptoms. Interestingly, one study found faster cognitive decline and greater worsening of balance and gait with STN-DBS than with GPi-DBS [9, 29] potentially indicating a specific accelerating effect of STN-DBS on cognitive decline.

Dysarthria, depression, and apathy were among the most common long-term adverse events [26, 27, 34, 37] reported in STN-DBS patients. Weight gain [28, 34], which was very frequently reported as a short-term adverse event, and weight loss [15] were also reported in those we analysed. Other adverse events included apraxia of eyelid opening [19, 28, 32], surgical complications such as brain haemorrhage and device infection [19, 24], skin perforation over the battery site [22], and one suicide attempt [21] and two suicides [24, 25].

Despite the frequent adverse events, some of which are severe, DBS of STN and GPi shows a very good long-term effect on both motor and non-motor symptoms in advanced PD. Compared to LCIG and CSAI, DBS appears to be the most durable DAT for advanced PD. This is partly due to the neuromodulatory nature of DBS [41], although studies have found a neuromodulatory effect of other DATs in PD patients

Table 1. Studies exploring long-term effect of subthalamic nucleus (STN) and globus pallidus pars interna (GPi) deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion (CSAI), and levodopa-carbidopa intestinal gel infusion (LCIG) in Parkinson's Disease "/" sign indicates that information in study was not reported

	Long-term effect of deep brain stimulation (DBS)							
	Author, year	Study type	Number of patients	Mean median follow--up (y)	Maximum follow up (y)	Target	Main findings	Main/serious adverse events
1	Aviles-Olmos et al., 2014	Prospective cohort	53	7.5	11	STN	41 followed for 5 y, 12 followed for 8-11 y. 'OFF' medication, UPDRS-III improvement (especially tremor and rigidity), but UPDRS-III increased over time. Speech intelligibility decreased at 5 and 8-y follow-up. UPDRS-III 'ON' med. deteriorated at 5 and 8-y follow-up, especially bradykinesia and axial symptoms and speech intelligibility. Dyskinesias and fluctuations improved at 5 and 8 years. ADL 'OFF' medication improved. PDQ-39 improved at 1 year but returned to baseline at 5 and 8 y post-op. Cognitive decline in 17.1% and 16.7% of patients at 5- and 8-y follow up	5 cases of transient delirium immediately after operation, 1 seizure, 4 cases of ICD, 1 case of hypomania
2	Bang Henriksen et al., 2014	Retrospective cohort	79	10	10	STN	24 (22 male, 2 female) out of 79 (52 male, 27 female) patients died during follow-up. 46% developed dementia; 42% went to nursing home	34% dysarthria, 26% hypersalivation, 26% dysphagia, 16.5% weight-gain, low level of post-op complications, 3 adjustments of electrode position (3.8%)
3	Barbosa et al., 2024	Retrospective cohort	109	8	/	STN	16% mortality rate. Falls in 73% and freezing in 47% were most frequent milestones, followed by dementia in 34% and hallucinations in 32%	/
4	Bonenfant et al., 2017	Retrospective cohort	25	3	3	GPi	Improvement of 65.9% in CGI-self-perceived, 20.6% improvement of UPDRS-III motor score at 3 years 'OFF' medication. 50% reduction of dyskinesia (UPDRS-IV). Cognition stable at 1-y follow-up, deteriorated at 3 years. PDQ-39 remained stable	1 removal of electrode because of infection
5	Bove et al., 2020	Retrospective study	175	7.8	10	STN	104 patients were available at follow-up. Dementia prevalence was 2.3% at 1st post-op. year, 8.5% at 5 years, and 29.8% at 10 years. Dementia cumulative incidence at 1, 5, and 10 years was 2.3%, 10.9%, and 25.7%, respectively. Predictors of dementia were higher age at operation, hallucinations, and perioperative cerebral haemorrhage	/
6	Bove et al., 2021	Retrospective study	51	17	24	STN	13 cases 13 years follow-up, 16 cases 17 years follow-up, 1 patient 24 years follow-up. In long term, dyskinesia and 'OFF' time improved for 75% and 58.7% respectively, dopaminergic drugs were reduced 50.6%, PDQ-39 improved for 13.6%	Freezing of gait, dysarthria, depression, apathy, weight gain. A few surgery-related and device-related adverse events. In 5 patients lead adjustment (reimplantation)
7	Castrioto et al., 2011	Observational, prospective	18	10	10	STN	7/18 patients included had previous pallidotomy. Improvement of UPDRS-III, tremor and bradykinesia. No effect on axial symptoms. UPDRS-II improved, dyskinesias and motor fluctuations improved, speech deteriorated	Weight loss over years, even in patients who gained weight. Neuropsychiatric side-effects, 3 patients developed ICD
8	Cavallieri et al., 2021	Retrospective cohort	138	8.4	17	STN	Preoperative higher frontal score and 'OFF' MDS-UPDRS-III predicted better outcome, presence of vascular change predicted worse outcome	/

Table 1 cont. Studies exploring long-term effect of subthalamic nucleus (STN) and globus pallidus pars interna (GPi) deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion (CSAI), and levodopa-carbidopa intestinal gel infusion (LCIG) in Parkinson's Disease "/" sign indicates that information in study was not reported

	Long-term effect of deep brain stimulation (DBS)							
	Author, year	Study type	Number of patients	Mean median follow-up (y)	Maximum follow up (y)	Target	Main findings	Main/serious adverse events
9	De Noordhout et al., 2022	Prospective, case control	15	12	12	STN	15 STN-DBS patients and 15 matched controls. DBS UPDRS-III scores 'ON' medication 'ON' stimulation were better than in control group, also dyskinesias were better in STN-DBS. PDQ-39 scores were same	/
10	Fasano et al., 2010	Prospective cohort	20	8	8	STN	Overall motor improvement at 5 years (55%), and 8 years (39%), no improvement of speech or axial symptoms. Decline in verbal fluency and frontal lobe cognitive functions. No change of depression or anxiety	/
11	Georgiev et al., 2021	Prospective cohort	28	/	4	STN	Motor and non-motor symptoms, depression, anxiety, PDQ-39 stable, and sleep all improved. Cognition deteriorated at 36 months and apathy increased at 38 months. Reduction of LEDD throughout study period	/
12	Gervais-Bernard et al., 2009	Clinical trial	42	/	5	STN	Initially 42 consecutive patients, 23 followed-up to 5 years. At 1 year follow-up, there was a reduction of UPDRS-III by 55% 'OFF' medication: tremor improved by 74%, rigidity by 66%, bradykinesia by 59%, postural stability by 17%, and gait by 37%. Cognition did not change. Speech, gait and postural stability got worse at 5-year follow-up	2 brain haemorrhages, 3 device infections, 2 phlebitis, 2 pulmonary embolisms, 2 patients lead repositioning. Dysarthria was present in 56%, depression in 39%, eye lead opening apraxia in 30.4%, and apathy in 4.3%
13	Hacker et al., 2023	Clinical trial	14	/	11	STN	Patients on STN-DBS compared at 5 and 11 years to patients on best medical treatment. No difference between groups in cognitive functions, especially not in phonemic verbal fluency or cognitive processing	/
14	Jost et al., 2020-1	Prospective, case control	38	3	3	STN	38 DBS patients compared to 38 patients on best medical treatment. After 3 years, STN-DBS significantly improved NMSS, PDQ-8, SCOPA-motor examination and complications and reduced LEDD. Significant between-group differences, all favouring STN- DBS, were found for NMSS, SCOPA-motor complications, LEDD (large effects), motor examination and PDQ-8 (moderate effects). Furthermore, significant differences were found for sleep/fatigue, urinary (large effects) and miscellaneous NMSS domains (moderate effects). NMSS total and PDQ-8 change scores correlated significantly	6 serious adverse events in 5 patients (skin perforation over battery site in two patients, disturbed wound healing, dopamine agonist withdrawal syndrome, suicide attempt, mania)
15	Jost et al., 2020-2	Prospective, case control	40	3	3	STN	40 DBS patients and 40 patients on best medical treatment. STN-DBS led to significantly better PDSS and PDQ-8 change scores, which were significantly correlated. We observed no significant effects for HADS and no significant correlations between change scores 40 in PDSS, HADS, and LEDD	/
16	Kishore et al., 2010	Observational prospective	45	5	5	STN	Benefits of STN stimulation on cardinal signs, motor complications (dyskinesias, fluctuations), and QoL of advanced PD were substantial and sustained until 5 years. Initial benefits in axial symptoms (gait and postural stability) and emotional and psychological aspects of QoL did not show similar stability. No impact on cognition or mood	/

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Table 1 cont. Studies exploring long-term effect of subthalamic nucleus (STN) and globus pallidus pars interna (GPi) deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion (CSAI), and levodopa-carbidopa intestinal gel infusion (LCIG) in Parkinson's Disease "/" sign indicates that information in study was not reported

Long-term effect of deep brain stimulation (DBS)								
	Author, year	Study type	Number of patients	Mean median follow--up (y)	Maximum follow up (y)	Target	Main findings	Main/serious adverse events
17	Krack et al., 2003	Prospective cohort	49	5	5	STN	54% improvement in motor functions and 49% improvement of ADL 'OFF' medication, speech did not improve. Except for dyskinesia that improved 'ON' medication, other motor functions including akinesia, speech, postural stability, and freezing of gait worsened between year 1 and year 5 ($P < 0.001$ for all comparisons). Cognition remained unchanged	1 case of large intracerebral haemorrhage. 1 patient committed suicide
18	Lezcano et al., 2016	Prospective cohort	69	5	5	STN	'OFF' medication improvement of UPDRS-II and III and activities of daily living. 'ON'-medication deterioration of UPDRS-III mainly because of axial signs. PDQ-39 improved at 1-y follow-up and deteriorated at 5-year follow-up. Cognitive deterioration at 5 years	1 possible suicide, 2 removals of device due to infection, 2 cerebral haemorrhages, 1 severe dementia in an elderly patient at time of op
19	Moro et al., 2010	Clinical trial	51	/	6	STN & GPI	5-6-y follow up in STN (n = 35) and GPi-DBS (n = 16). Both improved UPDRS-III, dyskinesias and ADL in double blind and in open assessment. Medication reduction only in STN-DBS group	In 75% of patients on STN-DBS 50% of patients on GPi-DBS. Cognitive decline, speech difficulties, balance and gait deterioration more common in STN-DBS than GPi-DBS group
20	Rizzone et al., 2014	Prospective cohort	25	/	11	STN	35% improvement in overall motor symptoms, 84.5% improvement in dyskinesias and 65% improvement of motor fluctuations. Cognition mostly stable, 22.7% developed dementia. UPDRS-II worsened manly due to symptoms poorly responsive to L-dopa	Speech problems, skin dehiscence, lead migration
21	Romito et al., 2009	Prospective cohort	20	5	5	STN	Improvement of overall motor symptoms for 54.2%. Improvement of dyskinesias and motor fluctuations. LEED decreased after operation and remained decreased at 5 years, but total stimulation energy delivered increase. Rest tremor, rigidity, gait, lower and upper limb akinesia, and total axial score were improved, in descending order. Postural stability and speech improved transiently	Speech problems
22	Schüpbach et al., 2005	Prospective cohort	37	5	5	STN	ADL improved 40% 'OFF' medication and 60% 'ON' medication, UPDRS III improved 54% 'OFF' medication and 73 % 'ON' medication. Overall, no cognitive deterioration was noted	Eyelid opening apraxia, weight gain, addiction to levodopa treatment, hypomania and disinhibition, depression, dysarthria, dyskinesias, and apathy
23	Volkman et al., 2004	Prospective cohort	11	5	5	GPI	Dyskinesias remained significantly reduced until 5-year follow-up. Initial improvement of motor fluctuations and 'OFF' medication motor symptoms as well as ADL was not sustained and declined. Replacement of GPi-DBS with STN-DBS in 4 patients restored initial benefit	/
24	Weaver et al., 2012	Clinical trial	159	3	3	STN & GPi	89 GPi and 70 STN. Motor functions improved in both targets and remained improved at 3-year follow up. HQoL improved at 6 months, but improvement diminished over time. Overall cognitive decline was faster in STN-DBS than Gpi-DBS	/

Table 1 cont. Studies exploring long-term effect of subthalamic nucleus (STN) and globus pallidus pars interna (GPi) deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion (CSAI), and levodopa-carbidopa intestinal gel infusion (LCIG) in Parkinson's Disease "/" sign indicates that information in study was not reported

Long-term effect of deep brain stimulation (DBS)								
	Author, year	Study type	Number of patients	Mean median follow-up (y)	Maximum follow up (y)	Target	Main findings	Main/serious adverse events
25	Wider et al., 2008	Prospective cohort	50	5	5	STN	Improvement of UPDRS-III, dyskinesias and 'OFF'-time	Dementia developed in 11 patients. Depression also reported
26	Yamamoto et al., 2017	Prospective cohort	31	/	5	STN	Motor functions stayed improved at 5-year follow-up, mobility subdomain of HQoL deteriorated, overall HQoL stayed unchanged. Cognition did not change	/
27	Zampogna et al., 2024	Retrospective, cohort	101	/	15	STN	101 patients 10-year follow-up, 56 patients 15-year follow-up: bradykinesia, especially appendicular bradykinesia, significantly worsened after surgery. Rigidity remained improved. Executive functions linked to bradykinesia, but not to rigidity. Long-term assessments were done 'ON' medication 'ON' stimulation	/
28	Zibetti et al., 2011	Prospective cohort	14	/	> 9	STN	Improvement of motor symptoms by 42%. Reduction of LEDD by 39%, ADL did not remain improved. 4 patients developed significant cognitive decline	Eye-lead opening apraxia, dysarthria
Long-term effect of levodopa-carbidopa intestinal gel infusion (LCIG)								
	Author, year	Study type	Number of patients	Mean median follow-up (y)	Maximum follow up (y)		Main findings	Main/serious adverse events
1	Antonini et al., 2021	Observational, prospective	60	2	2		GLORIA patient registry, Italian part. Decreased 'OFF' time, increased 'ON' time with dyskinesia, improved UPDRS II and UPDRS III total scores, NMSS, PDQ8	Weight loss, polyneuropathy, abdominal pain. Device malfunction, medical device change
2	Buongiorno et al., 2015	Observational, prospective	72	1.8	4		28 patients discontinued treatment due to lack of efficiency or adverse effects. Significant improvement of motor and non-motor fluctuations, mean 'OFF' time and some non-motor symptoms (constipation, fatigue and pain). There was a significant increase in time with dyskinesia in patients who had less than 50% of time with dyskinesia before LCIG. Less dyskinesias if patients had longer and more troublesome dyskinesias before LCIG	1 case with intestinal perforation and 1 case with abdominal cellulitis
3	Chaudhuri et al., 2023	Observational prospective	195	3	3		DUOGLOBE study, multicentre study. Significant improvement of 'OFF' time. Dyskinesias, non-motor symptoms, sleep all improved at 36 months. QoL improved to 24 months, and caregiver burden to 30 months	Serious adverse events in 54.9% of patients, 54.4% discontinued study. 27.2% of 196 patients discontinued study due to serious adverse events
4	De Fabregues et al., 2017	Observational prospective	37	/	10		1 or 2.7% arrived to 10-year control, 2 or 5.4% to 9-year control (108 months), 13 or 35.1% to 5-year control (60 months), 23 or 62.2% to 2-year control (24 months), and 30 or 81.1% to 1-year control (12 months). 'OFF' time improved, dyskinesias remained stable or improved. No overall cognitive deterioration. Improvement in attention, voluntary motor control and semantic fluency. Significant improvement of QoL at 3 years and reduction of caregivers' burden. 14 patients dropped out	Abdominal pain, granuloma, stoma dermatitis, leg pain, polyneuropathy, confusion, hallucinations, psychosis

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Table 1 cont. Studies exploring long-term effect of subthalamic nucleus (STN) and globus pallidus pars interna (GPi) deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion (CSAI), and levodopa-carbidopa intestinal gel infusion (LCIG) in Parkinson's Disease "/" sign indicates that information in study was not reported

	Author, year	Study type	Number of patients	Mean median follow--up (y)	Maximum follow up (y)	Target	Main findings	Main/serious adverse events
Long-term effect of deep brain stimulation (DBS)								
5	Fasano et al., 2023	Observational retrospective	387	/	5		COSMOS study: Out of 387 patients, the number of patients per LCIG group was: 1-2 years LCIG (n = 156); 2-3 years LCIG (n = 80); 3-4 years LCIG (n = 61); 4-5 years LCIG (n = 30); > 5 years LCIG (n = 60). There were reductions in 'OFF' time, dyskinesia duration, and severity across LCIG groups. Prevalence, severity, and frequency of many individual motor symptoms and some NMS were reduced amongst all LCIG groups, with few differences between groups	10 adverse events. Stoma site infection and unintentional medical device removal
6	Fernandez et al., 2018	Observational prospective	262	4.1	/		Discontinuation rate of 34%. Reduction of 'OFF' time and increase of 'ON' time without troublesome dyskinesias. ADL and QoL improved	94% of patients reported adverse events
7	Garri et al., 2022	Observational retrospective	79	3.9	/		25 patients died, 18 while on LCIG, 7 after LCIG discontinuation	3 severe cases of polyradiculoneuropathy, weight loss
8	Lopiano et al., 2019	Observational prospective	145	2.8	/		GREENFIELD registry. Improvement of 'OFF' time and dyskinesia duration, dyskinesia disability and painful dyskinesias. ADL also improved, as did QoL and sleep	49 serious adverse events
9	Slevin et al., 2015	Open-label prospective	62	/	/		Open-label, extension part of a double blinded, double dummy study, 52-week duration. Improvement of 'OFF' time and 'ON' time without troublesome dyskinesias	48 patients reported at least one adverse event. Complications of device insertion, abdominal pain, asthenia and pneumonia
10	Rus et al., 2022	Retrospective	130	4	14		42.7% drop off rate. Of these, 21% died for a reason not related to LCIG. Reasons for discontinuation were psychosis, switch to DBS, re-emergence of PD symptoms/ ineffectiveness of LCIG, other severe disease-related, severe device-related, or PEG-J-related adverse effects, lack of caregiver(s) and severe polyneuropathy	In 103 patients, 296 adverse effects were noted. Reasons listed in previous column
11	Standaert et al., 2017	Open-label, prospective	39	/	/		28 completed evaluations at 60th week. Improvement of non-motor symptoms, especially sleep/fatigue, attention/memory, gastrointestinal tract, urinary, sexual function, miscellaneous	37 patients (95%) experienced AE. Pain and stoma site infection were most common. Major depression, suicidal ideation
12	Zibetti et al., 2013	Observational prospective	59	2.08	/		LCIG improved motor complications and over 90% of patients reported an improvement in their quality of life, autonomy and clinical global status. 11 patients or 19% discontinued therapy	Events related to infusion devices, intestinal tube dislocation, stomal infection, weight loss
Long-term effect of continuous subcutaneous apomorphine infusion (CSAI)								
	Author, year	Study type	Number of patients	Mean median follow-up (y)	Maximum follow up (y)		Main findings	Main/serious adverse events
1	Bhidayasiri et al., 2019	Retrospective	52	3.7	/		36 patients from Thailand and 16 patients from Spain. 19/36 or 52.5% of patients from Thai cohort, and 10/16 patients or 62.5% from Spanish cohort discontinued treatment within 6 months. CSAI led to improvement of UPDRS III and daily 'OFF' time	Skin nodules, perceived lack of efficacy, hallucinations

Table 1 cont. Studies exploring long-term effect of subthalamic nucleus (STN) and globus pallidus pars interna (GPi) deep brain stimulation (DBS), continuous subcutaneous apomorphine infusion (CSAI), and levodopa-carbidopa intestinal gel infusion (LCIG) in Parkinson's Disease "/" sign indicates that information in study was not reported

Long-term effect of deep brain stimulation (DBS)								
	Author, year	Study type	Number of patients	Mean median follow--up (y)	Maximum follow up (y)	Target	Main findings	Main/serious adverse events
2	Borgemeester et al., 2017	New-user cohort, retrospective	45	2.2	/		All patients on CSAI from 2004 to 2016. At end of 2016, 16 or 32% of patients were still on CSAI (drop-off rate 68%). Daily 'ON' time and daily 'OFF' time improved, dyskinesias did not improve	Skin nodules, hypersalivation, excessive daytime sleepiness, oedema, visual hallucinations and orthostatic hypotension
3	Camgrand et al., 2023	Observational retrospective	279	1.8	7.6		From 2004 to 2021. Main reasons for discontinuation were adverse events in 43% of patients, switch to DBS in 25.5% and lack of efficacy in 20%. Discontinuations due to adverse events occurred earlier	Hallucinations, skin reactions, confusion and daytime sleepiness
4	Garcia Ruiz et al., 2008	Retrospective cohort	82	1.7	/		Reduction of 'OFF' time, total and motor UPDRS scores, dyskinesia severity and LEDD	Skin reactions (panniculitis and skin nodules), confusion, hallucinations, hypersexuality, sleepiness, orthostatic hypotension
5	Henriksen et al., 2021	Retrospective	101	6.4	/		Main reasons for stopping SCAI were adverse events, death, and dissatisfaction with treatment. In first 6 years of treatment, main reasons for discontinuation were hallucinations and somnolence	Somnolence, hallucinations, hypersexuality, dizziness, psychiatric change, rhinitis
6	Hughes et al., 1993	Observational prospective	22	3	5		Mean reduction of daily 'OFF' c.50% was maintained and incidence of neuropsychiatric toxicity remained low on long-term follow up	'ON'-phase dyskinesias, postural instability
7	Manson et al., 2002	Retrospective cohort	64	2.8	9		45 patients or 70% converted to monotherapy with CSAI. Dyskinesias reduction for 64% in monotherapy group, and for 30% in polytherapy group. 3 patients failed therapy for reasons given in next column	Reasons for failure: difficulty with compliance and adverse effects such as daytime somnolence, skin complications, and painful dystonia
8	Meira et al., 2021	Retrospective cohort	110	2	/		35% drop-out rate. In those who continued treatment, HQoL was maintained stable. PDQ-39 was only good baseline predictor of improvement after 2 years of treatment. Presence of dyskinesias, poorer psychological status, shorter disease duration, male sex, and worse 'OFF' state were predictors of discontinuation. Best candidates for CSAI were patients with: (i) poor baseline HQoL; and (ii) marked motor fluctuations	Skin nodules, hallucinations, confusion, ICD, sedation, drowsiness, insomnia, nausea, orthostatic hypotension
9	Pietz et al., 1998	Prospective cohort	25	3.7	5.5		25 on CSAI and 24 intermittent apomorphine injections. In CSAI, there was a reduction of daily 'OFF' time. Improvement of median H&Y. ADL also indicated improvement. Dyskinesias improved in 7 patients and remained same at a group level	Local inflammation at infusion site, psychiatric side effects (psychosis, hallucinations, illusions, confusion, nightmares) were most common. One patient developed an abscess, one patient necrotic changes around wound. Orthostatic hypotension in four patients. One patient developed hypersexuality
10	Sesar et al., 2017	Prospective cohort	230	2.2	/		132 patients were treated over a year. Total number of drop-offs was 137 (59.6%). Within first year 82 patients or 36.5% stopped CSAI, 62 or 27% of them in first 6 months	Hallucinations, skin rash, delusions, hypotension, nausea, skin nodules, dyskinesias, ICD, oedema, haemolytic anaemia

ADL — activities of daily living; CGI — clinical global impression; H&Y — Hoehn & Yahr scale; HADS — Hamilton anxiety and depression scale; HQoL — health-related quality of life; ICD — impulse control disorders; LEDD — levodopa equivalence daily dose; (MDS)-UPDRS — Movement Disorders Society-Unified Parkinson's Disease Rating Scale; NMSS — non-motor symptoms scale; ON — on medication; OFF — off medication; PDD — Parkinson's Disease sleeping scale; PDQ-39 — Parkinson's Disease questionnaire 39; PDQ-8 — Parkinson's Disease questionnaire 8; QoL — quality of life; SCOPA — scales for outcome in Parkinson's Disease

too [42]. However, the long-term retention of DBS is at least partly related to the fact that DBS is associated with maximum patient autonomy and independence and an acceptable adverse events profile, making it suitable as a long-term DAT option in advanced PD patients who are relatively young and cognitively spared.

Long term effect of levodopa-carbidopa intestinal gel infusions for PD

Twelve studies on the long-term effects of LCIG were included in this review (Tab. 1). We were primarily interested in the main adverse events reported in studies on the long-term effects of LCIG. In addition, the main study outcomes, study type, number of patients included, and mean/median and maximum years of follow-up were recorded and analysed. A detailed description of the search process and the selection of studies can be found in Supplementary material (B).

Nine of the studies were prospective [6, 43–50], three retrospective [51–53] and they reported on the findings of 1,527 patients with advanced PD. The average follow-up time was 2.96 ± 0.95 years. The longest follow-up time in the reviewed studies was 14 years. All studies reported significant improvements in motor symptoms (e.g. decrease in 'OFF' time, increase in 'ON' time, improvement in dyskinesias) and non-motor symptoms, including activities of daily living, HQoL and sleep [44, 47, 51, 54]. For example, in the study with the longest mean follow-up time of 4.1 years [46] the patients maintained a reduction of 'OFF' time of nearly four hours and an increase of 'ON' time of almost four hours without troublesome dyskinesias. The dropout rate was not consistently reported in the studies, but in the studies that reported it ranged from 34% (over a mean follow-up period of 4.1 years) [46] to 38% (over a mean follow-up period of 1.8 years) [43] to 42.7% (over a mean follow-up period of 4.0 years) [53]. The main reasons for discontinuation were adverse events, which were reported in all studies, but also insufficient efficacy of LCIG and switching to another treatment option [53]. The incidence of adverse events was rather high in almost all studies [44, 46, 49] ranging from 54% to 95%. Very common adverse events included local and device-related adverse events such as skin irritation around the percutaneous gastrostomy or cellulitis [45, 51], but also medication-related adverse events such as polyneuropathy [45, 52], weight loss [11], hallucinations and psychosis [45]. However, serious side effects such as peritonitis or severe polyneuropathy were rare [53].

To summarise, LCIG is a very effective treatment option for advanced PD despite the frequent adverse events and high discontinuation rate. The adverse event profile is very broad and includes device- and drug-related events, and ranges from mild to serious adverse events, the latter being rare. Compared to DBS, a broader range of patients, including older patients and patients with mild cognitive impairment, are suitable for this treatment option. Because levodopa has a lower potential to cause neuropsychiatric complications, and because the pharmacokinetic and pharmacodynamic properties of levodopa are quite favourable, it has certain advantages over CSAI, such as suitability in elderly patients with mild cognitive decline, and also in patients with certain neuropsychiatric complications such as impulse control disorder (ICD).

Long term effect of continuous subcutaneous apomorphine infusions for PD

Ten studies on the long-term effects of CSAI were included in this review (Tab. 1). The same information was extracted and analysed as for the long-term effects of LCIG. A detailed description of the search process and the selection of studies can be found in Supplementary material (C).

Three of the studies [5, 55, 56] were prospective (Tab. 1), and the remaining seven [57–63] were retrospective cohort studies, mostly based on real-life experience. In total, the studies reported on the outcomes of 1,010 patients treated with CSAI. The average follow-up time was 2.95 ± 1.41 years, which was close to the average follow-up time for patients with LCIG but shorter than the average follow-up time for patients with DBS. The maximum follow-up time for the studies that reported it was nine years [5, 62]. All studies reported an improvement in motor symptoms, such as a reduction in 'OFF' time and severity of dyskinesia, an increase in 'ON' time, and an overall improvement in motor status; some of the studies also reported an improvement in HQoL [63]. For example, in one of the studies with the longest mean follow-up time of 3.7 years [57] CSAI lead to a significantly reduced daily 'OFF' time of 3.8 hours. Similar results were reported in another study with the same mean follow-up time [55] in which in addition to the significant improvement of the daily 'OFF' time (50%) and the activities of daily living, the dyskinesias stayed largely unchanged. The dropout rate was quite high in all studies that reported it, ranging from 35–68% [58, 63] for a mean 2-year follow-up period. Two studies [56, 57] reported the highest dropout rate in the first six months after the introduction of CSAI. The reasons for treatment discontinuation were mainly adverse events, most of them local such as local inflammation, skin redness and skin nodules. Serious local adverse events such as abscesses and skin necrosis were rarely reported [55]. Other common adverse events were psychiatric complications (hallucinations, confusion, impulse control disorder such as hypersexuality), hypersomnolence, nightmares, drowsiness, orthostatic hypotension, oedema and nausea. Apart from the local advere events related to the route of administration of the drug, the other adverse events are seen with all other dopaminergic agonists. In addition to these adverse events, motor complications such as dyskinesias and postural instability were also reported [5]. Other reasons for treatment discontinuation included an objective lack of efficacy [59] or a perceived lack of efficacy [57], but also dissatisfaction with the treatment [61]. In one of the largest long-term cohorts of CSAI (N = 110) [63] worse PDQ-39 score (indicating poor HRQoL) was the only significant baseline predictor of a good outcome after

the introduction of CSAI. The presence of dyskinesias, worse psychological status, shorter disease duration, male gender. and worse 'OFF' medication status were all predictors of discontinuation of CSAI [63].

In summary, although characterised by high dropout rates due to adverse events, objective and perceived lack of efficacy and sometimes motor complications CSAI is still a very good DAT option for patients without neuropsychiatric complications and with reduced HQoL and pronounced motor fluctuations prior to initiation of therapy. The average long-term follow-up time of the studies analysed in this article is similar to the average follow-up time in LCIG and, as expected, significantly shorter than the average follow-up time in studies in DBS patients.

Switching and combining device-added therapies for PD

Thirteen studies on switching and combining DATs (Tab. 2) were included in this review. In addition to the reasons for switching and combining DATs, we were particularly interested in the number of patients who switched or combined DATs and in the outcomes of DAT modifications. A detailed description of the search process and the selection of studies can be found in Supplementary material (D).

Of the 13 included studies, seven reported the results of case series [64–70], one [71] reported the results of a single patient, and five reported the results of clinical studies (three retrospective [72–74] and two [46, 75] prospective). Overall, the studies reported the outcomes in 298 patients (169 who switched from one DAT to another and 130 who received combined treatment with two or more DATs; note that not all studies reported the number of patients who switched to another DAT or combined DATs separately). The main reason for switching and combining DATs was insufficient efficacy of the primary DAT, followed by adverse events of the primary DAT. In patients receiving combined treatment, the most common sequence of events was the addition of LCIG to DBS, most commonly to STN-DBS, because symptoms could not be adequately controlled with DBS alone [64–68, 70, 72, 74, 75]. Few studies reported an addition of LCIG to GPi-DBS [64, 66, 68] or to pedunculopontine-DBS (PPN-DBS) [68]. This is unsurprising, as both therapies, STN-DBS and LCIG are most commonly used to treat advanced PD. The time point after which LCIG was added to DBS was not consistently reported, but in the studies that reported it, it was at least five years after DBS [64, 67]. In a recent case report [71], the authors reported an immediate effect of adding GPi-DBS in a patient with intractable, biphasic dyskinesias on LCIG that could not be controlled by LCIG dose modification due to the well-known effect of GPi-DBS in patients with advanced PD with troublesome dyskinesias [4]. Two other studies have reported on the introduction of STN-DBS to LCIG-treated patients [65, 70]. In the first study [65], two patients originally treated with LCIG underwent additional bilateral STN-DBS due to intractable dyskinesias and other LCIG-related complications, such as treatment-related psychosis and impulse control disorders. In the second study [70], 7/10 patients originally treated with LCIG reported benefit after the introduction of STN-DBS. LCIG treatment was continued after the introduction of DBS in 6/10 patients, while the remainder continued the treatment on STN-DBS only. Indications for the introduction of STN-DBS were motor response fluctuations, gait disturbances, 'OFF'-dystonia, 'OFF'-anxiety, painful polyneuropathy, and discomfort due to LCIG.

Five studies reported on the combined use of CSAI with other DAT modalities [69, 72–74, 76]. In these studies, the most common sequence of events was CSAI followed by the addition of either DBS or LCIG. One study was prospective [76], in which the effects of both CSAI and STN-DBS were analysed sequentially in the same patient: both CSAI and DBS significantly improved daily 'OFF' periods, motor scores, non-motor symptoms, depression, apathy, sleep and HQoL. Global cognition did not change with either therapy, and verbal fluency worsened with STN-DBS.

In addition, in the largest CSAI cohort to date reporting a switch to DBS [73], four different scenarios were recognised: i. Temporary use of CSAI while waiting for DBS; ii. Use of CSAI after DBS complications before DBS reimplantation; iii. Use of CSAI after permanent removal of DBS; and iv. Use of CSAI with DBS due to a declining response to DBS. Overall, the main reason for the introduction of CSAI was inadequate control of motor symptoms under DBS. In the first two scenarios (i and ii), CSAI was used temporarily as a bridging therapy. As CSAI is the least invasive DAT (with the exception of the newly introduced CSFFI) it can be easily introduced or discontinued before or after the introduction of DBS. Interestingly, sequential use of CSAI and LCIG was reported in a double-centre study [72]. The reasons for switching from CSAI to LCIG were motor, such as dyskinesias, persistent fluctuations, 'OFF'-dystonia and freezing of gait, and also non-motor, such as psychosis, visual hallucinations, subjective cognitive impairment, skin nodules, and skin necrosis at the injection site. In the largest, multicentre retrospective study [74] reporting on switching and/or combining different DAT modalities, 47 patients who received CSAI as their first DAT were analysed. Most of these patients switched to DBS, as did all patients who initially received LCIG (N = 12). However, some of the patients originally receiving CSAI were switched to LCIG (N = 18). DBS as the first DAT in 57 patients was most commonly combined with LCIG (N = 25) or CSAI (N = 20) as the second DAT. The most common reasons for switching or combining DATs were insufficient therapeutic efficacy of the first therapy, followed by adverse effects, both device-related and non-device-related.

To summarise, switching and combining DATs is a possible, and even a recommended treatment strategy in cases where there is inadequate symptom control or where adverse events appear with the first DAT. The choice of the second

Table 2. Studies exploring effectiveness of switching and combining device aided therapies (DAT) in Parkinson's Disease (PD)

	Author, year	Study type	Number of patients	Number switching	Number of combinations	Main findings and reasons for switching and/or combining
1	Bautista et al., 2020	Case series	3	0	3	Due to recurrence of symptoms years after DBS, LCIG was introduced. In 1st patient 7 years after STN-DBS, in 2nd one 5 years after STN-DBS, and in 3rd. one 1 year after GPi-DBS. Good response of LCIG was observed in first two patients. In last patient, LCIG was discontinued 1 month after insertion
2	Boura et al., 2021	Case series	8	0	8	6 patients first on STN-DBS were added LCIG due to suboptimal effect of DBS. 2 patients first on LCIG were added STN-DBS due to intractable dyskinesias on LCIG
3	Fernandez-Pajarn et al., 2021	Prospective	20	20	0	20 prospectively analysed patients first on CSAI and then switched to bilateral STN-DBS. Both CSAI and DBS improved daily 'OFF', motor scores, non-motor symptoms, depression, apathy, sleep and HQoL. Global cognition did not change on either therapy, fluency worsened on STN-DBS. Overall, STN-DBS was more efficient, but motor condition improved more on CSAI. CSAI was introduced first as a bridging therapy to DBS
4	Georgiev et al., 2022	Retrospective cohorts, double centre	30	24	6	24 switches: 7 LCIG to STN–DBS, 1 LCIG to CSAI, 5 CSAI to STN–DBS, 8 CSAI to LCIG, 1 STN–DBS to LCIG, 1 LCIG to CSAI to STN–DBS, and 1 STN–DBS to CSAI to LCIG. 6 combined therapies: 5 STN–DBS+LCIG and 1 STN–DBS+CSAI to STN–DBS+LCIG. Inadequate control of motor symptoms was main reason for switching or combining DATs, but non-motor reasons (related to disease and/or DAT) were also identified as a cause
5	Elkouzi et al., 2019	Case series	6	0	6	3 patients treated with STN-DBS, 1 with bilateral GPi-DBS, 2 with unilateral GPi-DBS. In all patients, LCIG was added. Main reason was poor motor control. Three patients also had suboptimally placed electrodes. In all, motor fluctuations reduced, 4 patients reported improvement of HQoL
6	Klosterman et al., 2011	Case series	2	0	2	2 patients treated with STN-DBS in whom LCIG was introduced, in the 1st one 7 years, in the 2nd one 6 years, after DBS. Reduction of efficacy was reason for adding LCIG in first patient (prolongation of 'OFF' time), and in second debilitating dysarthria
7	Kumar et al., 2018	Case series	7	0	7	In 3 patients on bilateral STN-DBS (due to motor deterioration and depression), 1 patient on unilateral STN-DBS, 1 on bilateral GPi-DBS (due to suboptimal effect of DBS), and 2 patients on PPN-DBS (due to motor fluctuations in one, and no response to PPN-DBS in other) LCIG was introduced later. All improved well after adding LCIG, but best improvement was on STN-DBS
8	Mulroy et al., 2021	Case report	1	0	1	A patient on LCIG with complex, intractable biphasic dyskinesias who could not respond well to dose/medication modifications was added bilateral GPi-DBS, with immediate response to it
9	Purner et al., 2024	Retrospective study, multicentric	116	81	45	Data collected in a planned manner by a modular questionnaire. 148 DAT modifications in 116 patients associated with significant improvement in motor outcome, subjective clinical outcome and fewer side effects. Main reasons for DAT modification were insufficient symptom control and side effects of first DAT
10	Redigor et al., 2017	Prospective study	19	0	19	19 DBS + LCIG and 21 LCIG controls. Improvement of motor scores after LCIG. From DBS + LCIG group, 5 patients discontinued LCIG and remained on DBS, 5 discontinued DBS and remained on LCIG, 9 stayed on combined therapy of DBS + LCIG. Mean time until discontinuation of combined treatment 2.44 years. Reason for adding LCIG was development of refractory symptoms, such as axial symptoms, severe motor fluctuations and motor complications

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Table 2 cont. Studies exploring effectiveness of switching and combining device aided therapies (DAT) in Parkinson's Disease (PD)

	Author, year	Study type	Number of patients	Number switching	Number of combinations	Main findings and reasons for switching and/or combining
11	Sesar et al., 2019	Retrospective cohort	71	40	31	18 CSAI for bridging to DBS, 11 CSAI for bridging to DBS reimplantation, 12 CSAI after permanent DBS removal, 13 CSAI in patients with DBS and declining response. In all groups, CSAI significantly improved motor symptoms of disease. Main reason for switching/combining was inadequate control of motor symptoms with DBS. DBS type in these patients was not specified
12	Varma et al., 2003	Case series	7	4	3	6 patients on CSAI and 1 patient on intermittent apomorphine injections were treated for bridging to bilateral STN-DBS. 4 stopped CSAI after operation, and 3 continued combined CSAI+STN-DBS therapy. Improved motor condition, fewer fluctuations. No side-effects because of CSAI before operation were noted
13	Van Poppelen et al., 2021	Case series	19	0	19	Of 9 patients initially on DBS (8 STN-DBS, 1 GPi-DBS) to whom LCIG was added, 5 reported improvements. Of 10 patients initially treated with LCIG in whom DBS was added, 7 reported benefit. Main reasons for second therapy were medication-related motor response fluctuations. Specific number of patients who either switched or added LCIG was not reported

CSAI — continuous subcutaneous apomorphine infusions; DAT — device-aided therapy; HQoL — health-related quality of life; GPi-DBS — globus palliudus pars interna-deep brain stimulation; LCIG — levodopa-carbidopa intestinal gel infusions; PPN-DBS — pedunculopontine-deep brain stimulation; STN-DBS — subthalamic nucleus-deep brain stimulation

DAT depends on the main problem arsing from the first. For example, LCIG or CSAI should be considered for patients with inadequate motor control by DBS. In this case, LCIG is a better option than CSAI if neuropsychiatric side effects occur [74]. Switching from one DAT to another is more common than combining DATs, which is mostly used in patients with DBS with inadequate control of motor symptoms, when either LCIG or CSAI could be added.

Clinical implications

DATs are a safe and effective option for the treatment of advanced PD. The selection of patients for DAT should be based on current clinical recommendations [77], taking into account the specific needs and wishes of patients and carers.

The strongest evidence for long-term beneficial effects comes from DBS, which is partly due to the largest number of studies having been on DBS. It may also be due to the neuromodulatory nature of DBS and its technical implementation (i.e. complete implantation of the material into the body, no need for daily manipulation with the device, no skin punctures or open wounds associated with the pump therapies). In order to achieve the best possible treatment outcomes, an individualised approach is needed when selecting the best DAT for specific patients.

Switching and combining DATs has been shown to be effective and recommended in patients in whom the first treatment option is unable to control the motor symptoms of the particular disease. For example, LCIG or CSAI should be considered in patients with inadequate motor control by DBS; in the presence of neuropsychiatric adverse events, LCIG is a better option than CSAI [74]. CSAI has been widely used as a bridging therapy in many centres; a similar potential could be expected from CSFFI. In our experience patients whose symptoms are optimally controlled do not want to switch to a less invasive therapy (e.g. from LCIG or LECIG to CSFFI) regardless of its availability. Most of the available DATs should be considered as complementary rather than competing treatment options. Thus, the recent introduction of CSFFI should not be seen as a replacement for the older pump-based therapies such as CSAI, LCIG, LECIG, but rather as an extension of the therapeutic armamentarium for treating the complex clinical presentation of advanced PD.

Future directions

There remain some unresolved questions about the long-term effects of DATs. First, although it is generally believed that certain signs of advanced PD such as postural instability, gait disturbances and cognitive decline in DBS patients occur mainly as a result of disease progression, some observations have pointed to the possibility of emerging DBS-related postural instability and gait disturbances, including the freezing of gait in these patients, as well as the deterioration of verbal fluency. However, it is difficult to study these unresolved problems in controlled trials. Ideally, the long-term effect of DAT, especially the effect on specific disease symptoms, should be compared to the best medical treatment in a prospective long-term study. However, nowadays it would be unethical to withhold the introduction of DATs to advanced PD patients.

There is also a lack of prospective controlled studies on the combined use of DAT in PD. Based on current recommendations [77], patients are administered a single DAT, the effect of which and associated adverse events are assessed and managed during follow-ups. In certain cases, the need to add a DAT is recognised based on the main problem with the first DAT. In the future machine learning and other advanced statistical methods such as principal component analysis, could help categorise patients and identify specific phenotypes of PD suitable for treatment with specific DATs, or with specific combinations of DATs. This could only be done by pooling data from multicentre cohorts, which requires closer collaboration between centres internationally. This approach is even more important given the ever-changing and complex landscape of treatment options and availability for patients with advanced PD.

In this review article we did not consider CSFFI [8], LECIG [7], MRI-guided focused ultrasound [78] or the lesional functional neurosurgical approach [79], which has follen out of fashion following the introduction of DBS [79] and is rarely used to treat patients with advanced PD nowadays. Due to shorter availability of these treatement options more data is needed to establish their long term role compared to DBS, LCIG and CSAI.

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