RESEARCH ARTICLE

Nationwide Retrospective Analysis of Combinations of Advanced Therapies in Patients With Parkinson Disease

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Abstract

Background and Objectives

Advanced therapies (ATs; deep brain stimulation [DBS] or pump therapies: continuous subcutaneous apomorphine infusion [CSAI], levodopa/carbidopa intestinal gel [LCIG]) are used in later stages of Parkinson disease (PD). However, decreasing efficacy over time and/or side effects may require an AT change or combination in individual patients. Current knowledge about changing or combining ATs is limited to mostly retrospective and small-scale studies. The nationwide case collection Combinations of Advanced Therapies in PD assessed simultaneous or sequential AT combinations in Germany since 2005 to analyze their clinical outcome, their side effects, and the reasons for AT modifications.

Methods

Data were acquired retrospectively by modular questionnaires in 22 PD centers throughout Germany based on clinical records and comprised general information about the centers/patients, clinical (Mini-Mental Status Test/Montréal Cognitive Assessment, Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS], side effects, reasons for AT modification), and therapeutical (ATs with specifications, oral medication) data. Data assessment started with initiation of the second AT.

Results

A total of 148 AT modifications in 116 patients were associated with significantly improved objective (median decrease of MDS-UPDRS Part III 4.0 points [$p < 0.001$], of MDS-UPDRS Part IV 6.0 points [$p < 0.001$], of MDS-UPDRS Part IV—off-time item 1.0 points [$p < 0.001$]) and subjective clinical outcome and decreasing side effect rates. Main reasons for an AT modification were insufficient symptom control and side effects of the previous therapy.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Glossary

AT = advanced therapy; **CAT-PD** = Combinations of Advanced Therapies in PD; **CGI** = Clinical Global Impression—Improvement Scale; **CSAI** = continuous subcutaneous apomorphine infusion; **DBS** = deep brain stimulation; **LCIG** = levodopa-carbidopa intestinal gel; **LEDD** = levodopa-equivalent daily dosage; **MDS-UPDRS** = Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale; **MMST** = Mini-Mental Status Test; **MoCA** = Montréal Cognitive Assessment; **PD** = Parkinson disease; **STN-DBS** = DBS with target subthalamic nucleus.

Subgroup analyses suggest addition of DBS in AT patients with leading dyskinesia, addition of LCIG for leading other cardinal motor symptoms, and addition of LCIG or CSAI for dominant off-time. The most long-lasting therapy—until requiring a modification—was DBS.

Discussion

Changing or combining ATs may be beneficial when 1 AT is insufficient in efficacy or side effects. The outcome of an AT combination is comparable with the clinical benefit by introducing the first AT. The added AT should be chosen dependent on dominant clinical symptoms and adverse effects. Furthermore, prospective trials are needed to confirm the results of this exploratory case collection.

Classification of Evidence

This study provides Class IV evidence that, in patients with PD, changing or combining ATs is associated with an improvement in the MDS-UPDRS or subjective symptom reporting.

Introduction

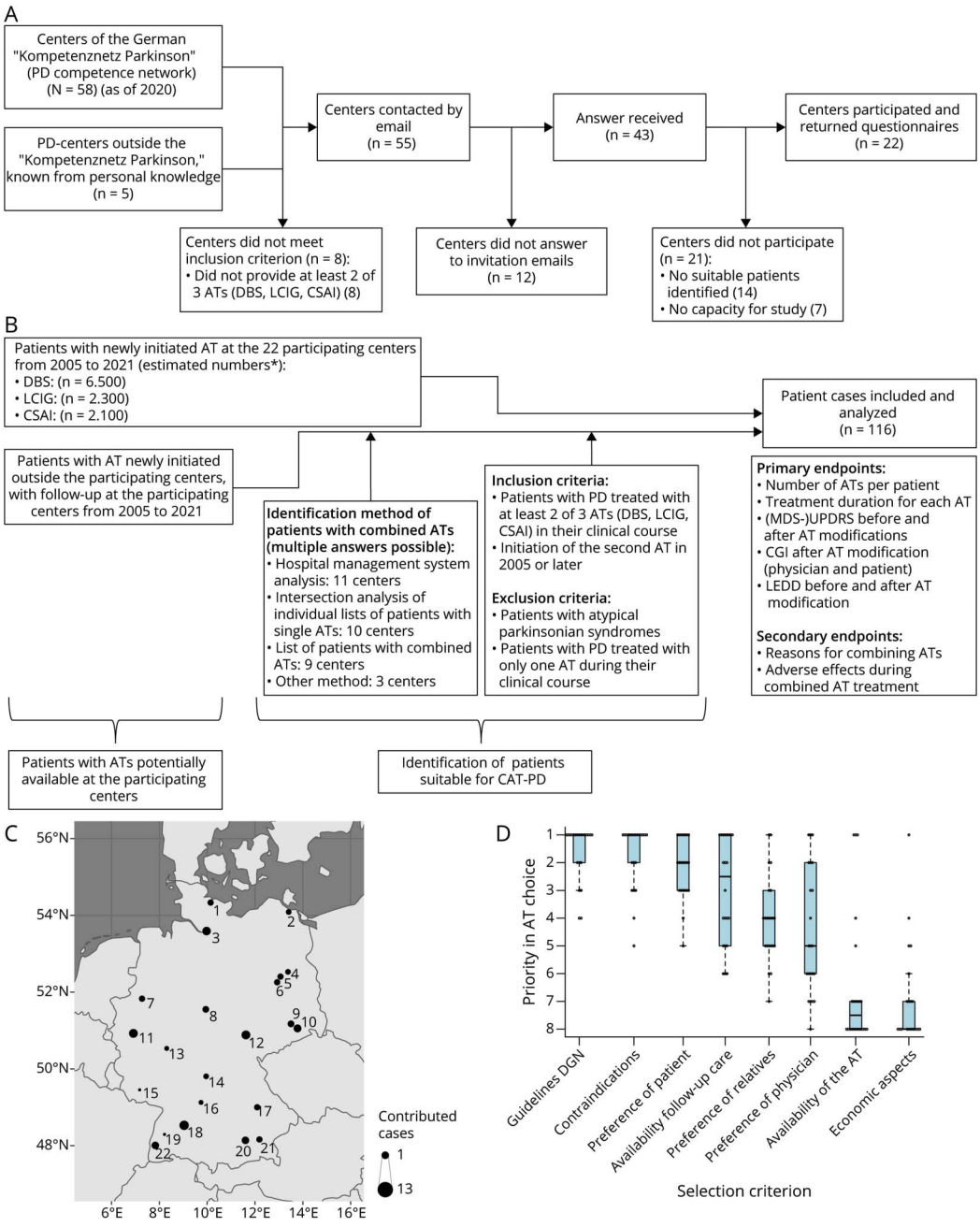
Parkinson disease (PD), the most common neurodegenerative movement disorder, is characterized by nigrostriatal dopaminergic neuron loss, leading up to the cardinal motor symptoms of bradykinesia, rigidity, resting tremor, and postural instability.[1,2] Early stages are usually well treated by oral dopaminergic replacement. With increasing neurodegeneration, however, motor complications, mainly off-periods, freezing and dyskinesia, can arise despite oral medication and significantly worsen patients' quality of life.[3] There is no clear consensus in defining advanced-stage PD.[4,5] In everyday clinical routine, the "1-2-5 rule" is a clinical tool to characterize advanced PD, including the criteria of ≥1 hour of troublesome dyskinesia per day, ≥2 hours of off-time per day, and intake of ≥5 daily doses of oral medication.[5] In these cases, when motor fluctuations become less controllable, device-aided therapies, such as deep brain stimulation (DBS) or pump therapies (continuous subcutaneous apomorphine infusion [CSAI] and levodopa/carbidopa intestinal gel [LCIG]), should be considered.[1,3] DBS and CSAI have been widely available since the 1990s[6,7]; LCIG received approval in the European Union in 2004.[4] However, symptom control by advanced therapies (ATs) may also decrease in the long term because of disease progression, and ATs, in addition, may result in adverse effects or complications, requiring further therapeutic modifications.[8-10] A change or a combination of ATs may be indicated here. However, current evidence for changing or combining ATs is limited to mostly small-scale and retrospective case collections, mainly covering defined AT combinations.

The "Combinations of Advanced Therapies in Parkinson's Disease" (CAT-PD) study was designed as a retrospective, nationwide, multicenter analysis to describe AT combinations applied simultaneously or sequentially in Germany since 2005. Reasons for combining ATs, the clinical outcome, and the side effect profiles were assessed. We aimed to determine, whether AT combinations are beneficial for patients with advanced-stage PD when 1 AT is insufficient in efficacy or side effects.

Methods

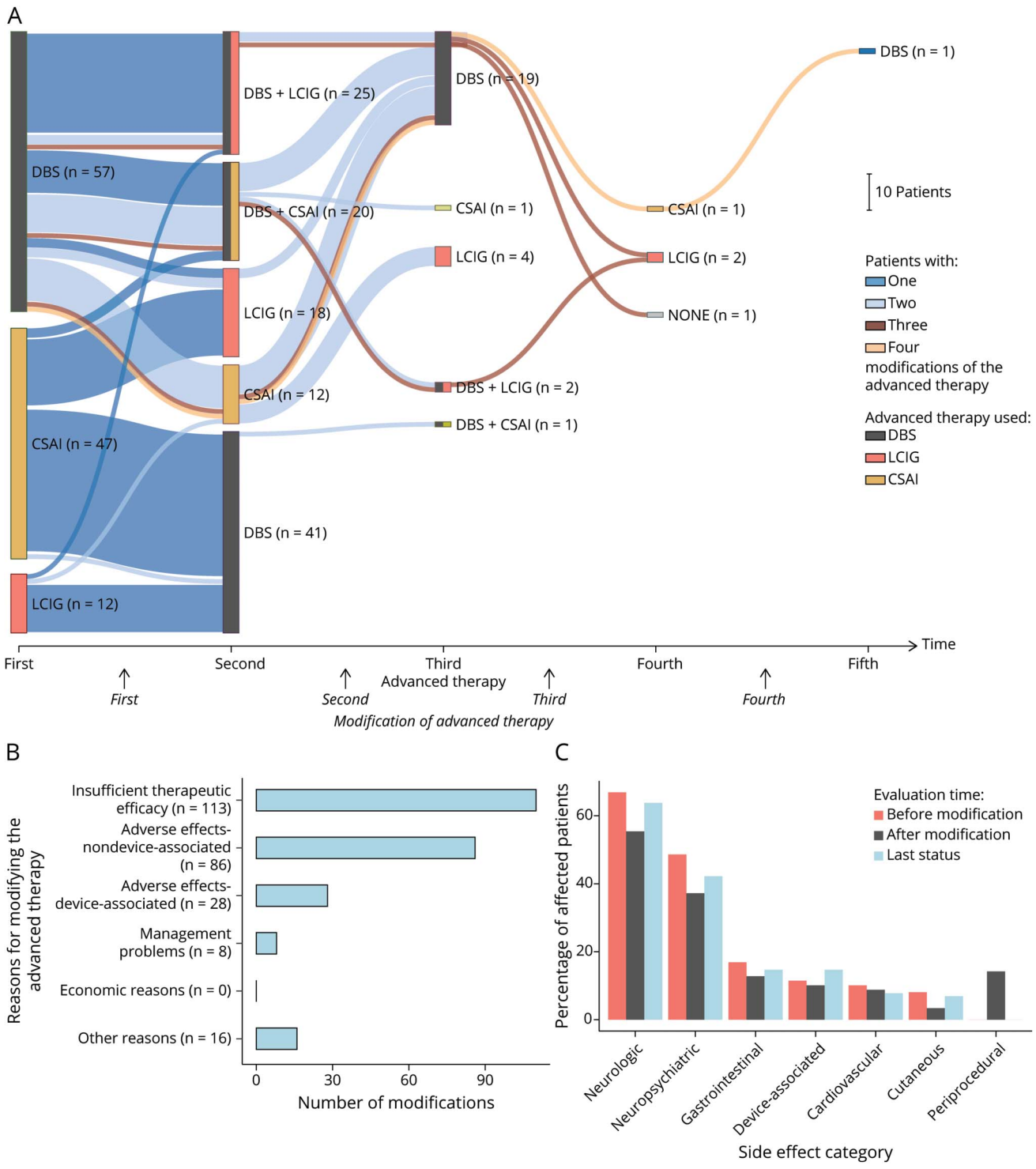
From 2019 to 2021, specialized PD centers across Germany participated in the CAT-PD study. All centers of the "Kompetenznetz Parkinson e.V.," the German PD competence network, and several additional established German PD centers were invited by email if they met the inclusion criterion of providing at least 2 of the 3 ATs licensed in Germany between 2005 and 2019: DBS, CSAI, or LCIG (Figure 1A). Centers were requested to include all patients with PD treated simultaneously or sequentially with at least 2 of the 3 ATs during their clinical course. Patients with atypical Parkinsonian syndromes and patients with PD having used only 1 AT in their treatment course were excluded (Figure 1B). A printed 2-module pseudonymized questionnaire was used to acquire demographic data, scores for Mini-Mental Status Test (MMST), Montréal Cognitive Assessment (MoCA, converted to MMST[11]), Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale (revised MDS-UPDRS [2008]; if not available, original UPDRS [1987] converted to MDS-UPDRS[12]), Clinical Global Impression—Improvement Scale (CGI, from −3: very

Figure 1 Selection of Participating Centers/Patients/ATs and End Points of CAT-PD



(A) Flowchart depicting the choice of the 22 participating PD centers shown in the map (C). (B) Flowchart depicting the patient sample of CAT-PD, chosen by inclusion/exclusion criteria, and the end points of CAT-PD. *The numbers were extrapolated from new installations per year. (C) Map of the participating centers throughout Germany. Centers are numbered from north to south and from east to west; size of the bubble depicts the number of contributed cases. (1) Klinik für Neurologie, Universitätsklinikum Schleswig-Holstein, Campus Kiel. (2) Klinik und Poliklinik für Neurologie, Universitätsmedizin Greifswald. (3) Klinik und Poliklinik für Neurologie, Universitätsklinikum Hamburg-Eppendorf. (4) Klinik für Neurologie, Charité Universitätsmedizin Berlin. (5) Klinik für Neurologie, Klinikum Ernst von Bergmann Potsdam. (6) Neurologisches Fachkrankenhaus für Bewegungsstörungen/Parkinson, Beelitz-Heilstätten. (7) Klinik für Neurologie, Christophorus-Klinik Dülmen. (8) Klinik für Neurologie, Universitätsmedizin Göttingen. (9) Klinik für Neurologie, Elblandklinikum Meißen. (10) Klinik und Poliklinik für Neurologie, Universitätsklinikum Carl Gustav Carus an der TU Dresden. (11) Klinik und Poliklinik für Neurologie, Uniklinik Köln. (12) Klinik für Neurologie, Universitätsklinikum Jena. (13) Gertrudis-Klinik Biskirchen, Parkinson-Zentrum, Leun-Biskirchen. (14) Neurologische Klinik und Poliklinik, Universitätsklinikum Würzburg. (15) Klinik für Neurologie, Marienhaus Klinikum St. Wendel-Ottweiler. (16) Klinik für Neurologie und Gerontoneurologie, DIAKONEO Diak Klinikum, Diakonie-Klinikum Schwäbisch Hall. (17) Klinik und Poliklinik für Neurologie der Universität Regensburg am medbo Bezirksklinikum Regensburg. (18) Neurologische Universitätsklinik, Universitätsklinikum Tübingen. (19) Parkinson-Klinik Ortenau, Wolfach. (20) Klinik und Poliklinik für Neurologie, Klinikum rechts der Isar der TU München. (21) Parkinson Fachklinik Haag i. OB. (22) Klinik für Neurologie und Neurophysiologie, Universitätsklinikum Freiburg. (D) Priority of different selection criteria for ATs in the participating centers. Guidelines of the DGN (German Society for Neurology), contraindications, and patients' preference were deemed most important. AT = advanced therapy; CAT-PD = Combinations of Advanced Therapies in PD; PD = Parkinson disease.

Figure 2 Documented AT Modifications, Their Reasons and Their Changes in Side Effect Profile



(A) Sankey plot of all AT modifications documented in CAT-PD. Colors of the streams sorted by overall number of modifications documented in the clinical course of the individual patients. Stream width correlates to number of patients with the respective AT modification. Colors of nodes indicating the AT (combination) used. The vast majority of patients had 1 AT modification and thereby used 2 out of the 3 ATs. The most common changes were the replacement of a CSAI by a DBS or LCIG or the addition of a pump therapy (CSAI or LCIG) to an existing DBS. (B) Aggregated reasons for modifying the ATs (further details in Table 2; multiple selection per modification permitted). The most important reasons for modifying the AT were insufficient therapeutic efficacy and adverse effects of the previous therapy. (C) Percentage of patients affected by different side effect categories. Cumulative data for all AT modifications are shown, detailed data in eTable 2 (links.lww.com/WNL/D156). The percentage of affected patients decreased after the AT modification and did not reach the baseline level at the last assessment (except for device-associated side effects). AT = advanced therapy; CAT-PD = Combinations of Advanced Therapies in PD; CGI = Clinical Global Impression—Improvement Scale; CSAI = continuous subcutaneous apomorphine infusion; DBS = deep brain stimulation; LCIG = levodopa-carbidopa intestinal gel; PD = Parkinson disease.

Table 1 Basic Demographic and Clinical Data of All Patients

Parameter	Median (range); number
Sex ratio—male:female = 79:37	
Age at motor symptom onset, y	47.5 (22.0–67.2); n = 90
Age at PD diagnosis, y	50.0 (24.0–75.0); n = 114
Age at initiation of first advanced therapy, y	60.1 (32.5–84.0); n = 115
Age at initiation of second advanced therapy, y	64.8 (37.0–85.6); n = 116
Age at initiation of third advanced therapy, y	68.2 (37.3–77.7); n = 27
Age at initiation of fourth advanced therapy, y	71.5 (45.1–72.9); n = 4
Age at initiation of fifth advanced therapy, y	71.5 (n = 1)
Current (or last documented) age, y	66.7 (37.3–86.7); n = 116
Interval diagnosis to first advanced therapy, y	10.0 (1.5–32.8); n = 113
Interval diagnosis to second advanced therapy = first modification, y	13.7 (2.5–35.2); n = 114
Interval diagnosis to third advanced therapy = second modification, y	16.2 (6.6–26.0); n = 27
Interval diagnosis to fourth advanced therapy = third modification, y	21.7 (12.4–22.9); n = 4
Interval diagnosis to fifth advanced therapy = fourth modification, y	22.5 (n = 1)
Cognitive status before initiation of second advanced therapy	
MoCA, points	25.0 (13.0–30.0); n = 50
MMST, points	26.0 (18.0–30.0); n = 21
MDS-UPDRS Part III before initiation of second advanced therapy, points	31.0 (8.0–82.0); n = 87
MDS-UPDRS Part IV before initiation of second advanced therapy, points	10.0 (5.0–18.0); n = 15
MDS-UPDRS Part IV subscores before initiation of second advanced therapy	
Time spent with dyskinesia, h	1.0 (0.0–12.0); n = 15
Time spent with dyskinesia, points	1.0 (0.0–3.0); n = 30
Time in off-state, h	2.0 (1.0–4.5); n = 9
Time in off-state, points	2.0 (0.0–4.0); n = 30

Abbreviations: AT = advanced therapy; MDS-UPDRS = Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale; MMST = Mini-Mental Status Test; MoCA = Montréal Cognitive Assessment; PD = Parkinson disease.

much worse, over 0: no change, to +3: very much improved), oral PD medication as levodopa-equivalent daily dosage (LEDD),[13,14] ATs with therapeutic specifications, reasons for AT combinations, and adverse effects. Starting with the application of the second AT (beginning of AT combination phase), this information was documented in a "milestone" module of the questionnaire for each relevant AT modification, whereby the addition of an AT to an existing one, the replacement of an AT by another one, and the omission of an AT were considered as milestone modifications. The change from the first to the second AT constellation was defined as "first AT modification" of the patient and the change from the second to the third AT constellation as "second AT modification" (see the Timeline in Figure 2A). The modular concept enabled coverage of every possible AT modification sequence by combining a variable number of "milestone" modules per patient. Clinical and therapeutic data around the modifications had to be documented at the latest available time point before the modification (data for "before modification") and at the first permanent therapy adjustment of the new AT in the first 3 months after the modification (data for "after modification"). Data about the first applied AT of the patient were gained in the "before modification" part of the "milestone" module of the first AT modification. Finally, the latest available status ("last status") of the upper mentioned clinical and therapeutic parameters was assessed in the "final module." Unknown items and items not available from the patient's clinical files should be indicated as "not available." Responses to open questions were summarized by umbrella terms within predefined main categories. Questionnaires were completed retrospectively and based on clinical

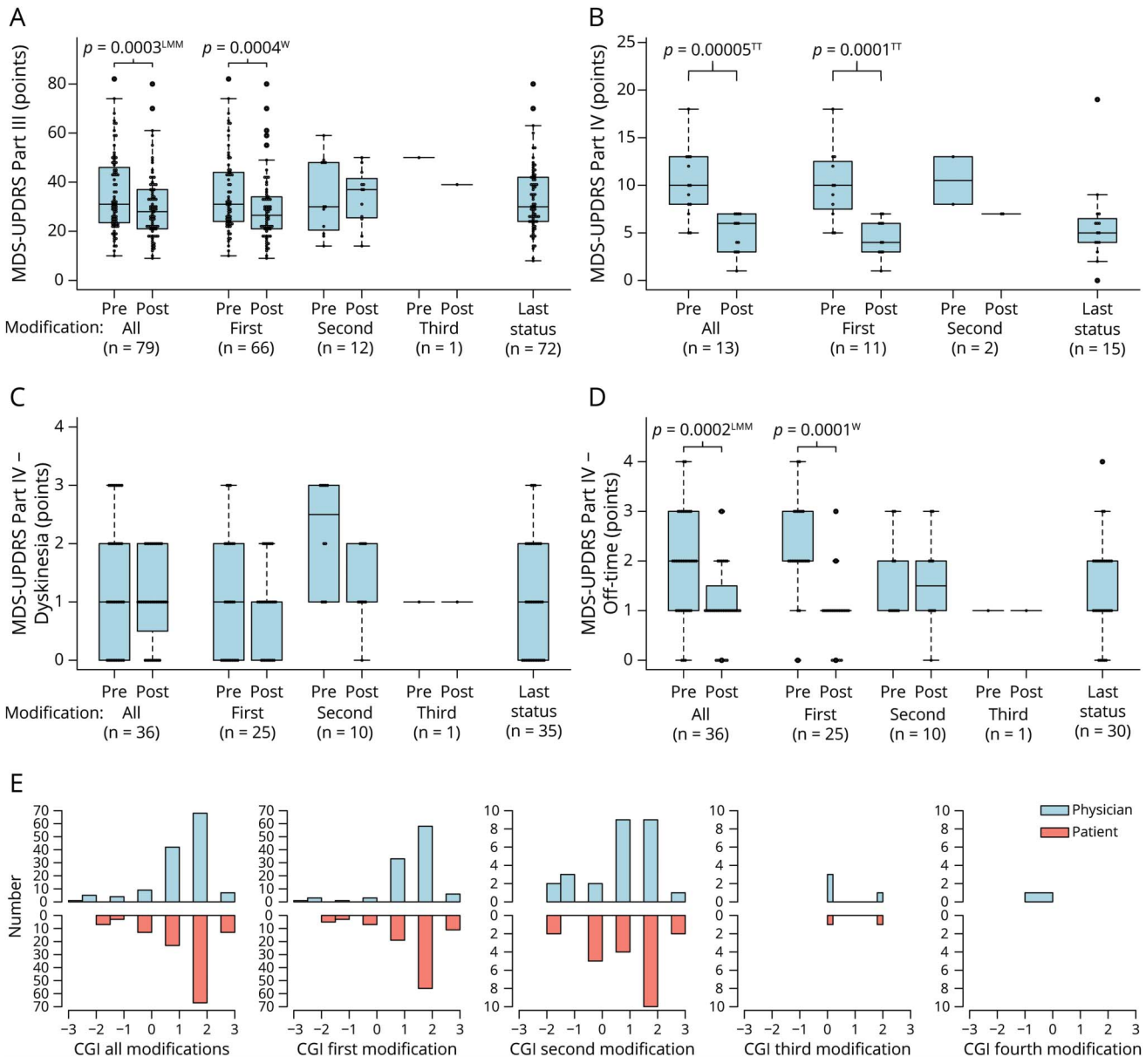
Table 2 Reasons for Modifications of the ATs, Sorted by Frequency (Multiple Selections per Modification Permitted, Corresponding Table to Figure 2B)

Reasons for modification of the advanced therapy	n (%)
Insufficient therapeutic efficacy of the previous therapy	113 (76.4)
Fluctuations	95 (64.2)
Insufficient motor symptom control	37 (25.0)
Freezing	8 (5.4)
Adverse effects, non–device-associated	86 (58.1)
General	
Therapy intolerance	1 (0.7)
Neurologic	
Dyskinesia	9 (6.1)
Disturbance of gait	9 (6.1)
Falls	9 (6.1)
Dystonia	7 (4.7)
Dysarthria	6 (4.1)
Dysphagia	2 (1.4)
Freezing	2 (1.4)
Vertigo	2 (1.4)
Polyneuropathy	1 (0.7)
Pain	1 (0.7)
Disturbance of vision	1 (0.7)
Spasticity	1 (0.7)
Fluctuations	1 (0.7)
Neuropsychiatric	
Hallucinations	22 (14.9)
Impulse control disorder	13 (8.8)
Drowsiness	7 (4.7)
Dopamine dysregulation syndrome	4 (2.7)
Delusion	4 (2.7)
Lack of drive	3 (2.0)
Punding	2 (1.4)
Intensive dreams	2 (1.4)
Fear	1 (0.7)
Delirium	1 (0.7)
Dementia	1 (0.7)
Change of personality	1 (0.7)
Suicide	1 (0.7)
Suicide attempt	1 (0.7)
Restlessness	1 (0.7)
Cardiovascular	
Orthostasic problems	2 (1.4)
Hypotension	1 (0.7)
Gastrointestinal	
Nausea	5 (3.4)
Diarrhea	1 (0.7)
Weight loss	1 (0.7)
Pseudohypersalivation	1 (0.7)
Cutaneous	
Skin nodules	7 (4.7)
Abdominal wall induration	4 (2.7)
Skin necrosis	2 (1.4)
Erythema	1 (0.7)
Adverse effects, device-associated	28 (18.9)
Infection of DBS impulse generator	7 (4.7)
Misplacement of electrodes	5 (3.4)
PEJ dislocation	4 (2.7)
Electrode dislocation	3 (2.0)
Abdominal pain	2 (1.4)
Pump malfunction	2 (1.4)
Battery exhaustion DBS	1 (0.7)
Electrode malfunction	1 (0.7)
Electrode infection	1 (0.7)
Lack of subcutaneous fat	1 (0.7)
Malfunction of DBS impulse generator	1 (0.7)
PEJ infection	1 (0.7)
Management problems	8 (5.4)
Problems with handling	7 (4.7)
Manipulation (on the device)	1 (0.7)
Economic reasons	0 (0.0)
Other reasons	16 (10.8)
Rejection of previous therapy	7 (4.7)
Bridging therapy	4 (2.7)
Indication for PEG/J due to dysphagia	2 (1.4)
New therapy attempt with DBS	1 (0.7)
Extensive need for apomorphine boli	1 (0.7)
Contraindication for therapy continuation	1 (0.7)

Abbreviations: AT = advanced therapy; CAT-PD = Combinations of Advanced Therapies in PD; DBS = deep brain stimulation; PD = Parkinson disease. Data are shown for all modifications and the whole sample. Percentages refer to 148 documented AT modifications in CAT-PD.

records. No identifying data were noted. eTable 1 (links.lww.com/WNL/D156) shows all data collected by the modules of the questionnaire with detailed explanations concerning data management. The original questionnaire in German is available in eAppendix 1 (links.lww.com/WNL/D152) and a translated English version is provided

Figure 3 Clinical Outcome of AT Combinations

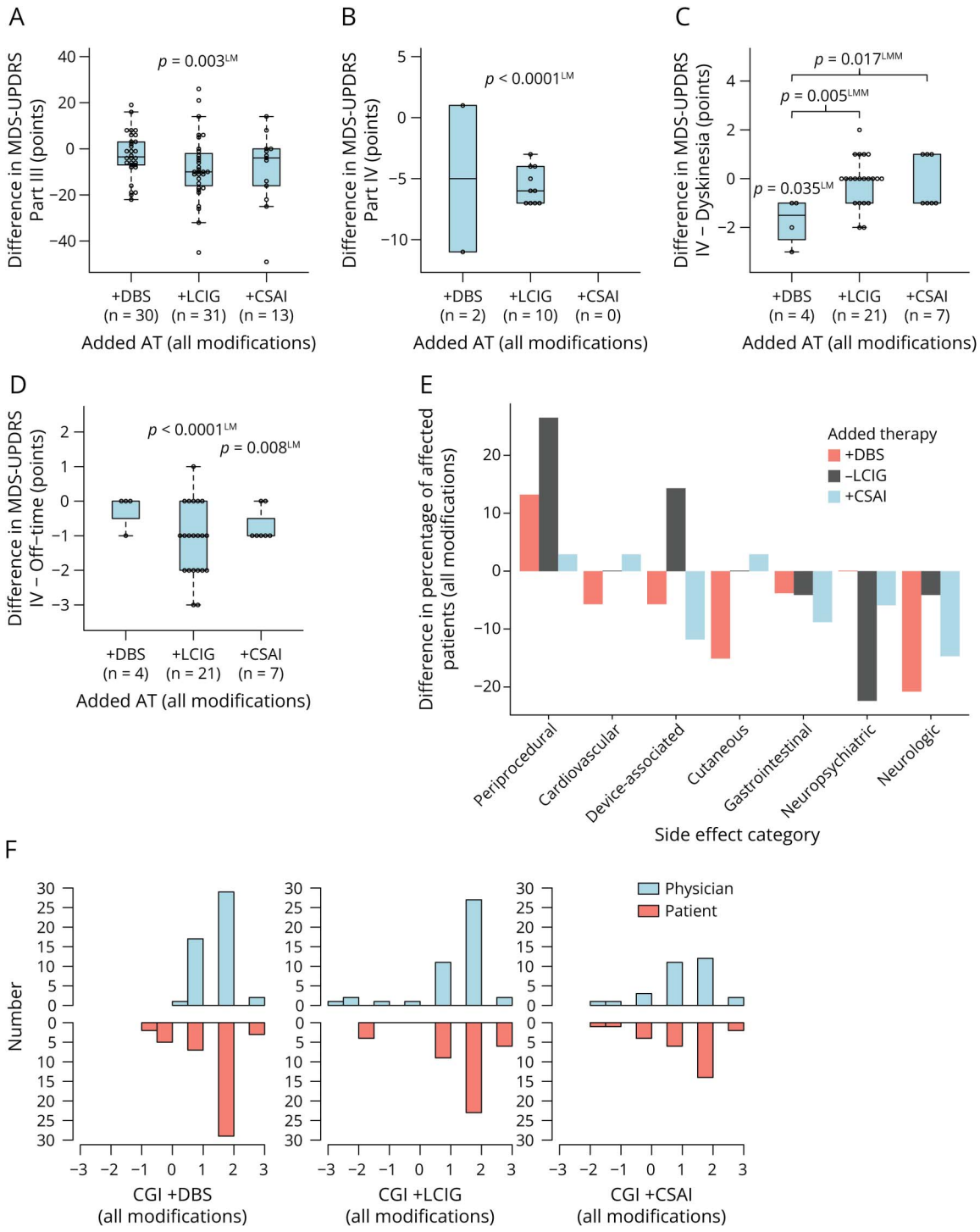


MDS-UPDRS Part III (A), IV (B), and Part IV—dyskinesia (item 4.1) (C)/off-time (item 4.3) (D) scores premodification and postmodification. With the exception of the dyskinesia item, all evaluated MDS-UPDRS scores decreased significantly in the cumulative analysis of all modifications and in the first modification, pointing to an objective clinical benefit by AT combinations. (E) Clinical Global Impression score by physicians (blue) and patients (red) for all modifications and stratified for first, second, third, and fourth modification. The used scale ranges from −3 (very much worse) over 0 (no change) to +3 (very much improved). Both physicians and patients mainly perceived the AT modifications as beneficial. n: number of pairwise available data. For modifications not mentioned in individual score figures, no data were available. AT = advanced therapy; LMM/TT/W = significant in linear mixed model/paired *t* test/Wilcoxon signed-rank test; MDS-UPDRS = Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PD = Parkinson disease.

in eAppendix 2 (links.lww.com/WNL/D153). Furthermore, several key characteristics of the participating centers (number of treated patients with PD per year, number of new installations of the ATs per year, identification method of patients suitable for CAT-PD, applied selection criteria for ATs in individual patients) were collected. In the coordinating center, the Department of Neurology of the University Hospital rechts der Isar of the Technical University of Munich, Germany, data were integrated into a central digital database and subjected to statistical evaluation.

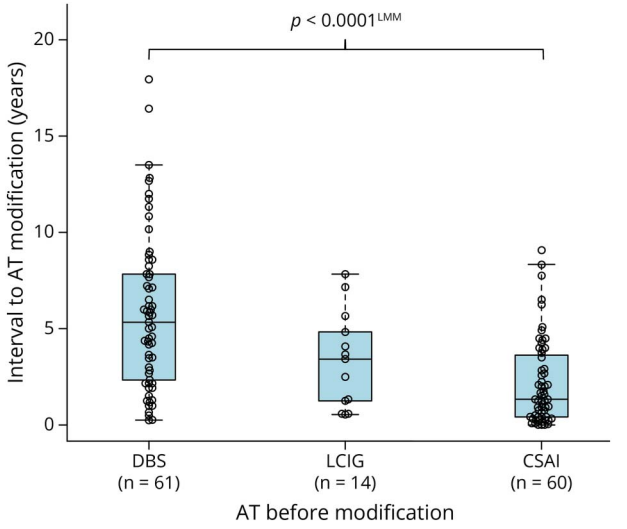
Primary end points of CAT-PD comprised the number of ATs per patient, the treatment duration for each AT, and dynamics of upper mentioned clinical and therapeutic parameters by AT modifications (Figure 1B). Reasons for combining ATs and adverse effects during combined AT treatment were defined as secondary end points.

Figure 4 Clinical Outcome of AT Combinations, Stratified by the Added AT



MDS-UPDRS Part III (A), IV (B), and Part IV—dyskinesia (item 4.1) (C)/off-time (item 4.3) (D) scores before and after all available modifications, stratified by the added AT. For DBS, a significant improvement of the dyskinesia item was observed; for LCIG, a significant benefit for MDS-UPDRS Part III, IV, and the off-time item; for CSAI, only for the off-time item. (E) Dynamics (difference postmodification − premodification) of side effects, stratified by the added AT. (F) Clinical Global Impression score by physicians (blue) and patients (red) for all modifications, stratified by the added AT. The used scale ranges from −3 (very much worse) over 0 (no change) to +3 (very much improved). Both physicians and patients mainly perceived the AT modifications as beneficial for all added ATs. n: number of pairwise available data. For modifications not mentioned in individual score figures, no data were available. Note: Addition of the numbers in this figure results in a smaller total number than the n for all modifications of the respective score in Figure 2 because the analyses in Figure 2 also comprise modifications with omission of an AT (e.g., DBS + LCIG > DBS) which are not considered in this figure. AT = advanced therapy; DBS = deep brain stimulation; LCIG = levodopa-carbidopa intestinal gel; LMM/LM = significant in linear mixed model/linear model; MDS-UPDRS = Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PD = Parkinson disease.

Figure 5 Time of Use of the 3 ATs Before Requiring AT Modification



DBS was the most long-lasting AT, CSAI the shortest. AT = advanced therapy; CSAI = continuous subcutaneous apomorphine infusion; DBS = deep brain stimulation; LCIG = levodopa-carbidopa intestinal gel; n = number of available data.

Statistics were performed with R, version 4.0.3 (the R Foundation, Vienna, Austria), in combination with RStudio, version 1.3.1093 (Boston, MA). For the comparison of scores before and after the modifications, only pairwise data per patient were considered. Normal distribution was evaluated by using the Shapiro-Wilk normality test, statistical differences over the AT changes in the whole cohort by a linear mixed model (for score differences subsuming all modifications because of data interdependency of individual patients), by using the Wilcoxon signed-rank test, or by a paired t test (for not normally or normally distributed score differences of individual modifications, respectively), whereby $p < 0.05$ was defined as statistically significant. No correction for multiple testing was performed. For subgroup analyses, a linear mixed model was applied for evaluation of intergroup differences because of group data interdependency. For intragroup evaluations in subgroup analyses, the linear mixed model (theoretically expected to be required because of data interdependency of individual patients within the group) was replaced by a linear model because—in reality—no interdependent data were identified.

Standard Protocol Approvals, Registrations, and Patient Consents

Lead ethics approval was granted by the Ethics Committee of the Technical University of Munich (No. 303/19S). No standard informed patient consent was required because of the pseudonymized and retrospective data acquisition. Several ethics committees of participating centers additionally approved CAT-PD, where deemed necessary (see eMethods, links.lww.com/WNL/D155). This study report was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies, where applicable.[15]

Data Availability

Anonymized raw data of CAT-PD can be requested from the individual centers. P.L. and D.P. take responsibility for the integrity of the data and the accuracy of the data analysis.

Results

Fifty-five of 63 selected German PD centers met the inclusion criterion of being able to provide at least 2 of 3 available ATs and were invited by email to take part in CAT-PD; of these, 22 returned questionnaires (Figure 1, A and C). All 22 responding centers could provide the installation of all 3 ATs, either by themselves or in cooperation with larger PD centers nearby (especially in case of DBS, eFigure 1, links.lww.com/WNL/D154). 116 patient cases (37 female, 79 male), comprising 148 AT modifications, were identified in most centers by analyzing diagnoses and/or procedures in their hospital management system or by searching AT patient lists of their movement disorders department. One center retrospectively collected further candidates in a patient support group and 2 others by personal knowledge of patients treated with combined ATs (Figure 1B). In most of the centers, German PD therapy guidelines, contraindications, and patients' preference were deemed most important for selecting the appropriate AT in individual patients (Figure 1D).

In the median, motor symptoms started at the age of 47.5 years; PD diagnosis was confirmed 2.5 years later. The first AT was, in the median, applied in 10.0 years and the subsequent AT modifications 13.7, 16.2, 21.7, and 22.5 years after PD diagnosis (Table 1, eFigure 2, links.lww.com/WNL/D154). Most of the 116 patients (n = 89) had 1 AT modification and used 2 ATs in their clinical course, while smaller subgroups had 2 (n = 23), 3 (n = 3), or even 4 (n = 1) modifications or used all 3 ATs (n = 8). The most common AT changes were the replacement of a CSAI by a DBS (n = 40) or LCIG (n = 18) or the addition of a pump therapy to an existing DBS (DBS + LCIG, n = 24; DBS + CSAI, n = 19). The 2 pump therapies were used sequentially in some patients, but never simultaneously (Figure 2A, eFigure 3).

Of 111 DBS therapies documented in all patients and modifications, 2 were unilateral DBS of the subthalamic nucleus (STN-DBS), 104 were bilateral STN-DBS, 4 were bilateral DBS of the globus pallidus internus, and 1 was a bilateral DBS of the pedunculopontine nucleus. No patient changed the DBS target during the documented clinical course. Daily LCIG dosage before the AT modifications was (median [range]) 1,356.0 (616.0–2,388.0) mg over an application time

of 16.0 (13.5–24.0) hours (n = 15), after the AT modifications was 1,463.3 (385.0–4,960.0) mg over 16.0 (14.0–24.0) hours (n = 49), and at the last documented status was 1,500.0 (385.0–2,940.0) mg over 16.0 (13.5–24.0) hours (n = 43). Respective values for CSAI were 84.0 (10.0–357.7) mg (n = 63) over 17.5 (10.0–24.0) hours (n = 62, 1 data point missing), 76.5 (10.0–288.0) mg (n = 63) over 16.0 (9.0–24.0) hours (n = 35), and 76.5 (30.0–144.0) mg over 16.5 (6.0–24.0) hours (n = 14).

Before the first AT modification (i.e., before initiation of the second AT), patients were in the median affected by moderate PD cardinal symptoms (MDS-UPDRS Part III 31.0 points) but suffered from disabling motor complications of dyskinesia (MDS-UPDRS item 4.1 1.0 points, corresponding to 0%–25% of waking hours) and off-time (MDS-UPDRS item 4.3 2.0 points, corresponding to 26%–50% of waking hours) (Table 1). Besides PD, most of the patients were characterized by additional neurologic or non-neurological comorbidities (eFigure 4, links.lww.com/WNL/D154).

The most important reasons for modifying the AT were insufficient therapeutic efficacy concerning motor symptoms (n = 113; most common motor fluctuations [n = 95]) and non–device-associated (n = 86) or device-associated (n = 28) adverse effects of the previous therapy (Figure 2B, Table 2).

For many side effect categories, the percentage of affected patients decreased after the respective modification and did not reach the baseline level at the last assessment (Figure 2C, eTable 2, links.lww.com/WNL/D156). No significant changes of LEDD and MMST were observed for individual and aggregated modifications in the whole sample, with the exception of the LEDD for the second modification, where a nearly doubled number of DBS resulted in a significant reduction of LEDD (eFigures 5–8, links.lww.com/WNL/D154). With the exception of the dyskinesia item, all evaluated MDS-UPDRS scores decreased significantly in the cumulative analysis of all modifications and in the first modification of the whole patient cohort (Figure 3, A–D, eTable 3; see also eFigures 9 and 10 for dyskinesia/off-time in hours and eTable 4 for nonpairwise score data). Both physicians and patients mainly perceived the AT modifications as beneficial, as shown by the CGI scores (Figure 3E).

Further subgroup analyses, stratified by the added AT after the modification (+DBS, +LCIG, +CSAI), included all available subgroup modifications, independent of subsequent simultaneous or sequential AT continuation, because of otherwise unreasonably small subgroup size. Intragroup statistics showed a significant decrease in MDS-UPDRS scores parts III and IV after addition of LCIG therapy, in dyskinesias after addition of DBS, and in off-time after addition of LCIG and CSAI. All other subgroup scores were characterized by a nonsignificant trend for a clinical benefit. Intergroup analyses revealed significant differences only for the dyskinesia item, where DBS was most beneficial (Figure 4, A–D, eTable 5, links.lww.com/WNL/D156). The side effect profile differed according to ATs: Periprocedural and device-associated complications were most common after addition of LCIG (+26.5% and +14.3% compared with the previous AT, respectively), whereas neuropsychiatric problems markedly decreased (−22.4%). Both DBS and CSAI reduced device-associated adverse effects (−5.7% and −11.8%) and neurologic complications (−20.8% and −14.7%) effectively; DBS addition reduced furthermore cutaneous side effects (−15.1%) (Figure 4E, eTable 6). Again, most of both physicians and patients perceived a clinical improvement by AT modifications, independent of the added AT, as conveyed by the CGI scores (Figure 4F). The most long-lasting AT in the cohort was DBS, requiring AT modification after a median of 5.3 years (range 0.3–18.0) in comparison with 3.4 years (0.5–7.8) for LCIG and 1.3 years (0.1–9.1) for CSAI (Figure 5).

This study provides Class IV evidence that, in patients with PD, changing or combining ATs is associated with an improvement in the MDS-UPDRS or subjective symptom reporting.

Discussion

The introduction of ATs significantly broadened the spectrum of PD therapies in later disease stages. Earlier application of all 3 ATs in the phase of advanced PD[1,16-18] has the potential to prolong the AT interval in individual patients, especially when taking the rising life expectancy into consideration. Recently, a study published data pointing to clinical benefit by early CSAI application in advanced PD in a small-scale trial,[17] a concept similar to the EARLYSTIM study for DBS by the authors of another study.[18] This contrasts studies addressing AT long-term efficacy and showing a decreasing disease control because of progression of neurodegeneration and relevant therapy discontinuation rates due to side effects and complications.[1,9,10,19,20] Therefore, a rising number of patients with advanced PD requiring an optimization of ATs by changing or combining therapies can be expected in the future.

Previously, AT combinations were mostly described in retrospective case collections with a limited sample size (n < 10).[21-30] To date, only 5 cohort studies (n > 10) have been published,[20,31-34] the largest one comprising 54 evaluated individuals.[33] Only few analyses consider patients with more than 1 AT change.[22,31-33] No randomized blinded trials are available. The vast majority of studies to date attribute the decision to combine ATs to insufficient motor control[21-26,29-35] and adverse effects of the previous AT[21,25,26,31-35] and document a relevant clinical improvement by combining ATs, in regard to main symptoms of PD[20,24,30,32] or motor complications.[20-23,25,26,29,30,35] In 2 studies, CSAI was used as bridging therapy to DBS,[20,33] 2 special cases used DBS for controlling biphasic-like dyskinesias induced by LCIG

therapy,[27,28] and 1 study used LCIG as a rescue for DBS-unresponsive new freezing of gait after STN-DBS.[23] Taken together, previous studies pointed to a clinical benefit by AT combinations but were limited by their small sample size and coverage of defined AT combinations. The reasons for combining ATs, however, were comparable with this study, CAT-PD.

In our study, centers rated guidelines of the Deutsche Gesellschaft für Neurologie (German Society for Neurology) as most important for AT choice, recommending AT introduction in advanced PD with relevant motor fluctuations and dyskinesia.[36] Score dynamics showed a significant drop (in median) of −4.0 points for MDS-UPDRS Part III, of −6.0 points for MDS-UPDRS Part IV, and of −1.0 points (corresponding to −2.0 hours) for the MDS-UPDRS Part IV off-time for the cumulative individual pairwise data of all AT changes in the whole cohort. For the first modification, the respective medians were −6.0 points (MDS-UPDRS Part III), −6.0 points (MDS-UPDRS Part IV), and −1.0 points (corresponding to −2.0 hours off-time reduction) (eTable 3, links.lww.com/WNL/D156). These results point to an objective clinical benefit for the overall sample and the first AT modification, ranging in a comparable magnitude reported in the randomized efficacy trials for DBS,[18,37-39] CSAI,[7] and LCIG.[40] Changing or combining of ATs seems to achieve a similar benefit in regard to motor function or motor complications as their initial application. For dyskinesia time, a trend toward improvement (score difference for the whole cohort and the first modification of 0.0 and 0.0 points, −0.5 and −2.0 hours, respectively) was observed. The small sample size for the second, third, and fourth AT modification did not permit to draw statistically robust conclusions about their effects on clinical improvement and side effects. Overall, side effect rates were reduced by AT modifications, which are particularly important, because side effects were one of the main reasons for AT changes in our study.

To assess the effect of individual AT modifications, subgroup analyses were performed, stratified by the added AT. For DBS addition, a significant objective clinical improvement was documented for dyskinesias (MDS-UPDRS item 4.1 in the median: −1.5 points), whereas other motor symptoms (assessed by MDS-UPDRS Part III, in the median: −3.5 points) and the off-time (change in MDS-UPDRS item 4.3 in the median: 0.0 points) showed only nonsignificant trends toward clinical benefit. Previous randomized and real-life trials largely are in line with these observations, even in regard to the effect size, whereby the UPDRS-III improvement was rated significant in most of them. In contrast to CAT-PD, however, off-time was significantly reduced in these studies.[6,18,19,37-39] For LCIG addition, the analyzed MDS-UPDRS scores suggested significant improvement of PD cardinal symptoms (−10.0 points), motor complications (MDS-UPDRS Part IV in the median: −6.0 points), and off-time (−1.0 points), but not of dyskinesia (0.0 points), which is again in line with previous evidence, with the exception of MDS-UPDRS Part III (previous studies without significant improvement) and a more pronounced effect on Part IV in our analysis.[4,6,40] For CSAI addition, a significant benefit was shown only for off-time (−1.0 points) in CAT-PD, while other motor symptoms (−4.0 points) and dyskinesia (−1.0 points) were characterized by nonsignificant trends toward improvement. This is in line with prior randomized and retrospective data, even in regard to effect size.[7,10,37,41] Differences of individual scores in our study compared with previous trials could be due to the highly selected patient population with more than 1 AT in their course, in contrast to patients using only 1 AT in previous studies. However, the high agreement of our subgroup analyses with previous randomized and nonrandomized large-cohort AT trials emphasizes the robustness of the results of CAT-PD and suggests a similar clinical effectiveness of combined ATs compared with their initial application.

Periprocedural and device-associated complications are well-described for LCIG therapy.[4,40] By contrast, neuropsychiatric side effects are less common compared with DBS (especially depression and cognitive impairment) and CSAI (especially hallucinations and impulse control disorders), making LCIG the first choice AT for patients with neuropsychiatric comorbidities.[36,42] These phenomena are mirrored in the side effect subgroup analysis of CAT-PD, furthermore showing improvement of the most common neurologic side effects (dyskinesia and motor fluctuations) by addition of DBS and CSAI and alleviation of cutaneous complications by DBS.

AT combinations resulted in a relevant subjective clinical improvement, as documented by the CGI scores of patients and their physicians for both the whole sample and the subgroups.

Possible mechanisms for the observed benefit comprise synergistic effects of the different ATs. In contrast to the dopaminergic pump therapies, DBS is believed to influence neuronal firing rate, synaptic transmission, and even neurogenesis[2]; neuronal circuits responsible for dyskinesia development are potentially reorganized.[30] Unilateral symptoms control is feasible by asymmetric stimulation settings,[21] and LEDD reduction can decrease dopaminergic and psychiatric side effects.[22,30] On the other hand, a continuous medication delivery by AT pumps minimizes dopaminergic plasma level variations, thereby reducing associated motor fluctuations.[1,3]

Summarizing the results of the whole cohort, the subgroup analyses, and previous evidence, our analysis supports the following conclusions:

1. In patients suffering from insufficient symptom control despite usage of 1 AT (and optimized concomitant oral medication) or from relevant side effects of the first AT, an AT combination, either simultaneous or sequential, should be considered.

2. The choice of the added AT should depend on the dominant symptoms and side effects: Addition of DBS seems to improve patients with leading dyskinesia, whereas LCIG mainly improves cardinal motor symptoms and off-time, and CSAI mitigates off-time. LCIG seems to be most beneficial in case of neuropsychiatric side effects, while DBS ameliorates cutaneous adverse effects of the previous AT.
3. In our opinion, simultaneous combination of 2 pump ATs is not reasonable because of 2 required pump units. By contrast, sequential use is feasible and documented. Combining DBS with a pump therapy has been documented in CAT-PD as well and possibly results in synergistic effects.

Analyzing the time of use of the first AT in CAT-PD until a modification was required, DBS seems to have the most long-lasting clinical effectiveness, followed by LCIG. The shortest time until AT modification was observed for CSAI. Although CAT-PD comprises a highly selected patient group, trials concerned with long-term usage of the 3 ATs agree with this impression. Clinical benefit for more than 15 years is documented in some patients for DBS[19] and for more than 5 years for LCIG.[43] CSAI, although being clinically effective for more than 3 years, is often used as a bridging therapy because of its less-invasive procedures[10] and is characterized by a relevant dropout in studies because of side effects (mainly neuropsychiatric and cutaneous),[10,41] thereby resulting in the shortest time of use of all 3 ATs.

ATs are relatively expensive and economic aspects have to be addressed when considering AT combination. In a recent review, Smilowska et al. documented incremental costs of up to 12.314€ in 2 years or up to 36.400€ in lifetime for DBS in German patients, each compared with best medical treatment. For LCIG, analogous investigations calculate additional 188.864€ in 3 years and for CSAI, 74.696€ in 3 years. While highest expenses for DBS arise by new installation and battery replacement (devices, surgery, hospitalization), LCIG and CSAI are characterized by high continuous drug provision costs.[44] Cost reduction efforts need to be discussed for AT combinations because an addition of costs in AT combinations is expected (devices, surgery, hospitalization, and continuous drug provision). No data so far exist concerning real-life costs of combined ATs, compared with best medical treatment, however. Possible strategies comprise usage of rechargeable DBS impulse generators and the addition of catechol-O-methyltransferase inhibitors for reducing the flow rate of levodopa-carbidopa intestinal gel.[44] Interestingly, economic aspects were rated as least important for AT choice by the centers in CAT-PD and were denied as a trigger for AT modifications in all cases.

Leveraging a nationwide network of PD centers, here we present, the largest collection of AT combinations to date, enabling us—in contrast to a relevant number of previous trials—to consider a large variety of AT changes and including a relevant sample of patients (n = 27) with even more than 1 AT modification in their clinical course. The large cohort allowed for subgroup analyses, which permitted to provide differentiated suggestions for clinical practice. Inclusion of specialized PD centers with systematic patient assessment in everyday clinical routine, allowed the collection of retrospective data based on clinical records that covered the required scores and parameters in a high percentage of data sets. The multicenter analysis minimized potential investigator and center-specific bias and suggests that our conclusions can be generalized. This is particularly true because all recruiting PD centers could directly or indirectly (in cooperation with other PD centers nearby) provide the new installation of all 3 ATs covered by CAT-PD, thereby avoiding a center-specific patient selection and recruitment bias.

CAT-PD has several limitations. First, the retrospective data collection based on clinical records in a highly selected patient group inherently implies incomplete data sets, leading up to smaller sample sizes than the overall cohort for some analyses. Furthermore, the data sets for the clinical evaluation of the second, third, and fourth AT modifications were much smaller than for the first modification, preventing statistically robust clinical conclusions for these AT changes. This was a challenge for some subgroup analyses, as well. For some patients, it was not possible to determine whether the clinical assessment was documented during ON or OFF (expected in ON). A matched control group with best medical or AT treatment was not available in this case collection. Second, because we relied on nonblinded clinical routine data, an examiner bias could not be excluded: The desire for or expectancy of clinical success after AT modifications might have resulted in better scoring by the treating team. Third, there was a variability in clinical outcome, and some patients did not benefit from the AT modification. Further research is needed to determine predictive factors for clinical improvement in individual patients by AT combinations.

In conclusion, CAT-PD suggests an improved outcome for motor symptoms and complications after AT modification, even comparable with the clinical benefit by introducing the first AT. From the clinician's point of view, an AT combination, either simultaneous or sequential, should be considered when the first AT loses efficacy or has to be modified because of side effects or complications. AT choice should then be guided by leading clinical symptoms and side effects. Further and prospective large scale studies are required for more detailed outcome analyses, including more sophisticated AT subgroup analyses, and for the development of evidence-based clinical decision pathways.

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Disclosure

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Continued

Appendix *(continued)*

Name	Location	Contribution
Andrea A. Kühn, MD	Klinik für Neurologie, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, and Berlin Institute of Health, NeuroCure Cluster of Excellence, Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Ilona Csoti, MD	Gertrudis-Klinik Biskirchen, Parkinson-Zentrum, Leun-Biskirchen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Birgit Herting, MD	Klinik für Neurologie und Gerontoneurologie, DIAKONEO Diak Klinikum, Diakonie-Klinikum Schwäbisch Hall, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Simone van de Loo, MD	Klinik für Neurologie und Gerontoneurologie, DIAKONEO Diak Klinikum, Diakonie-Klinikum Schwäbisch Hall, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Aniz Ahammed Basheer, MD	Klinik für Neurologie, Marienhaus Klinikum St. Wendel-Ottweiler, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Robert Liszka, MD	Klinik für Neurologie, Marienhaus Klinikum St. Wendel-Ottweiler, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Wolfgang H. Jost, MD	Parkinson-Klinik Ortenau, Wolfach, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jiri Koschel, MD	Parkinson-Klinik Ortenau, Wolfach, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Bernhard Haller, PhD	Institut für KI und Informatik in der Medizin, Klinikum rechts der Isar der TU München, Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Paul Lingor, MD	Klinik und Poliklinik für Neurologie, Klinikum rechts der Isar der TU München, Munich, Germany; Deutsches Zentrum für Neurodegenerative Erkrankungen e.V. (DZNE), Standort München; Munich Cluster for Systems Neurology (SyNergy), Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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