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´s 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 CAT-PD assessed simultaneous or sequential AT combinations in Germany since 2005 in order to analyze their clinical outcome, their side effects and the reasons for AT modifications.

Methods: Data was acquired retrospectively by modular questionnaires in 22 PD-centers throughout Germany based on clinical records and comprised general information about the centers/patients, clinical (MMST/MoCA, 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: 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. 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 one AT is insufficient in terms of efficacy or side effects. The outcome of an AT combination is comparable to the clinical benefit by introducing the first AT. The added AT should be chosen dependent on dominant clinical symptoms and adverse effects. Further, 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´s 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 due to 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 one AT is insufficient in terms of 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 two of the three ATs licensed in Germany between 2005 and 2019: DBS, CSAI or LCIG (*Figure 1A*). Centers were requested to include all PD patients treated simultaneously or sequentially with at least two of the three ATs during their clinical course. Patients with atypical Parkinsonian syndromes and PD patients having used only one AT in their treatment course were excluded (*Figure 1B*). A printed two-module pseudonymized questionnaire was used to acquire

demographic data, scores for Mini-Mental Status Test (MMST), Montréal Cognitive Assessment (MoCA, converted to MMST[11]), 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 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, the change from the second to the third AT constellation as "second AT modification" etc. (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 three months after the modification (data for "after modification"). Data about the first applied AT of the patient was 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 pre-defined main categories. Questionnaires were completed retrospectively and based on clinical records. No identifying data were noted. *eTable 1* shows all data collected by the modules of the questionnaire with detailed explanations concerning data management. The original questionnaire in German is available in *Supplement 3* and a translated English version is provided in *Supplement 4*. Furthermore, several key characteristics of the participating centers (number of treated PD patients 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 was integrated into a central digital database and subjected to statistical evaluation.

Primary endpoints 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 endpoints.

Statistics were performed with R, version 4.0.3 (The R Foundation, Vienna, Austria), in combination with RStudio, version 1.3.1093 (Boston, MA, USA). For the comparison of scores before and after the modifications, only pairwise data per patient was considered. Normal distribution was evaluated by 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 due to data interdependency of individual patients), by 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 inter-group differences due to group data interdependency. For intra-group evaluations in subgroup analyses, the linear mixed model (theoretically expected to be required due to data interdependency of individual patients within the group) was replaced by a linear model, as – in reality – no interdependent data was identified.

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 due to the pseudonymized and retrospective data acquisition. Several ethics committees of participating centers additionally approved CAT-PD, where deemed necessary (see *Supplement 1*).

This study report was written in accordance with the STROBE guidelines for observational studies, where applicable.[15]

Data availability

Anonymized raw data of CAT-PD can be requested from the individual centers.

Results

55 of 63 selected German PD-centers met the inclusion criterion of being able to provide at least two of three available ATs and were invited by email to take part in CAT-PD; of these, 22 returned questionnaires (*Figure 1A, C*). All 22 responding centers could provide the installation of all three ATs, either by themselves or in cooperation with larger PD-centers nearby (especially in case of DBS, *eFigure 1*). 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, two others by personal knowledge of patients treated with combined ATs (*Figure 1B*). In the majority of 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 10.0 years, the subsequent AT modifications 13.7, 16.2, 21.7, and 22.5 years after PD diagnosis (*Table 1*, *eFigure 2*). Most of the 116 patients (n=89) had one AT modification and used two ATs in their clinical course, while smaller subgroups had two (n=23), three (n=3) or even four (n=1) modifications, or used all three 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 two pump therapies were used sequentially in some patients, but never simultaneously (*Figure 2A*, *eFigure 3*).

Of n=111 DBS-therapies documented in all patients and modifications, n=2 were unilateral DBS of the Subthalamic Nucleus (STN-DBS), n=104 were bilateral STN-DBS, n=4 were bilateral DBS of the Globus Pallidus internus (GPi-DBS), and n=1 was a bilateral DBS of the Pedunculopontine Nucleus (PPN-DBS). No patient changed the DBS target during the documented clinical course. Daily LCIG-dosage before the AT modifications was (median [range]) 1356.0 [616.0 – 2388.0] mg over an application time of 16.0 [13.5 – 24.0] hours (n=15), after the AT modifications 1463.3 [385.0 – 4960.0] mg over 16.0 [14.0 – 24.0] hours (n=49), and at the last documented status 1500.0 [385.0 – 2940.0] 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, one 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).

Prior to the first AT modification (i.e., prior to initiation of the second advanced therapy), patients were in the median affected by moderate PD cardinal symptoms (MDS-UPDRS Part III 31.0 points), but suffered from disabling motor complications in terms 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, the majority of patients were characterized by additional neurological or non-neurological comorbidities (*eFigure 4*).

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*). 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*). 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 3A-D, eTable 3;* see also *eFigures 9-10* for dyskinesia/off-time in hours and *eTable 4* for non-pairwise 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, due to otherwise unreasonably small subgroup size. Intra-group 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 non-significant trend for a clinical benefit. Inter-group analyses revealed significant differences only for the dyskinesia item, where DBS was most beneficial (*Figure 4A-D, eTable 5*). 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 to 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 neurological complications (-20.8% and -14.7%) effectively, DBS addition reduced furthermore cutaneous side effects (-15.1%) (*Figure 4E, eTable 6*). Again, the majority 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 to 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 three 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, Fernández-Pajarín and colleagues 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 Schuepbach et al.[18] This contrasts studies addressing AT long-term efficacy and showing a decreasing disease control due to progression of neurodegeneration and relevant therapy

discontinuation rates due to side effects and complications.[1, 9, 10, 19, 20] Therefore, a rising number of advanced PD patients 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 five 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 one 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 two studies, CSAI was used as bridging therapy to DBS,[20, 33] two special cases used DBS for controlling biphasic-like dyskinesias induced by LCIG-therapy,[27, 28] and one 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 to the present study, CAT-PD.

In our study, centers rated guidelines of the DGN (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*). 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 appears to achieve a similar benefit in regard to motor function or motor complications as their initial application. For dyskinesia time, a trend towards improvement (score difference for the whole cohort and the first modification 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 is particularly important, since side effects were one of the main reasons for AT changes in our study.

To assess the effect of individual AT modifications, subgroups 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 non-significant trends towards 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 non-significant trends towards 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 to previous trials could be due to the highly selected patient population with more than one AT in their course, in contrast to patients using only one AT in previous studies. However, the high agreement of our subgroup analyses with previous randomized and non-randomized large-cohort AT trials emphasizes the robustness of the results of CAT-PD and suggests a similar clinical effectiveness of combined ATs compared to their initial application.

Periprocedural and device-associated complications are well-described for LCIG therapy.[4, 40] In contrast, neuropsychiatric side effects are less common compared to 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 neurological 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 thought 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] 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:

- In patients suffering from insufficient symptom control despite usage of one 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.
- 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.
- In our opinion, simultaneous combination of two pump ATs is not reasonable due to two required pump units. In 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 three ATs agree with this impression. Clinical benefit for more than 15 years is documented in some patients for DBS[19] and for more than five years for LCIG.[43] CSAI, although being clinically effective for more than three years, is often used as a bridging therapy due to its less invasive procedures[10] and is characterized by a relevant dropout in studies due to side effects (mainly neuropsychiatric and cutaneous)[10, 41], thereby resulting in the shortest time of use of all three 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 to best medical treatment. For LCIG, analogous investigations calculate additional 188.864€ in 3 years, 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, as an addition of costs in AT

combinations is expected (devices, surgery, hospitalization, and continuous drug provision). No data so-far exists concerning real-life costs of combined ATs, compared to best medical treatment, however. Possible strategies comprise usage of rechargeable DBS impulse generators and the addition of Catechol-O-methyltransferase (COMT) 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, to the best of our knowledge, 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 one 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 datasets. The multicenter analysis minimized potential investigator and center-specific bias and suggests that our conclusions can be generalized. This is particularly true, as all recruiting PD-centers could directly or indirectly (in cooperation with other PD-centers nearby) provide the new installation of all three 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 datasets, leading up to smaller sample sizes than the overall cohort for some analyses. Furthermore, the datasets 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, as we relied on non-blinded 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 to 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 due to 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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Data responsibility statement

PL and DP take responsibility for the integrity of the data and the accuracy of the data analysis.

Authors´ roles

1: Study design, 2: Study execution, 3: Data analysis, 4: Writing of the manuscript draft, 5: Editing of the final manuscript version.

DP: 1, 2, 3, 4, 5; MH: 2, 5; DW: 2, 5; MTB: 2, 5; HJ: 2, 5; TP: 2, 5; EG: 2, 5; MPN: 2, 5; BF: 2, 5; LK: 2, 5; PG: 3, 5; BHas: 2, 5; AJ: 2, 5; AW: 2, 3, 5; NS: 2, 5; MR: 2, 5; CvR: 2, 5; US: 2, 5; MW: 2, 5; AA: 2, 5; GE: 2, 5; DG: 2, 5; ZK: 2, 5; WM: 2, 5; SP: 2, 5; PPG: 2, 5; VR: 2, 5; JS: 2, 5; MS: 2, 5; ET: 2, 5; SW: 2, 5; SB: 2, 5; AF: 2, 5; CWI: 2, 5; PK: 2, 5; AK: 2, 5; IC: 2, 5; BHert: 2, 5; SvdL: 2, 5; AAB: 2, 5; RL: 2, 5; WJ: 2, 5; JK: 2, 5; BHal: 1, 3, 5; PL: 1, 2, 3, 4, 5.

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Abbreviations

AT	Advanced therapy
CGI	Clinical global impression – Improvement scale
COMT	Catechol-O-methyltransferase
CSAI	Continuous subcutaneous apomorphine infusion
DBS	Deep brain stimulation
DGN	Deutsche Gesellschaft für Neurologie (German Society for Neurology)
GPi-DBS	DBS with target Globus Pallidus internus
LCIG	Levodopa-carbidopa intestinal gel
LEDD	Levodopa-equivalent daily dosage
MDS-UPDRS	Unified Parkinson´s disease rating scale (Movement Disorder Society-sponsored revision from 2008)
MMST	Mini-mental status test
MoCA	Montréal cognitive assessment
PD	Parkinson´s disease

391	PPN-DBS	DBS with target Pedunculopontine Nucleus
392	STN-DBS	DBS with target Subthalamic Nucleus

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Figure Titles and Legends

Figure 1: Selection of participating centers / patients / ATs and endpoints 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 endpoints 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.

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 one AT modification and thereby used two out of the three 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*. 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).

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 pre and post modification. 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 was available. *LMM / TT / W* : Significant in linear mixed model / paired t-test / Wilcoxon signed rank test.

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 pre and post 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 post – pre modification) 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 was 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*, as 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. *LMM / LM* : Significant in linear mixed model / linear model.

Figure 5: Time of use of the three ATs before requiring AT modification

DBS was the most long-lasting AT, CSAI the shortest. *n:* Number of available data.

Tables and Table Legends

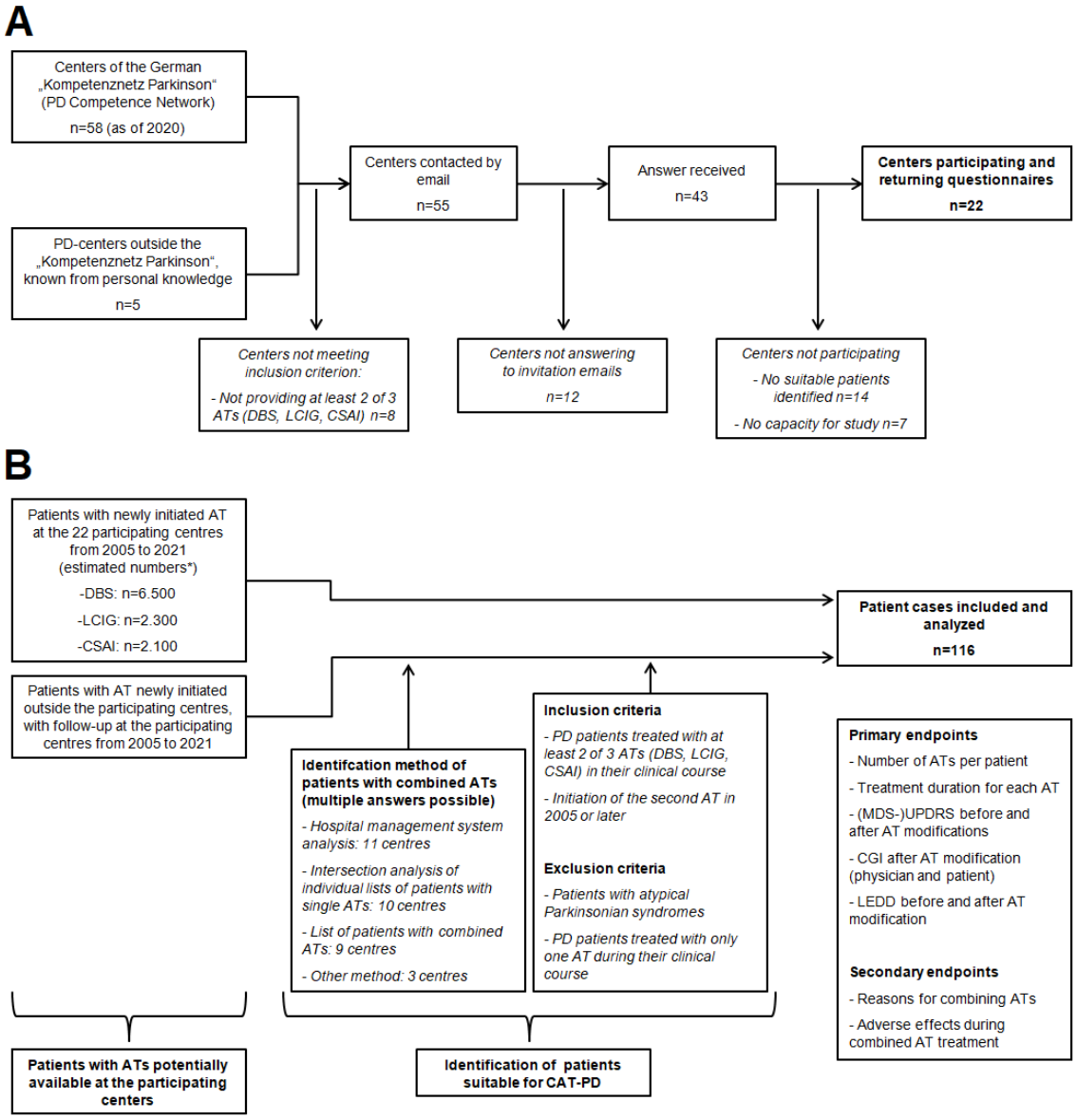
Table 1: Basic demographic and clinical data of all patients

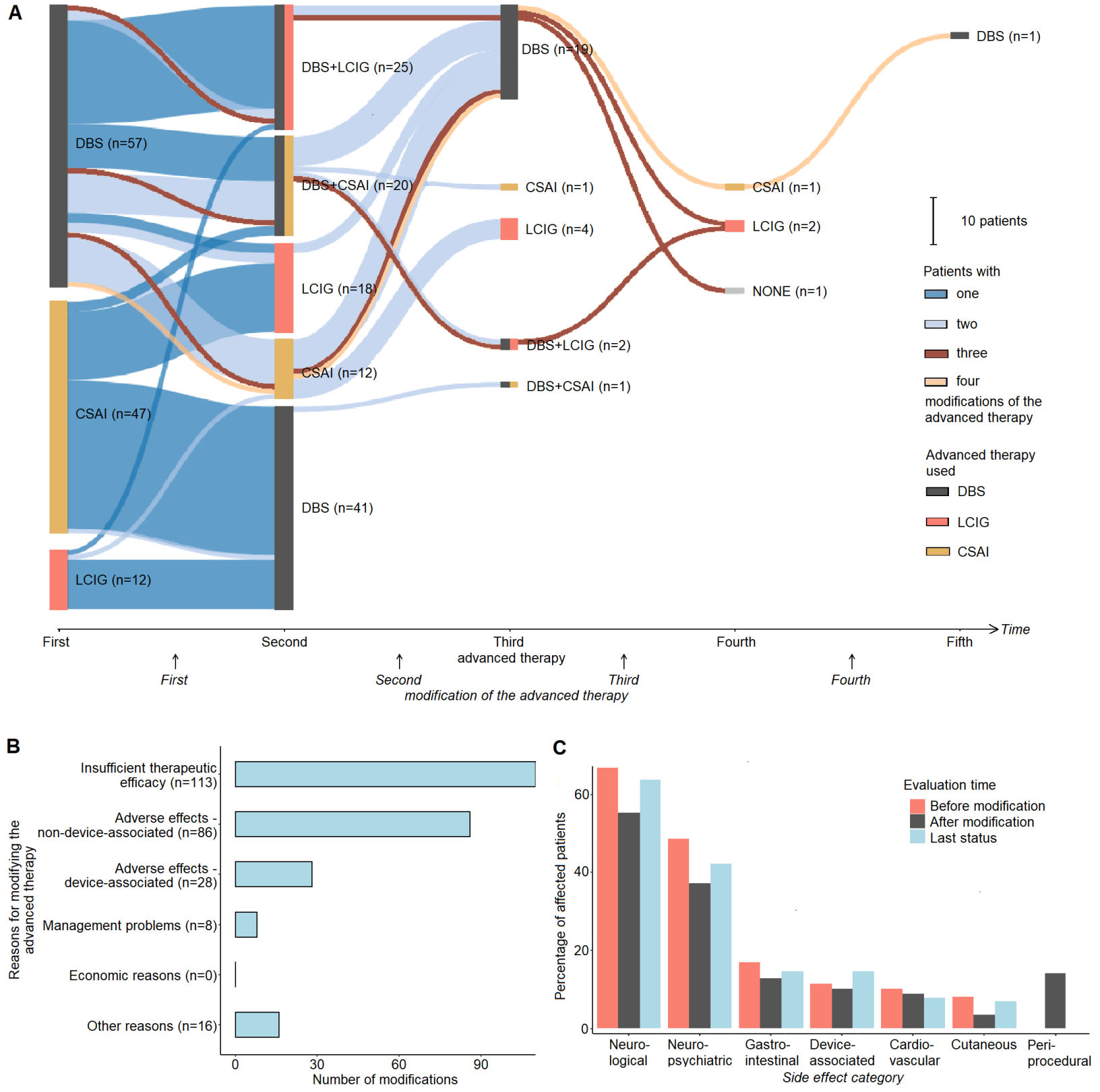
Parameter	Median ([Range]; number)
Gender-ratio male : female = 79 : 37	
Age at motor symptom onset (years)	47.5 ([22.0 – 67.2]; n=90)
Age at PD diagnosis (years)	50.0 ([24.0 – 75.0]; n=114)
Age at initiation of first advanced therapy (years)	60.1 ([32.5 – 84.0]; n=115)
Age at initiation of second advanced therapy (years)	64.8 ([37.0 – 85.6]; n=116)
Age at initiation of third advanced therapy (years)	68.2 ([37.3 – 77.7]; n=27)
Age at initiation of fourth advanced therapy (years)	71.5 ([45.1 – 72.9]; n=4)
Age at initiation of fifth advanced therapy (years)	71.5 (n=1)
Current (or last documented) age (years)	66.7 ([37.3 – 86.7]; n=116)
Intervall diagnosis to first advanced therapy (years)	10.0 ([1.5 – 32.8]; n=113)
Intervall diagnosis to second advanced therapy = first modification (years)	13.7 ([2.5 – 35.2]; n = 114)
Intervall diagnosis to third advanced therapy = second modification (years)	16.2 ([6.6 – 26.0]; n=27)
Intervall diagnosis to fourth advanced therapy = third modification (years)	21.7 ([12.4 – 22.9]; n=4)
Intervall diagnosis to fifth advanced therapy = fourth modification (years)	22.5 (n=1)
Cognitive status before initiation of second advanced therapy - MoCA (points) - MMST (points)	 25.0 ([13.0 – 30.0]; n=50) 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 (hours) - Time spent with dyskinesia (points) - Time in OFF-State (hours) - Time in OFF-State (points)	 1.0 ([0.0 – 12.0]; n=15) 1.0 ([0.0 – 3.0]; n=30) 2.0 ([1.0 – 4.5]; n=9) 2.0 ([0.0 – 4.0]; n=30)

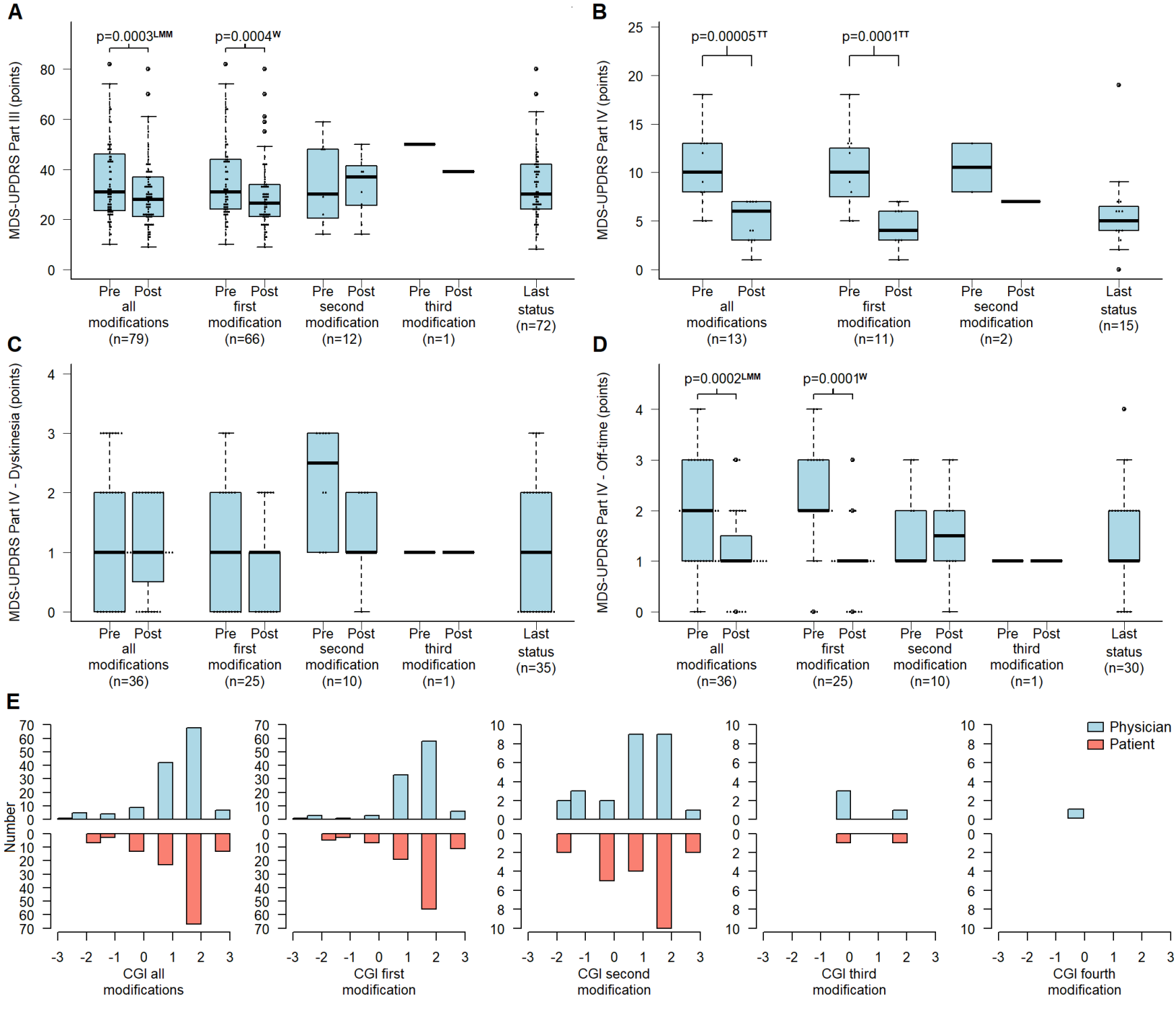
Table 2: Reasons for modifications of the ATs, sorted by frequency (multiple selections per modification permitted, corresponding table to *Figure 2B*)

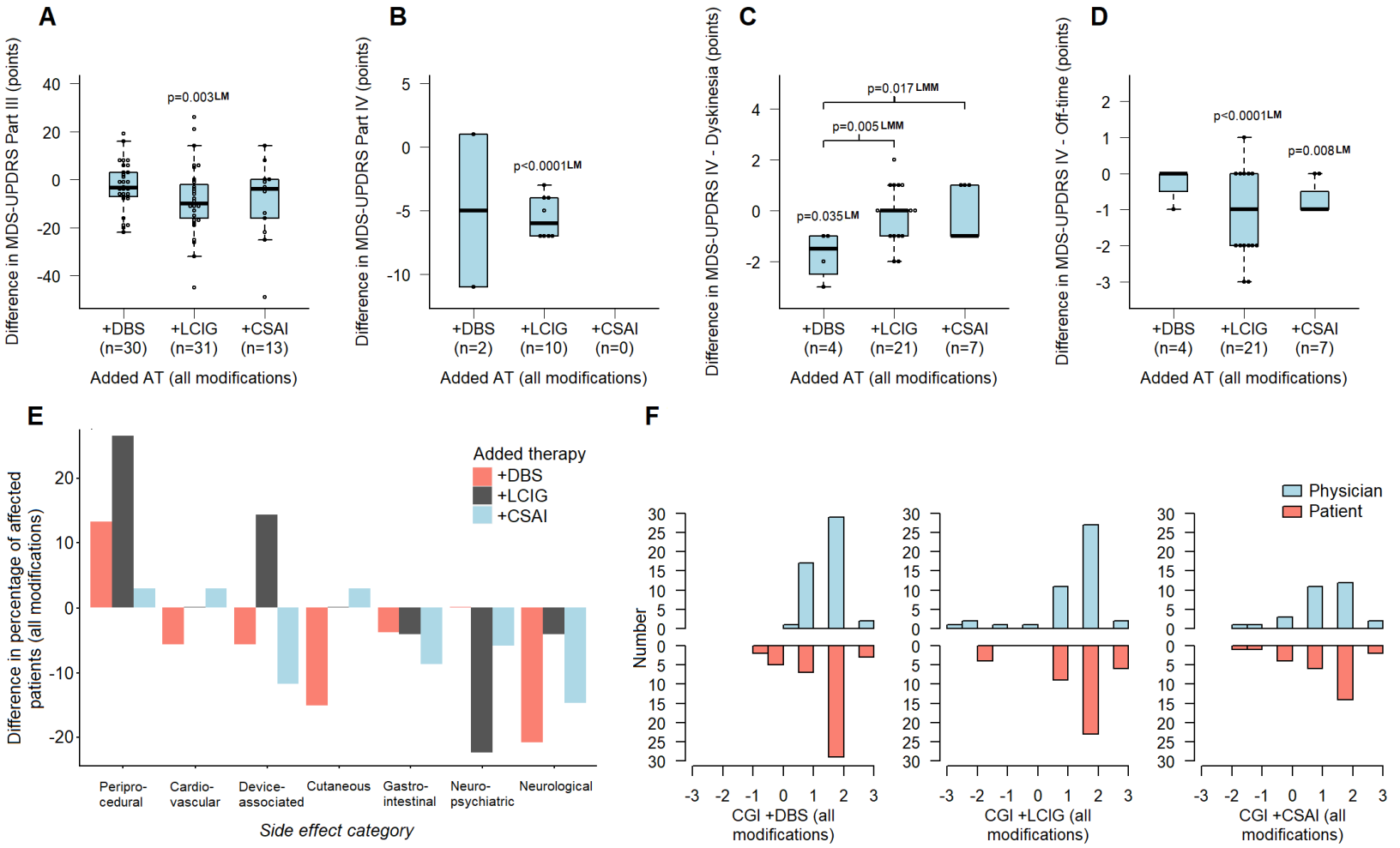
Data is shown for all modifications and the whole sample. Percentages refer to n=148 documented AT modifications in CAT-PD.

Reasons for modification of the advanced therapy	n	Percentage
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
Neurological		
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


A
Centers of the German „Kompetenznetz Parkinson“ (PD Competence Network)
n=58 (as of 2020)
PD-centers outside the „Kompetenznetz Parkinson“, known from personal knowledge
n=5
Centers contacted by email
n=55
Answer received
n=43
Centers participating and returning questionnaires
n=22
Centers not meeting inclusion criterion:
- Not providing at least 2 of 3 ATs (DBS, LCIG, CSAI) n=8
Centers not answering to invitation emails
n=12
Centers not participating
- No suitable patients identified n=14
- No capacity for study n=7
B
Patients with newly initiated AT at the 22 participating centres from 2005 to 2021 (estimated numbers*)
-DBS: n=6.500
-LCIG: n=2.300
-CSAI: n=2.100
Patients with AT newly initiated outside the participating centres, with follow-up at the participating centres from 2005 to 2021
Patient cases included and analyzed
n=116
Identifcation method of patients with combined ATs (multiple answers possible)
- Hospital management system analysis: 11 centres
- Intersection analysis of individual lists of patients with single ATs: 10 centres
- List of patients with combined ATs: 9 centres
- Other method: 3 centres
Inclusion criteria
- PD patients treated with at least 2 of 3 ATs (DBS, LCIG, CSAI) in their clinical course
- Initiation of the second AT in 2005 or later
Exclusion criteria
- Patients with atypical Parkinsonian syndromes
- PD patients treated with only one AT during their clinical course
Primary endpoints
- Number of ATs per patient
- Treatment duration for each AT
- (MDS-)UPDRS before and after AT modifications
- CGI after AT modification (physician and patient)
- LEDD before and after AT modification
Secondary endpoints
- Reasons for combining ATs
- Adverse effects during combined AT treatment
Patients with ATs potentially available at the participating centers
Identification of patients suitable for CAT-PD
C
54°N
52°N
50°N
48°N
6°E
8°E
10°E
12°E
14°E
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Contributed cases
1
13
D
Priority in AT choice
1
2
3
4
5
6
7
8
Guidelines DGN
Contraindications
Preference of patient
Availability follow-up care
Preference of relatives
Preference of physician
Availability of the AT
Economic aspects
Selection criterion

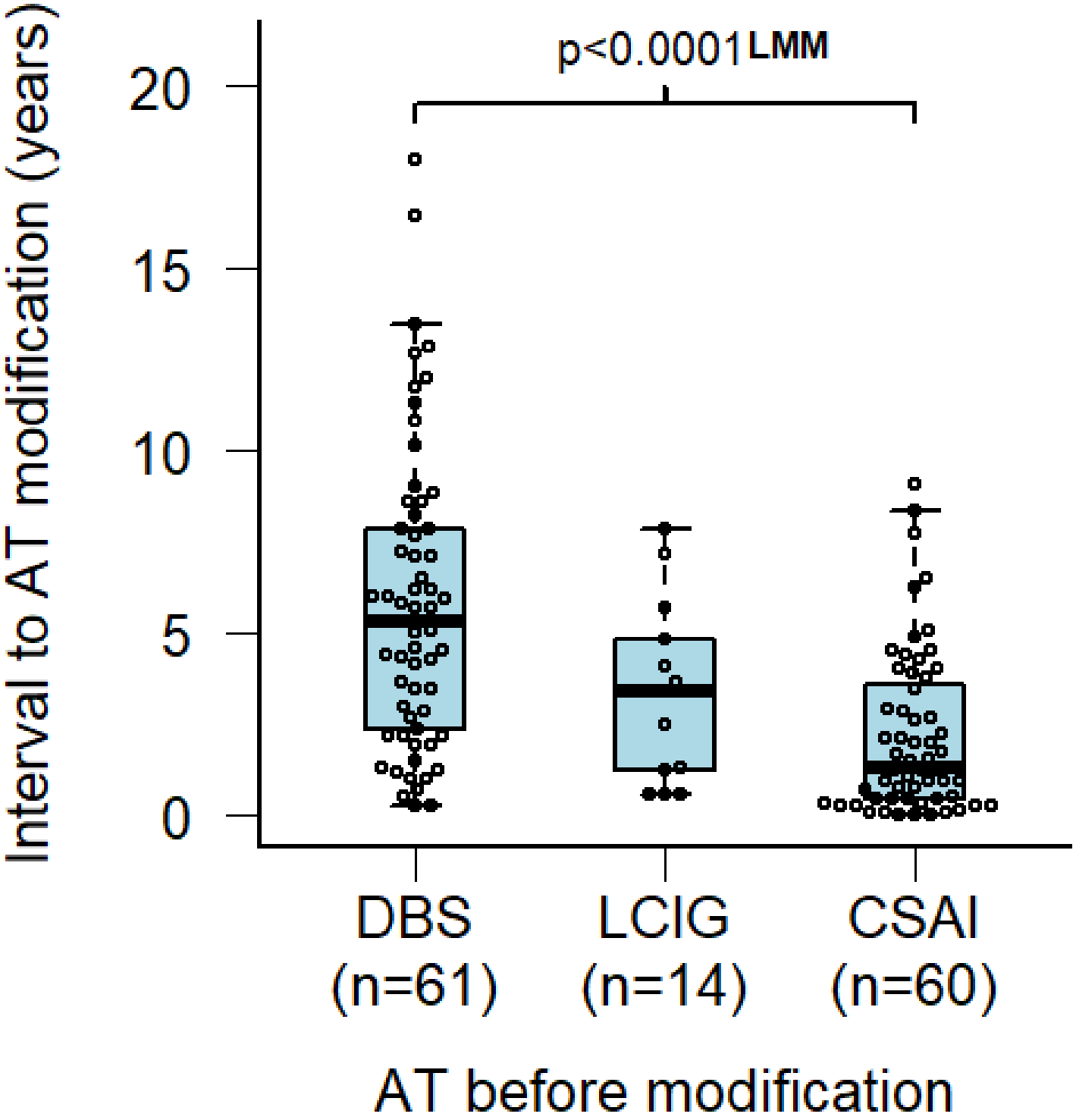

A
DBS (n=57)
CSAI (n=47)
LCIG (n=12)
DBS+LCIG (n=25)
DBS+CSAI (n=20)
LCIG (n=18)
CSAI (n=12)
DBS (n=41)
DBS (n=19)
CSAI (n=1)
LCIG (n=4)
DBS+LCIG (n=2)
DBS+CSAI (n=1)
CSAI (n=1)
LCIG (n=2)
NONE (n=1)
DBS (n=1)
10 patients
Patients with
one
two
three
four
modifications of the advanced therapy
Advanced therapy used
DBS
LCIG
CSAI
First
Second
Third
advanced therapy
Fourth
Fifth
Time
First
Second
Third
Fourth
modification of the advanced therapy
B
Insufficient therapeutic efficacy (n=113)
Adverse effects - non-device-associated (n=86)
Adverse effects - device-associated (n=28)
Management problems (n=8)
Economic reasons (n=0)
Other reasons (n=16)
Reasons for modifying the advanced therapy
0
30
60
90
Number of modifications
C
Evaluation time
Before modification
After modification
Last status
Percentage of affected patients
0
20
40
60
Neuro-logical
Neuro-psychiatric
Gastro-intestinal
Device-associated
Cardio-vascular
Cutaneous
Peri-procedural
Side effect category


A
p=0.0003LMM
p=0.0004W
MDS-UPDRS Part III (points)
Pre Post
all modifications (n=79)
first modification (n=66)
second modification (n=12)
third modification (n=1)
Last status (n=72)
B
p=0.00005TT
p=0.0001TT
MDS-UPDRS Part IV (points)
all modifications (n=13)
first modification (n=11)
second modification (n=2)
Last status (n=15)
C
MDS-UPDRS Part IV - Dyskinesia (points)
all modifications (n=36)
first modification (n=25)
second modification (n=10)
third modification (n=1)
Last status (n=35)
D
p=0.0002LMM
p=0.0001W
MDS-UPDRS Part IV - Off-time (points)
all modifications (n=36)
first modification (n=25)
second modification (n=10)
third modification (n=1)
Last status (n=30)
E
Physician
Patient
Number
CGI all modifications
CGI first modification
CGI second modification
CGI third modification
CGI fourth modification


A
Difference in MDS-UPDRS Part III (points)
p=0.003LM
+DBS (n=30)
+LCIG (n=31)
+CSAI (n=13)
Added AT (all modifications)
B
Difference in MDS-UPDRS Part IV (points)
p<0.0001LM
+DBS (n=2)
+LCIG (n=10)
+CSAI (n=0)
Added AT (all modifications)
C
Difference in MDS-UPDRS IV - Dyskinesia (points)
p=0.017 LMM
p=0.005 LMM
p=0.035LM
+DBS (n=4)
+LCIG (n=21)
+CSAI (n=7)
Added AT (all modifications)
D
Difference in MDS-UPDRS IV - Off-time (points)
p<0.0001LM
p=0.008LM
+DBS (n=4)
+LCIG (n=21)
+CSAI (n=7)
Added AT (all modifications)

E
Difference in percentage of affected patients (all modifications)
Added therapy
+DBS
+LCIG
+CSAI
Peripro-cedural
Cardio-vascular
Device-associated
Cutaneous
Gastro-intestinal
Neuro-psychiatric
Neurological
Side effect category

F
Number
Physician
Patient
CGI +DBS (all modifications)
CGI +LCIG (all modifications)
CGI +CSAI (all modifications)


p<0.0001 LMM
Interval to AT modification (years)
20
15
10
5
0
DBS
(n=61)
LCIG
(n=14)
CSAI
(n=60)
AT before modification

Supplement 1: Methods

eTable 1: Data acquired by the modular questionnaire with explanations concerning data management

Questionnaire module / documented parameter	Explanation (where necessary)
A) General information about the participating center	
Number of treated PD patients per year	
Number of newly treated PD patients per year for DBS, CSAI, LCIG	
B) General information about the patient	
Year of birth	*
Gender	Male/female
Month/year of first PD symptoms	*
Month/year of PD diagnosis	*
Other diagnoses	Free answers. For statistical evaluation, answers were subsumed in umbrella terms in the gross categories internal medicine, neurological/ neuropsychiatric, surgical/ orthopedic, dermatological, urological/ gynecological, ophthalmological/ ENT (e.g. „atrial fibrillation“ was subsumed in „cardiac arrhythmias“ in „internal diagnoses“)
C) Milestone module	**Completed for each relevant modification of the AT (addition of an AT to an existing one, replacement of an AT by another one, omission of an AT; starting with the initiation of the second AT = beginning of the AT combination phase).**
Therapeutic data	**Evaluation before and after modifying the AT**
Month/year of the modification of the AT, of the evaluation point before and after the modification	*
Oral medication	LEDD calculation according to Schade et al. (2020) and Tomlinson et al. (2010)
DBS (if applicable) - Month/year of implantation - Electrode location	 * Uni-/ bilateral, STN/ GPi/ others
CSAI (if applicable) - Month/year of installation - Daily dosage, running time	 * LEDD calculation according to Schade et al. (2020) and Tomlinson et al. (2010)
LCIG (if applicable) - Month/year of installation - Morning dosage, maintainance dosage, additional boli, running time	 * LEDD calculation according to Schade et al. (2020) and Tomlinson et al. (2010)

Clinical data	**Evaluation before and after modifying the AT**
MMST and/or MoCA	For merged analysis, integration of the MoCA-results into the MMST according to Lawton et al. (2016)
(MDS-)UPDRS - Parts I, II, III, IV - Part IV – Dyskinesia - Part IV – OFF-Time	Unified Parkinson´s disease rating scale (Movement Disorder Society-sponsored revision from 2008). If only original UPDRS from 1987 available, integration into MDS-UPDRS according to Hentz et al. (2015) Points or hours Points or hours
Side effects of the therapy	Multiple free answers possible, filled into predefined gross categories: Periprocedural, device-associated, neurological, neuropsychiatric, cardiovascular, gastrointestinal, cutaneous. For statistical evaluation, answers were aggregated by umbrella terms in larger categories (see *Results* section, e.g. „syncope“ was subsumed in „orthostasis problems“ in the category „cardiovascular“). Some umbrella terms were provided as examples.
CGI (in comparison to status before the modification) - Physician´s point of view - Patient´s point of view	Numerical rating: -3: very much worse -2: much worse -1: minimally worse 0: no change 1: minimally improved 2: much improved 3: very much improved
Reasons for modifying the therapy	Multiple free answers possible, filled into predefined larger categories: Insufficient therapy efficacy, adverse effects – non-device-associated, adverse effects – device-associated, economic reasons, management problems, others. For statistical evaluation, answers were aggregated by umbrella terms in larger categories (see *Results* section, e.g. „Off-phases“ was subsumed in „fluctuations“ in the category „insufficient therapy efficacy“).
D) Final module	**Documentation of the current or latest available status („last status“)**
Therapeutic and clinical data	Identical to milestone module (CGI and reasons for modifying the therapy not included)

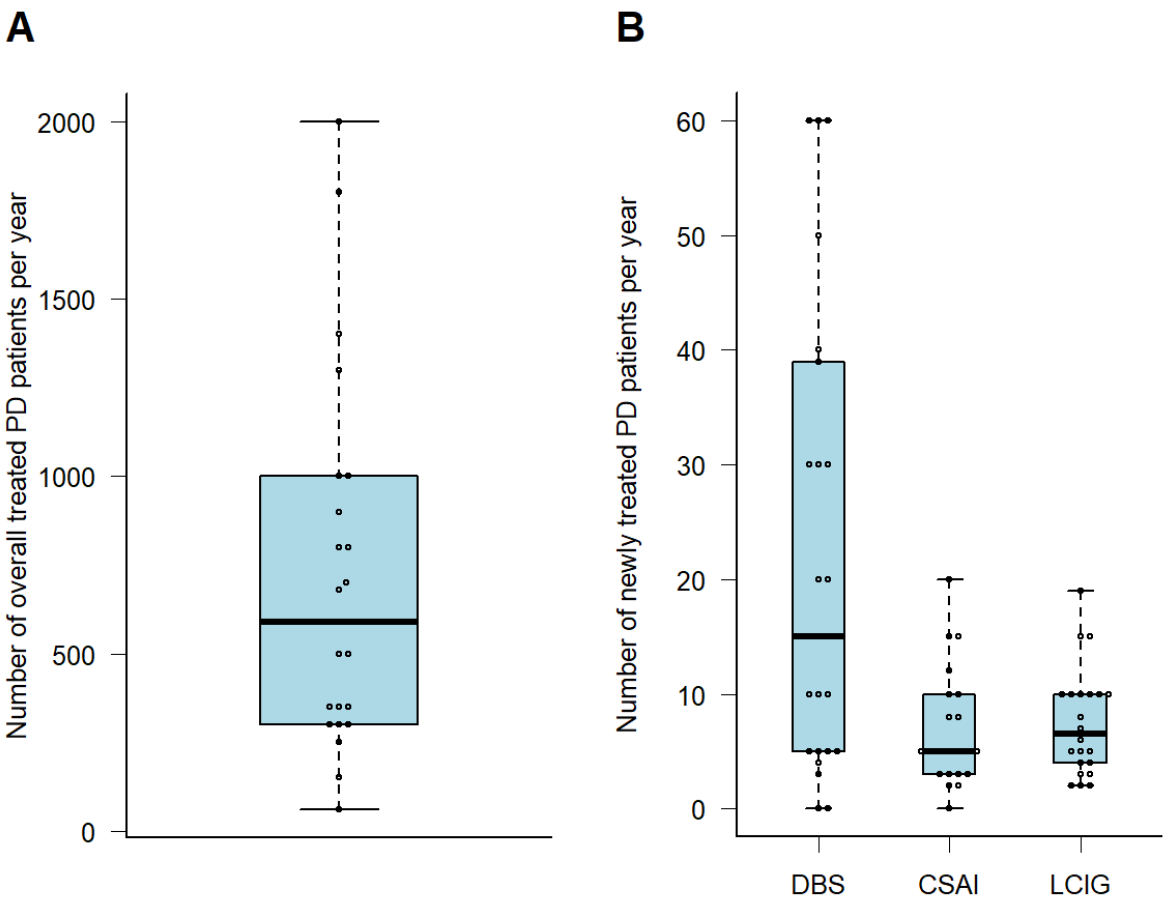
* for calculations, the first of the month (where month and year were given) or the first of January (where only the year was given) were assumed.

Ethics approvals

In addition to the lead ethics approval, granted by the Ethics Committee of the Technical University of Munich (No. 303/19S), the following ethics committees approved CAT-PD, where deemed necessary:

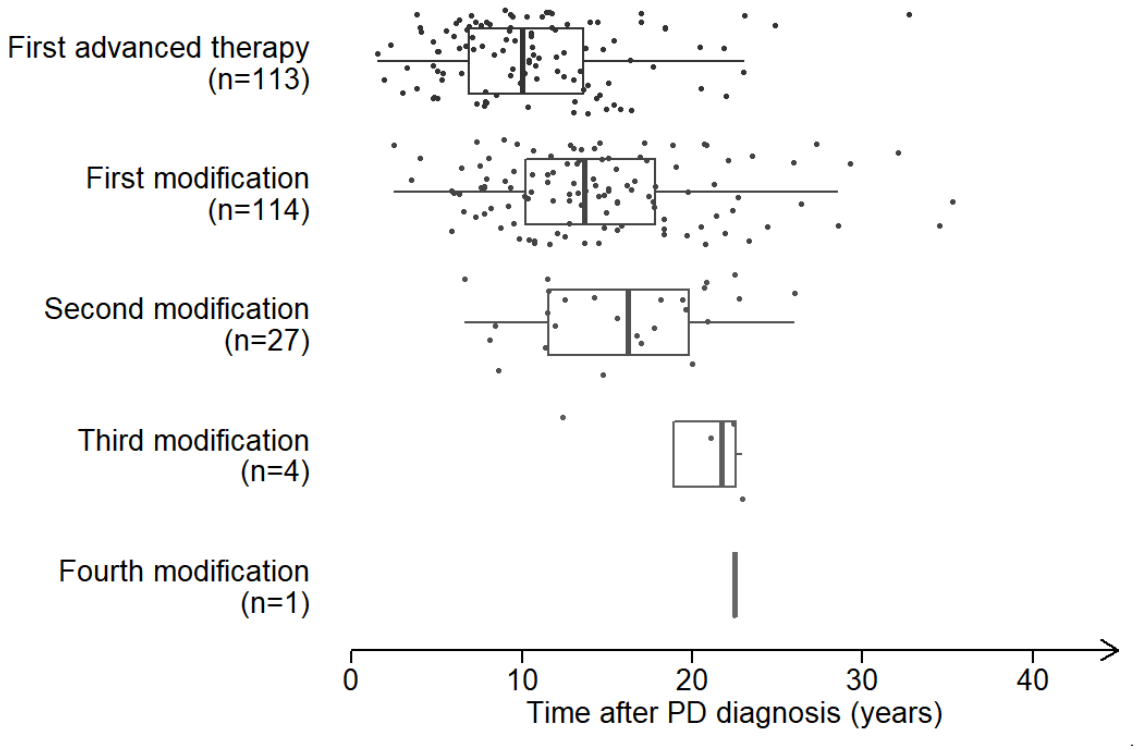
- University of Cologne (No. 20-1451)
- Technical University of Dresden (No. BO-EK-48012020)
- Ethik-Kommission der Albert-Ludwigs-Universität Freiburg (No. 20-1021)
- Christian-Albrechts-University of Kiel (No. B216/20)
- Landesärztekammer Brandenburg (No. AS 25(bB/2020)
- Ärztekammer Hamburg (No. 2021-10395-BO-bet))

Supplement 2: Results

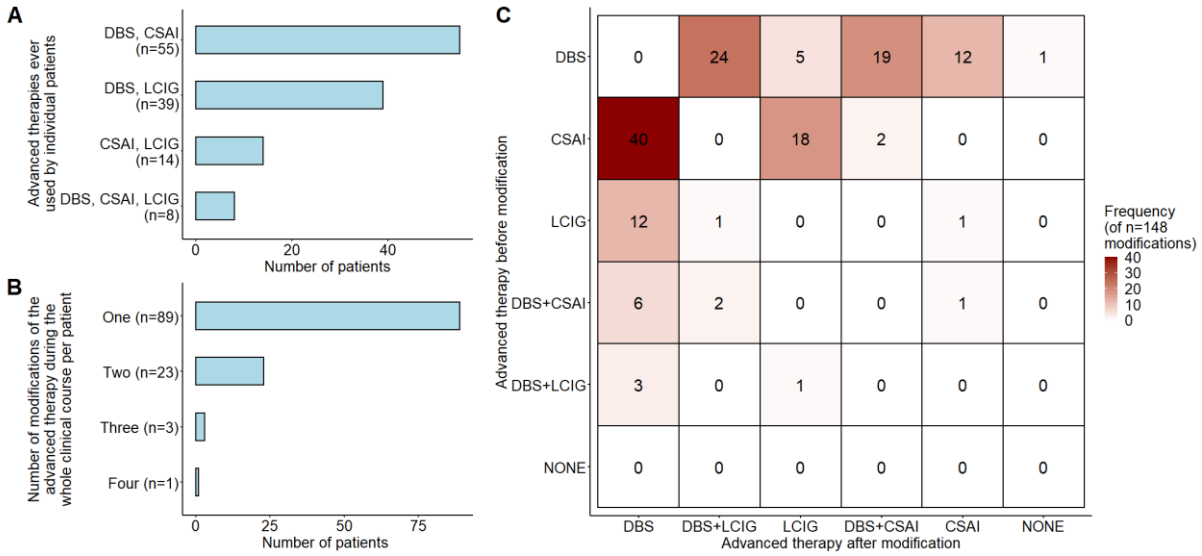


eFigure 1: Treatment indicators of the participating 22 centers

A: Number of overall treated PD patients per year. **B:** Number of patients newly treated with the respective AT per year.

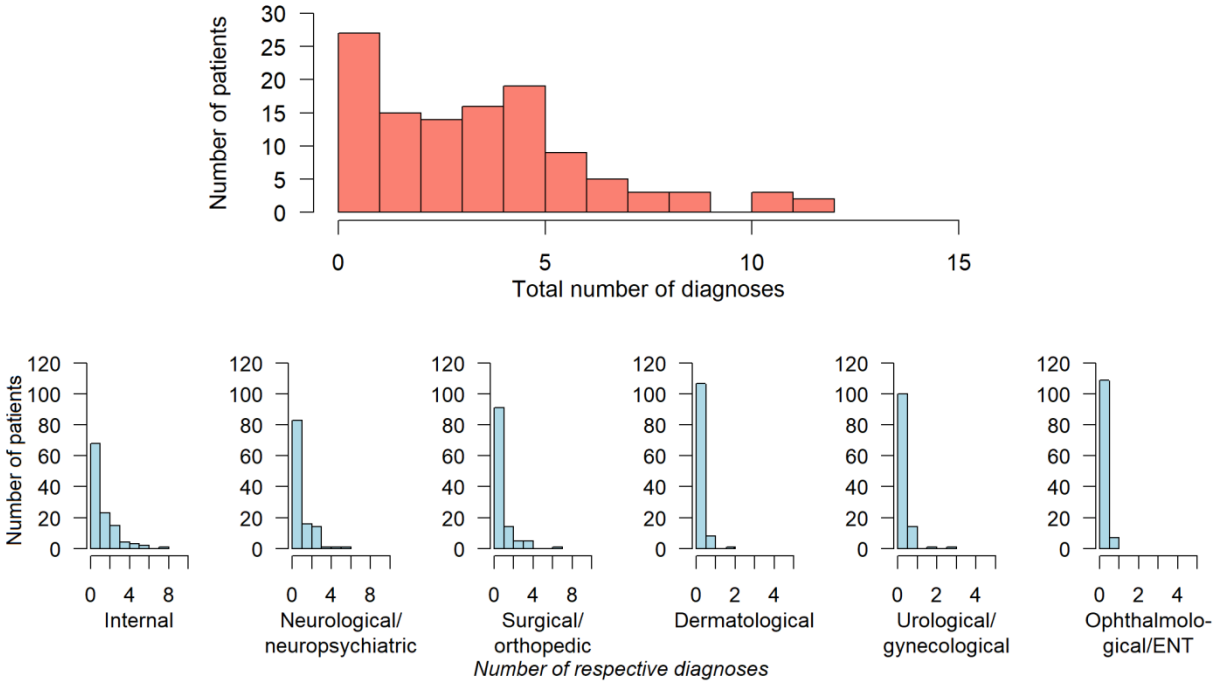


eFigure 2: Timing of AT modifications after PD diagnosis (corresponding figure to parts of *Table 1 (main manuscript)*)



eFigure 3: Detailed analysis of the 148 AT modifications shown in *Figure 2A (main manuscript)*

A: Advanced therapies ever used by individual patients. Most people used DBS and a pump therapy. The (sequential) combination of two pumps or the (sequential) usage of all three ATs were rare. **B:** Number of AT modifications during the documented clinical course. The vast majority of patients had one AT modification and thereby used two out of the three ATs. **C:** Crosstable of the frequency of the documented modifications. As the initiation of the first AT was not considered in CAT-PD, the row "NONE" is empty. The most common changes (darker red tones) 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.



eFigure 4: Number of concomitant diagnoses in all patients, ordered by main categories

The following diagnoses were mentioned in the questionnaires, summarized and counted in the main categories:

Internal: asthma, COPD, OSAS, pneumonia, cardiac arrhythmia, coronary heart disease, heart failure, myocardial infarction, myocarditis, hypertension, thromboembolism, diabetes, pancreatitis, diverticulosis, diverticulitis, rheumatological diseases, neoplasm (thyroid, lungs, heart, liver, pancreas, gut, hematological), other diseases of thyroid/ lungs/ liver/ kidney/ pancreas/ gut/ blood.

Neurological /neuropsychiatric: anxiety disorder, delirium, dementia, depression, dystonia, epilepsy, hallucinations, headache, intracranial hemorrhage, ischemic stroke, neuropathy, polyneuropathy, pain syndrome, REM-sleep behavioral disorder, restless legs syndrome.

Surgical/orthopedic: appendectomy, arthrosis, back problems (including disc surgery, spinal stenosis, scoliosis), cholecystectomy, endoprosthesis, hernia, ileus, osteoporosis, trauma.

Dermatological: allergy, neoplasm (basalioma, spinalioma, melanoma), psoriasis.

Urological/gynecological: neoplasms (bladder, breast, prostate, testicles, uterus), prostate hyperplasia.

Ophthalmological/Ear-nose-throat (ENT): Cataract, glaucoma, presbyacusis

eTable 2: Side effects stratified by modification

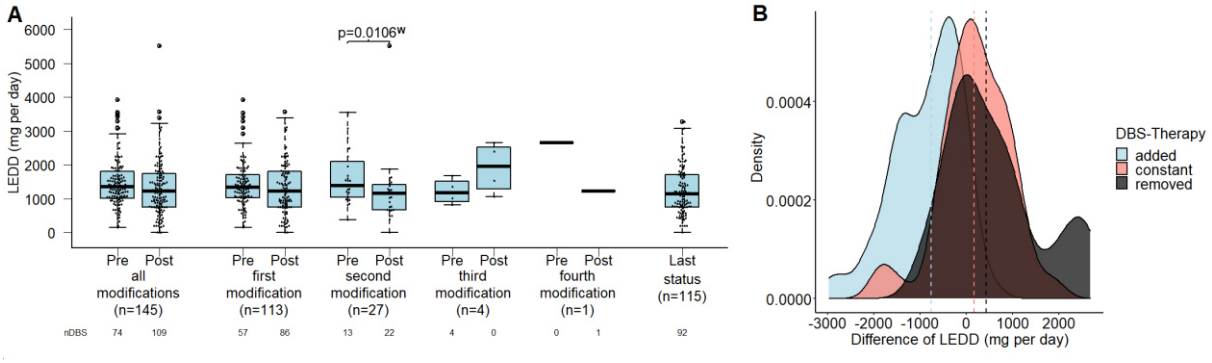
n (upper headline): Number of patients in the respective modification group / last status (reference for *percentage* calculations). *n (lower headline)*: Number of patients affected by the respective side effect group / side effect. Multiple selections per patient permitted.

	All modifications				**First modification**				**Second modification**				**Third modification**				**Fourth modification**				**Last status**	
	n=148				n=116				n=27				n=4				n=1				n=116	
	Pre		**Post**		**Pre**		**Post**		**Pre**		**Post**		**Pre**		**Post**		**Pre**		**Post**			
	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*
Neurological	**99**	***66.9***	**82**	***55.4***	**78**	***67.2***	**60**	***51.7***	**16**	***59.3***	**17**	***63.0***	**4**	***100.0***	**4**	***100.0***	**1**	***100.0***	**1**	***100.0***	**74**	***63.8***
Akathisia	0	*0.0*	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Dysarthria	14	*9.5*	14	*9.5*	10	*8.6*	11	*9.5*	3	*11.1*	2	*7.4*	1	*25.0*	1	*25.0*	0	*0.0*	0	*0.0*	13	*11.2*
Dyskinesia	36	*24.3*	25	*16.9*	24	*20.7*	15	*12.9*	8	*29.6*	8	*29.6*	4	*100.0*	2	*50.0*	0	*0.0*	0	*0.0*	27	*23.3*
Dysphagia	6	*4.1*	6	*4.1*	5	*4.3*	4	*3.4*	1	*3.7*	2	*7.4*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	5	*4.3*
Dystonia	10	*6.8*	2	*1.4*	9	*7.8*	2	*1.7*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	7	*6.0*
Epilepsy	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Propensity to falls	2	*1.4*	1	*0.7*	0	*0.0*	0	*0.0*	2	*7.4*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Freezing	22	*14.9*	9	*6.1*	19	*16.4*	8	*6.9*	3	*11.1*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	10	*8.6*
Disturbance of gait	21	*14.2*	22	*14.9*	14	*12.1*	15	*12.9*	4	*14.8*	4	*14.8*	2	*50.0*	2	*50.0*	1	*100.0*	1	*100.0*	17	*14.7*
Polyneuropathy	1	*0.7*	1	*0.7*	1	*0.9*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	3	*2.6*
Restless Legs Syndrome	1	*0.7*	1	*0.7*	1	*0.9*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	2	*1.7*
Pain	5	*3.4*	7	*4.7*	5	*4.3*	7	*6.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	5	*4.3*
Vertigo	3	*2.0*	2	*1.4*	3	*2.6*	2	*1.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Distubance of vision	0	*0.0*	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Sensory disorder	1	*0.7*	2	*1.4*	0	*0.0*	1	*0.9*	1	*3.7*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Spasticity	1	*0.7*	1	*0.7*	0	*0.0*	1	*0.9*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Falls	21	*14.2*	14	*9.5*	16	*13.8*	10	*8.6*	4	*14.8*	3	*11.1*	1	*25.0*	1	*25.0*	0	*0.0*	0	*0.0*	18	*15.5*
Therapy insufficiency	10	*6.8*	3	*2.0*	9	*7.8*	2	*1.7*	1	*3.7*	0	*0.0*	0	*0.0*	1	*25.0*	0	*0.0*	0	*0.0*	4	*3.4*
Fluctuations	62	*41.9*	25	*16.9*	51	*44.0*	13	*11.2*	7	*25.9*	8	*29.6*	3	*75.0*	3	*75.0*	1	*100.0*	1	*100.0*	22	*19.0*
Neuropsychiatric	**72**	***48.6***	**55**	***37.2***	**55**	***47.4***	**47**	***40.5***	**16**	***59.3***	**7**	***25.9***	**1**	***25.0***	**1**	***25.0***	**0**	***0.0***	**0**	***0.0***	**49**	***42.2***
Adjustment disorder	0	*0.0*	2	*1.4*	0	*0.0*	2	*1.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Fear	7	*4.7*	6	*4.1*	7	*6.0*	6	*5.2*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	7	*6.0*
Lack of drive	12	*8.1*	2	*1.4*	10	*8.6*	1	*0.9*	2	*7.4*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	3	*2.6*
Delirium	2	*1.4*	1	*0.7*	1	*0.9*	1	*0.9*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Dementia	2	*1.4*	3	*2.0*	1	*0.9*	2	*1.7*	0	*0.0*	0	*0.0*	1	*25.0*	1	*25.0*	0	*0.0*	0	*0.0*	9	*7.8*
Depression	31	*20.9*	29	*19.6*	27	*23.3*	25	*21.6*	4	*14.8*	4	*14.8*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	24	*20.7*
Desorientation	0	*0.0*	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Dopamine dysregulation syndrome	3	*2.0*	2	*1.4*	2	*1.7*	2	*1.7*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Fatigue	0	*0.0*	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Hallucinations	28	*18.9*	11	*7.4*	20	*17.2*	10	*8.6*	8	*29.6*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	11	*9.5*
Impulse control disorder	16	*10.8*	4	*2.7*	11	*9.5*	2	*1.7*	4	*14.8*	1	*3.7*	1	*25.0*	1	*25.0*	0	*0.0*	0	*0.0*	5	*4.3*
Lack of concentration	2	*1.4*	0	*0.0*	2	*1.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Mild cognitive impairment	3	*2.0*	1	*0.7*	3	*2.6*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Panic attacks	0	*0.0*	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Change of personality	3	*2.0*	0	*0.0*	1	*0.9*	0	*0.0*	2	*7.4*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*

Punding	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Sleep disturbance	8	*5.4*	4	*2.7*	7	*6.0*	3	*2.6*	1	*3.7*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	3	*2.6*
Somnolence	0	*0.0*	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Suicide	5	*3.4*	1	*0.7*	5	*4.3*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Suicidal thoughts	5	*3.4*	0	*0.0*	5	*4.3*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Suicide attempt	1	*0.7*	1	*0.7*	1	*0.9*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Drowsiness	4	*2.7*	2	*1.4*	2	*1.7*	2	*1.7*	2	*7.4*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Vivid dreams	2	*1.4*	1	*0.7*	2	*1.7*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Restlessness	2	*1.4*	2	*1.4*	1	*0.9*	2	*1.7*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	2	*1.7*
Misrecognition	0	*0.0*	3	*2.0*	0	*0.0*	3	*2.6*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Delusion	4	*2.7*	1	*0.7*	3	*2.6*	1	*0.9*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	2	*1.7*
Gastrointestinal	**25**	***16.9***	**19**	***12.8***	**20**	***17.2***	**15**	***12.9***	**4**	***14.8***	**3**	***11.1***	**1**	***25.0***	**1**	***25.0***	**0**	***0.0***	**0**	***0.0***	**17**	***14.7***
Stomach pain	2	*1.4*	3	*2.0*	1	*0.9*	2	*1.7*	1	*3.7*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	3	*2.6*
Diarrhea	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Flatulence	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Weight loss	4	*2.7*	0	*0.0*	1	*0.9*	0	*0.0*	2	*7.4*	0	*0.0*	1	*25.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Weight gain	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Colitis	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Constipation	15	*10.1*	13	*8.8*	13	*11.2*	10	*8.6*	1	*3.7*	2	*7.4*	1	*25.0*	1	*25.0*	0	*0.0*	0	*0.0*	12	*10.3*
Esophageal hernia	0	*0.0*	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Pseudohypersalivation	2	*1.4*	1	*0.7*	2	*1.7*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Reflux	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Sodburn	1	*0.7*	1	*0.7*	1	*0.9*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Nausea	5	*3.4*	0	*0.0*	4	*3.4*	0	*0.0*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	2	*1.7*
Device-associated	**17**	***11.5***	**15**	***10.1***	**13**	***11.2***	**14**	***12.1***	**3**	***11.1***	**1**	***3.7***	**1**	***25.0***	**0**	***0.0***	**0**	***0.0***	**0**	***0.0***	**17**	***14.7***
Battery exhaustion DBS	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Abdominal pain	1	*0.7*	1	*0.7*	0	*0.0*	1	*0.9*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Burried Bumper	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Electrode malfunction	1	*0.7*	1	*0.7*	1	*0.9*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Electrode dislocation	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Misplacement of electrode	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Electrode infection	3	*2.0*	0	*0.0*	3	*2.6*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Problems with handling	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Intracranial hemorrhage	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Breakage of DBS cable	0	*0.0*	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Lack of subcutaneous fat	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Malfunction of DBS impulse generator	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Dislocation of DBS impulse generator	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Hematoma around DBS impulse generator	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Infection of DBS impulse generator	5	*3.4*	0	*0.0*	4	*3.4*	0	*0.0*	0	*0.0*	0	*0.0*	1	*25.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Allergical reaction due to DBS impulse generator	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
PEJ-Dislocation	2	*1.4*	4	*2.7*	1	*0.9*	4	*3.4*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	6	*5.2*
PEJ-Infection	2	*1.4*	5	*3.4*	1	*0.9*	4	*3.4*	1	*3.7*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	4	*3.4*
PEJ-Malfunction	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	4	*3.4*
Pneumonia	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*

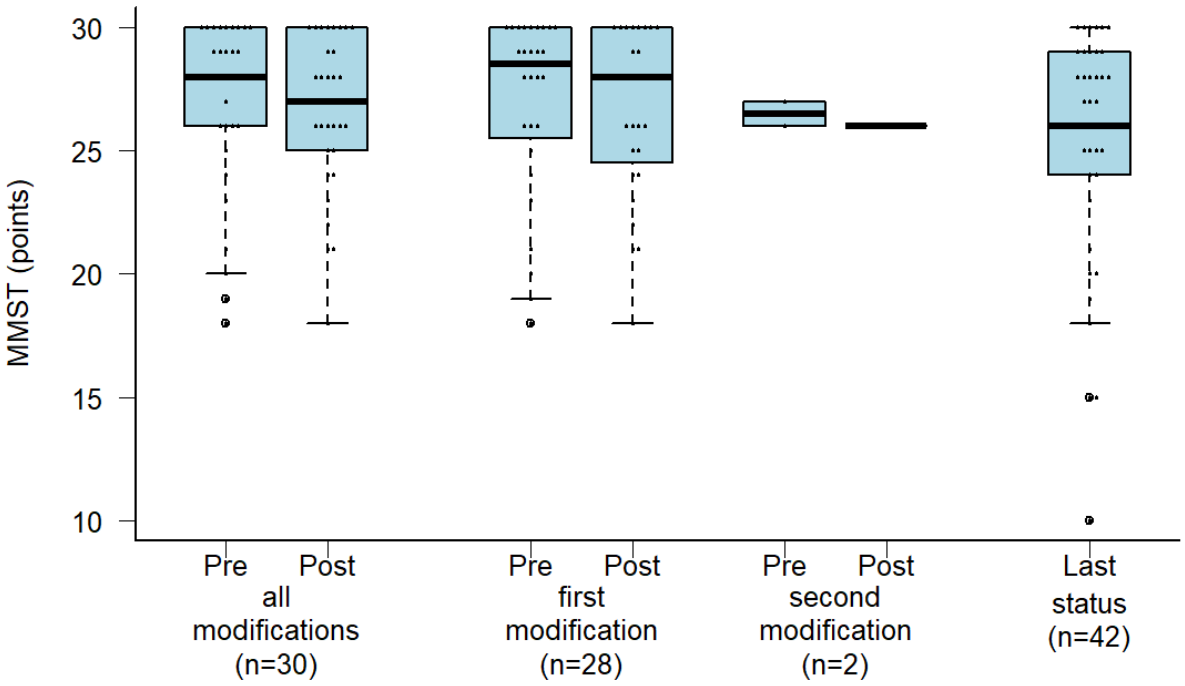
Pump malfunction	2	*1.4*	2	*1.4*	1	*0.9*	2	*1.7*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Hypergranulation around PEJ-insertion	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Disorder of wound healing	1	*0.7*	1	*0.7*	1	*0.9*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Cardiovascular	**15**	***10.1***	**13**	***8.8***	**12**	***10.3***	**11**	***9.5***	**3**	***11.1***	**2**	***7.4***	**0**	***0.0***	**0**	***0.0***	**0**	***0.0***	**0**	***0.0***	**9**	***7.8***
Cardiac disease	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Hypotension	4	*2.7*	4	*2.7*	3	*2.6*	3	*2.6*	1	*3.7*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	2	*1.7*
Dyspnea	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Myocardial infarction	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Edema	0	*0.0*	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Orthostatic problems	13	*8.8*	10	*6.8*	10	*8.6*	8	*6.9*	3	*11.1*	2	*7.4*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	8	*6.9*
Cardiac arrhythmia	1	*0.7*	1	*0.7*	1	*0.9*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Cutaneous	**12**	***8.1***	**5**	***3.4***	**11**	***9.5***	**5**	***4.3***	**1**	***3.7***	**0**	***0.0***	**0**	***0.0***	**0**	***0.0***	**0**	***0.0***	**0**	***0.0***	**8**	***6.9***
Abdominal wall induration	4	*2.7*	1	*0.7*	3	*2.6*	1	*0.9*	1	*3.7*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Dermatitis	1	*0.7*	0	*0.0*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Erythema	2	*1.4*	3	*2.0*	2	*1.7*	3	*2.6*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	6	*5.2*
Skin nodules	7	*4.7*	0	*0.0*	7	*6.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Skin necrosis	2	*1.4*	1	*0.7*	2	*1.7*	1	*0.9*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Hypergranulation	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Infection	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	1	*0.9*
Phlegmone	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Periprocedural			**21**	***14.2***			**19**	***16.4***			**1**	***3.7***			**1**	***25.0***			**0**	***0.0***		
Abscess			0	*0.0*			0	*0.0*			0	*0.0*			0	*0.0*			0	*0.0*		
Bleeding			4	*2.7*			4	*3.4*			0	*0.0*			0	*0.0*			0	*0.0*		
Malpuncture			3	*2.0*			2	*1.7*			0	*0.0*			1	*25.0*			0	*0.0*		
Peritonitis			0	*0.0*			0	*0.0*			0	*0.0*			0	*0.0*			0	*0.0*		
Phlegmone			0	*0.0*			0	*0.0*			0	*0.0*			0	*0.0*			0	*0.0*		
Pneumonia			1	*0.7*			1	*0.9*			0	*0.0*			0	*0.0*			0	*0.0*		
Pneumoperitoneum			0	*0.0*			0	*0.0*			0	*0.0*			0	*0.0*			0	*0.0*		
Pain			2	*1.4*			2	*1.7*			0	*0.0*			0	*0.0*			0	*0.0*		
Disorder of wound healing			4	*2.7*			4	*3.4*			0	*0.0*			0	*0.0*			0	*0.0*		
Wound infection			5	*3.4*			4	*3.4*			1	*3.7*			0	*0.0*			0	*0.0*		

PEJ: percutaneous endoscopic jejunostomy



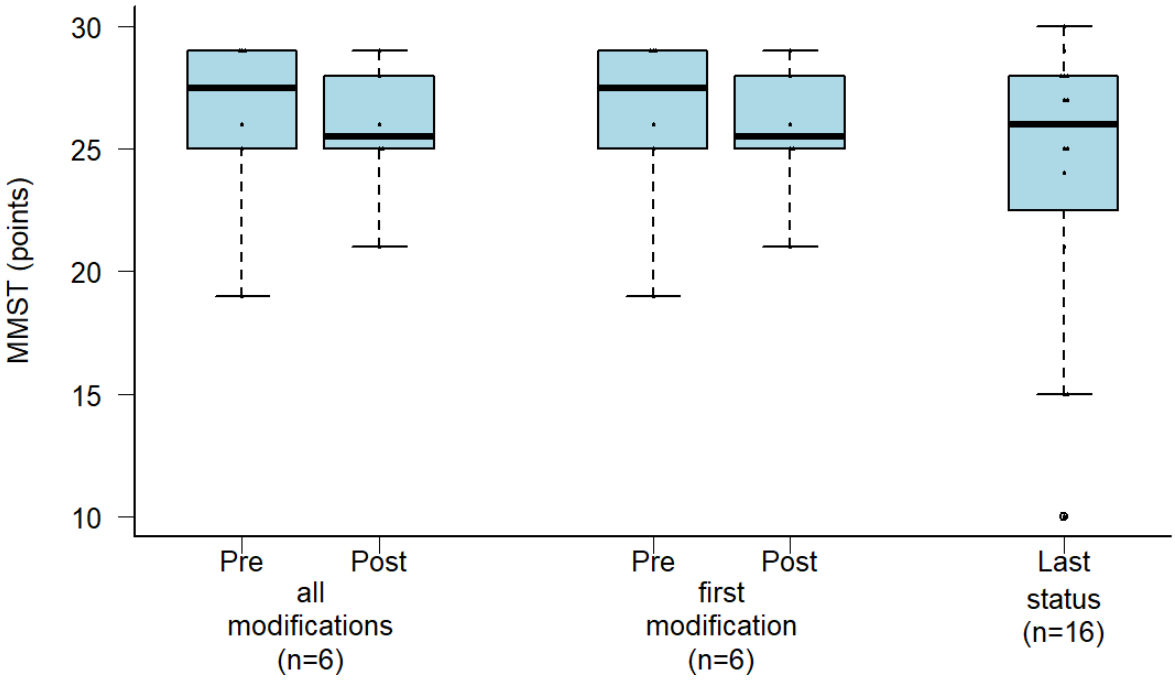
eFigure 5: Analysis of the Levodopa-equivalent daily dosage (LEDD) of oral medication and ATs

A: LEDD of oral medication and ATs, if applicable (CSAI and LCIG) before and after the individual AT modifications. *W*: Significant in Wilcoxon signed rank test. *nDBS:* Number of patients with DBS. **B:** Difference of LEDD (after versus before the respective modification) displayed in a density plot, stratified by modifications in DBS therapy. As expected, the LEDD decreased or increased in case of DBS addition or removal, and was nearly constant, when DBS status remained unchanged. Dashed lines show the respective median: -765 mg/d in "added DBS" group, +427.5 mg/d in "removed DBS" group, +167.2 mg/d in "constant DBS" group. Cumulative data for all AT modifications in the whole sample is shown.



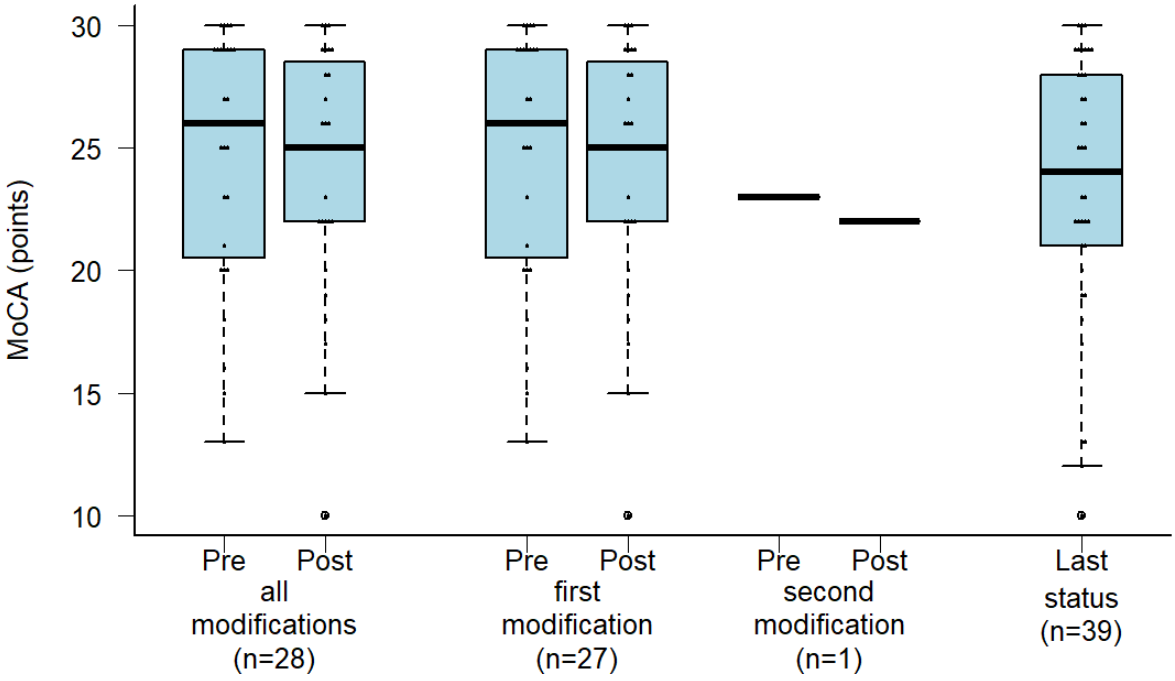
eFigure 6: Mini-Mental Status Test (MMST) for AT modifications and the last status

In contrast to *eFigure 7*, MoCA data is included in this figure, see *Methods* section. *n:* Number of pairwise available data (whole sample). No data was available for the third and fourth modification.



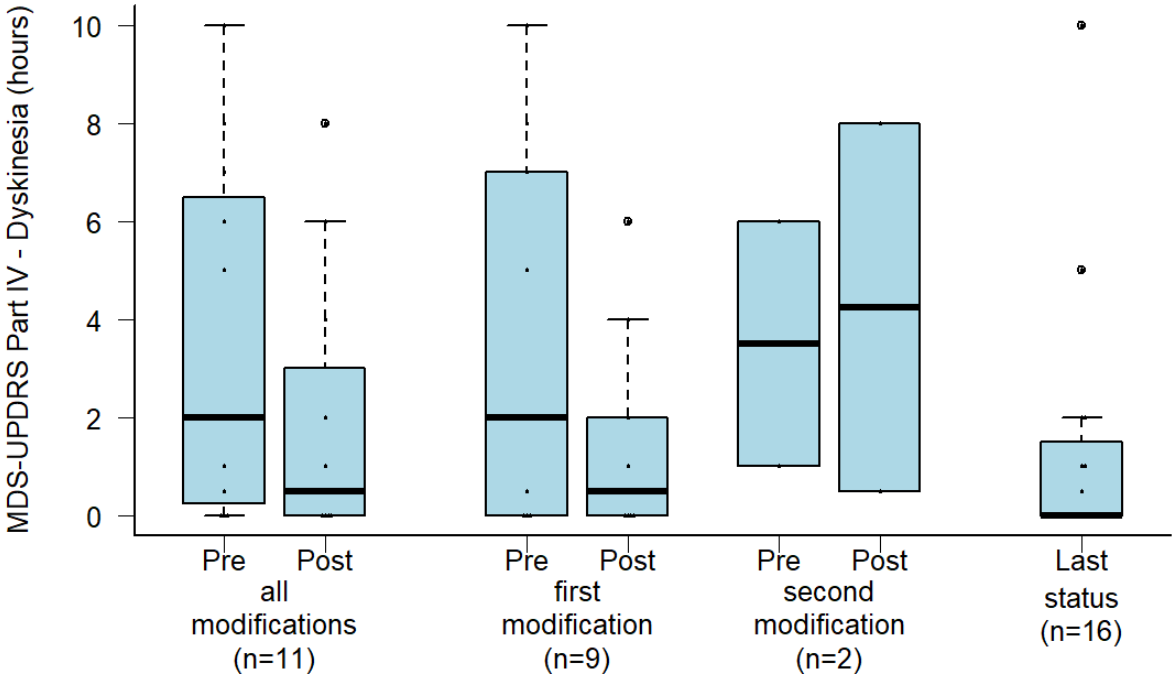
eFigure 7: Mini-Mental Status Test (MMST) for AT modifications and the last status

In contrast to *eFigure 6*, MoCA data is not included in this figure. *n:* Number of pairwise available data (whole sample). No data was available for the second, third and fourth modification.



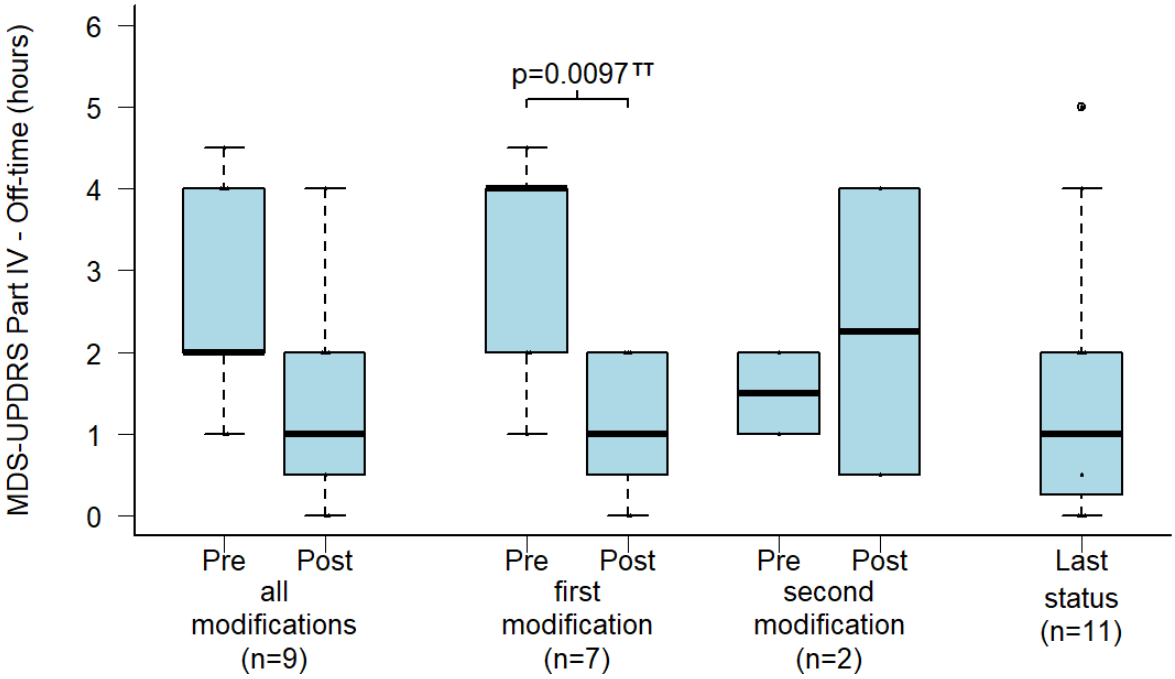
eFigure 8: Montréal Cognitive Assessment (MoCA) for AT modifications and the last status

This data was integrated into the MMST data for *eFigure 6*, see *Methods* section. *n:* Number of pairwise available data (whole sample). No data was available for the third and fourth modification.



eFigure 9: Time (hours) with troublesome dyskinesia for the modifications and the last status (MDS-UPDRS Item 4.1, see also *Figure 3C (main manuscript)* for score in points)

n: Number of pairwise available data (whole sample). No data was available for the third and fourth modification.



eFigure 10: Off-time (hours) for AT modifications and the last status (MDS-UPDRS Item 4.3, see also *Figure 3D (main manuscript)* for score in points)

n: Number of pairwise available data (whole sample). No data was available for the third and fourth modification. *TT*: Significant in paired t-test.

eTable 3: LEDD, clinical scores and their differences before and after the AT modifications and at the last documented status

Median ([Range]; number; corresponding data to *Figure 3 (main manuscript)* and *eFigures 5* to *10*. Only pairwise per patient available data considered for the whole sample (in contrast to *eTable 4*). For difference calculations, in a first step the difference of the respective parameter was calculated individually per patient. In a second step, medians and ranges of these individually calculated results were calculated. Due to this patient- and stepwise calculation procedure, the medians of the differences (row "Difference") do not always match the difference of medians between the "Pre"- and "Post"-row (that result from cumulated data). n/a: not available.

		LEDD (mg per day)	MMST (points)	MoCA (points)	MMST including MoCA (points)	MDS-UPDRS Part III (points)	MDS-UPDRS Part IV (points)	MDS-UPDRS Part IV - Dyskinesia (hours)	MDS-UPDRS Part IV - Dyskinesia (points)	MDS-UPDRS Part IV - Off-time (hours)	MDS-UPDRS Part IV - Off-time (points)	CGI - Physician	CGI - Patient
All Modifi-cations (n=148)	Pre	1,350.0 ([150.0 - 3927.0]; n=145)	27.5 ([19.0 - 29.0]; n=6)	26.0 ([13.0 - 30.0]; n=28)	28.0 ([18.0 - 30.0]; n=30)	31.0 ([10.0 - 82.0]; n=79)	10.0 ([5.0 - 18.0]; n=13)	2.0 ([0.0 - 10.0]; n=11)	1.0 ([0.0 - 3.0]; n=36)	2.0 ([1.0 - 4.5]; n=9)	2.0 ([0.0 - 4.0]; n=36)	-	-
	Post	1,215.6 ([0.0 - 5,511,1]; n=145)	25.5 ([21.0 - 29.0]; n=6)	25.0 ([10.0 - 30.0]; n=28)	27.0 ([18.0 - 30.0]; n=30)	28.0 ([9.0 - 80.0]; n=79)	6.0 ([1.0 - 7.0]; n=13)	0.5 ([0.0 - 8.0]; n=11)	1.0 ([0.0 - 2.0]; n=36)	1.0 ([0.0 - 4.0]; n=9)	1.0 ([0.0 - 3.0]; n=36)	2.0 ([-3.0 - 3.0]; n=136)	2.0 ([-2.0 - 3.0]; n=126)
	Diffe-rence	-100.0 ([-2,980.0 - 2,685.0]; n=148)	-0.5 ([-3.0 - 2.0]; n=6)	0.0 ([-12.0 - 6.0]; n=28)	0.0 ([-8.0 - 8.0]; n=30)	-4.0 ([-49.0 - 26.0]; n=79)	-6.0 ([-11.0 - 1.0]; n=13)	-0.5 ([-6.5 - 2.0]; n=11)	0.0 ([-3.0 - 2.0]; n=36)	-2.0 ([-4.5 - 2.0]; n=9)	-1.0 ([-3.0 - 1.0]; n=36)	-	-
First modi-fication (n=116)	Pre	1,340.0 ([150.0 - 3,927.0]; n=113)	27.5 ([19.0 - 29.0]; n=6)	26.0 ([13.0 - 30.0]; n=27)	28.5 ([18.0 - 30.0]; n=28)	31.0 ([10.0 - 82.0]; n=66)	10.0 ([5.0 - 18.0]; n=11)	2.0 ([0.0 - 10.0]; n=9)	1.0 ([0.0 - 3.0]; n=25)	4.0 ([1.0 - 4.5]; n=7)	2.0 ([0.0 - 4.0]; n=25)	-	-
	Post	1,230.0 ([0.0 - 3,555.0]; n=113)	25.5 ([21.0 - 29.0]; n=6)	25.0 ([10.0 - 30.0]; n=27)	28.0 ([18.0 - 30.0]; n=28)	26.5 ([9.0 - 80.0]; n=66)	4.0 ([1.0 - 7.0]; n=11)	0.5 ([0.0 - 6.0]; n=9)	1.0 ([0.0 - 2.0]; n=25)	1.0 ([0.0 - 2.0]; n=7)	1.0 ([0.0 - 3.0]; n=25)	2.0 ([-3.0 - 3.0]; n=105)	2.0 ([-2.0 - 3.0]; n=101)
	Diffe-rence	-85.5 ([-2,671.0 - 2,685.0]; n=113)	-0.5 ([-3.0 - 2.0]; n=6)	0.0 ([-12.0 - 6.0]; n=27)	0.0 ([-8.0 - 8.0]; n=28)	-6.0 ([-49.0 - 26.0]; n=66)	-6.0 ([11.0 - 1.0]; n=11)	-2.0 ([-6.5 - 0.5]; n=9)	0.0 ([-2.0 - 2.0]; n=25)	-2.0 ([-4.5 - 0.0]; n=7)	-1.0 ([-3.0 - 0.0]; n=25)	-	-
Second modi-fication (n=27)	Pre	1,388.3 ([375.0 - 3,545.0]; n=27)	n/a	23.0 (n=1)	26.5 ([26.0 - 27.0]; n=2)	30.0 ([14.0 - 59.0]; n=12)	10.5 ([8.0 - 13.0]; n=2)	3.5 ([1.0 - 6.0]; n=2)	2.5 ([1.0 - 3.0]; n=10)	1.5 ([1.0 - 2.0]; n=2)	1.0 ([1.0 - 3.0]; n=10)	-	-
	Post	1,150.0 ([0.0 - 5,511.1]; n=27)	n/a	22.0 (n=1)	26.0 ([26.0 - 26.0]; n=2)	37.0 ([14.0 - 50.0]; n=12)	7.0 ([7.0 - 7.0]; n=2)	4.3 ([0.5 - 8.0]; n=2)	1.0 ([0.0 - 2.0]; n=10)	2.3 ([0.5 - 4.0]; n=2)	1.5 ([0.0 - 3.0]; n=10)	1.0 ([-2.0 - 3.0]; n=26)	2.0 ([-2.0 - 3.0]; n=23)
	Diffe-rence	-215.0 ([-2,980.0 - 1,966.1]; n=27)	n/a	-1.0 (n=1)	-0.5 ([-1.0 - 0.0]; n=2)	0.5 ([-20.0 - 10.0]; n=12)	-3.5 ([-6.0 - 1.0]; n=2)	0.8 ([-0.5 - 2.0]; n=2)	-1.0 ([-3.0 - 1.0]; n=10)	0.8 ([-0.5 - 2.0]; n=2)	0.0 ([-1.0 - 1.0]; n=10)	-	-
Third modi-fication (n=4)	Pre	1,182.0 ([812.5 - 1671.1]; n=4)	n/a	n/a	n/a	50.0 (n=1)	n/a	n/a	1.0 (n=1)	n/a	1.0 (n=1)	-	-
	Post	1,960.0 ([1,064.0 - 2,655.0]; n=4)	n/a	n/a	n/a	39.0 (n=1)	n/a	n/a	1.0 (n=1)	n/a	1.0 (n=1)	0.0 ([0.0 - 2.0]; n=4)	1.0 ([0.0 - 2.0]; n=2)
	Diffe-rence	546.7 ([-144.4 - 1,842.5]; n=4)	n/a	n/a	n/a	-11.0 (n=1)	n/a	n/a	0.0 (n=1)	n/a	0.0 (n=1)	-	-
Fourth modi-fication (n=1)	Pre	2,655.0 (n=1)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	-	-
	Post	1,225.0 (n=1)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.0 (n=1)	n/a
	Diffe-rence	-1,430.0 (n=1)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	-	-
Last status (n=116)		1,140.0 ([0.0 - 3,266.7]; n=115)	26.0 ([10.0 - 30.0]; n=16)	24.0 ([10.0 - 30.0]; n=39)	26.0 ([10.0 - 30.0]; n=42)	30.0 ([8.0 - 80.0]; n=72)	5.0 ([0.0 - 19.0]; n=15)	0.0 ([0.0 - 10.0]; n=16)	1.0 ([0.0 - 3.0]; n=35)	1.0 ([0.0 - 5.0]; n=11)	1.0 ([0.0 - 4.0]; n=30)	-	-

eTable 4: LEDD and clinical scores before and after the modifications and at the last status.

Median ([Range]; number. All available data considered (in contrast to *eTable 3*, where only pairwise data is considered). n/a: not available.

		LEDD (mg per day)	MMST (points)	MoCA (points)	MMST including MoCA (points)	MDS-UPDRS Part III (points)	MDS-UPDRS Part IV (points)	MDS-UPDRS Part IV - Dyskinesia (hours)	MDS-UPDRS Part IV - Dyskinesia (points)	MDS-UPDRS Part IV - Off-time (hours)	MDS-UPDRS Part IV - Off-time (points)	CGI - Physician	CGI - Patient
All modifications (n=148)	Pre	1,345.0 ([150.0 - 3927.0]; n=146)	26.0 ([18.0 - 30.0]; n=22)	25.0 ([5.0 - 30.0]; n=54)	28.0 ([13.0 - 30.0]; n=63)	31.0 ([8.0 - 82.0]; n=105)	10.0 ([5.0 - 18.0]; n=17)	1.5 ([0.0 - 12.0]; n=18)	1.0 ([0.0 - 3.0]; n=41)	2.0 ([0.0 - 4.5]; n=12)	2.0 ([0.0 - 4.0]; n=41)	-	-
	Post	1,212.8 ([0.0 - 5,511,1]; n=146)	25.5 ([21.0 - 30.0]; n=10)	25.0 ([10.0 - 30.0]; n=39)	26.0 ([18.0 - 30.0]; n=41)	28.0 ([7.0 - 80.0]; n=89)	5.0 ([0.0 - 14.0]; n=16)	0.0 ([0.0 - 8.0]; n=18)	1.0 ([0.0 - 2.0]; n=45)	0.8 ([0.0 - 4.0]; n=14)	1.0 ([0.0 - 3.0]; n=43)	2.0 ([-3.0 - 3.0]; n=136)	2.0 ([-2.0 - 3.0]; n=126)
First modification (n=116)	Pre	1,335.0 ([150.0 - 3,927.0]; n=114)	26.0 ([18.0 - 30.0]; n=21)	25.0 ([13.0 - 30.0]; n=50)	28.0 ([18.0 - 30.0]; n=58)	31.0 ([8.0 - 82.0]; n=87)	10.0 ([5.0 - 18.0]; n=15)	1.0 ([0.0 - 12.0]; n=15)	1.0 ([0.0 - 3.0]; n=30)	2.0 ([0.0 - 4.5]; n=9)	2.0 ([0.0 - 4.0]; n=30)	-	-
	Post	1,222.8 ([0.0 - 3,555.0]; n=114)	26.5 ([21.0 - 30.0]; n=10)	25.0 ([10.0 - 30.0]; n=33)	28.0 ([18.0 - 30.0]; n=35)	27.0 ([7.0 - 80.0]; n=73)	4.0 ([0.0 - 14.0]; n=13)	0.0 ([0.0 - 6.0]; n=16)	1.0 ([0.0 - 2.0]; n=34)	0.5 ([0.0 - 4.0]; n=12)	1.0 ([0.0 - 3.0]; n=32)	2.0 ([-3.0 - 3.0]; n=105)	2.0 ([-2.0 - 3.0]; n=101)
Second modification (n=27)	Pre	1,388.3 ([375.0 - 3,545.0]; n=27)	27.0 (n=1)	19.5 ([5.0 - 30.0]; n=4)	26.0 ([13.0 - 30.0]; n=5)	33.0 ([14.0 - 59.0]; n=17)	10.5 ([8.0 - 13.0]; n=2)	6.0 ([1.0 - 9.0]; n=3)	2.5 ([1.0 - 3.0]; n=10)	2.0 ([1.0 - 3.0]; n=3)	1.0 ([1.0 - 3.0]; n=10)	-	-
	Post	1,150.0 ([0.0 - 5,511.1]; n=27)	n/a	23.0 ([22.0 - 26.0]; n=5)	26.0 ([26.0 - 28.0]; n=5)	31.0 ([14.0 - 50.0]; n=15)	7.0 ([4.0 - 7.0]; n=3)	4.3 ([0.5 - 8.0]; n=2)	1.0 ([0.0 - 2.0]; n=10)	2.3 ([0.5 - 4.0]; n=2)	1.5 ([0.0 - 3.0]; n=10)	1.0 ([-2.0 - 3.0]; n=26)	2.0 ([-2.0 - 3.0]; n=23)
Third modification (n=4)	Pre	1,182.0 ([812.5 - 1671.1]; n=4)	n/a	n/a	n/a	50.0 (n=1)	n/a	n/a	1.0 (n=1)	n/a	1.0 (n=1)	-	-
	Post	1,960.0 ([1,064.0 - 2,655.0]; n=4)	n/a	22.0 (n=1)	26.0 (n=1)	39.0 (n=1)	n/a	n/a	1.0 (n=1)	n/a	1.0 (n=1)	0.0 ([0.0 - 2.0]; n=4)	1.0 ([0.0 - 2.0]; n=2)
Fourth modification (n=1)	Pre	2,655.0 (n=1)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	-	-
	Post	1,225.0 (n=1)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.0 (n=1)	n/a
Last status (n=116)		1,140.0 ([0.0 - 3,266.7]; n=115)	26.0 ([10.0 - 30.0]; n=16)	24.0 ([10.0 - 30.0]; n=39)	26.0 ([10.0 - 30.0]; n=42)	30.0 ([8.0 - 80.0]; n=72)	5.0 ([0.0 - 19.0]; n=15)	0.0 ([0.0 - 10.0]; n=16)	1.0 ([0.0 - 3.0]; n=35)	1.0 ([0.0 - 5.0]; n=11)	1.0 ([0.0 - 4.0]; n=30)	-	-

eTable 5: Clinical scores, stratified by added AT subgroup, before and after the AT modifications (corresponding data to *Figure 4A-D and F (main manuscript)*)

Median ([Range]; number. Only pairwise data of all available modifications considered, independent of subsequent simultaneous or sequential AT continuation. For difference calculations, in a first step the difference of the respective parameter was calculated individually per patient. In a second step, medians and ranges of these individually calculated results were calculated. Due to this patient- and stepwise calculation procedure, the medians of the differences (line "Difference") do not always match the difference of medians between the "Pre"- and "Post"-row (that result from cumulated data). n/a: not available.

		MDS-UPDRS Part III (points)	MDS-UPDRS Part IV (points)	MDS-UPDRS Part IV - Dyskinesia (points)	MDS-UPDRS Part IV - Off-time (points)	CGI - Physician	CGI - Patient
DBS added (all modifications)	Pre	26.0 ([12.0 - 64.0]; n=30)	11.5 ([5.0 - 18.0]; n=2)	3.0 ([2.0 - 3.0]; n=4)	1.5 ([1.0 - 3.0]; n=4)	-	-
	Post	25.5 ([9.0 - 55.0]; n=30)	6.5 ([6.0 - 7.0]; n=2)	1.0 ([0.0 - 2.0]; n=4)	1.5 ([1.0 - 2.0]; n=4)	2.0 ([0.0 - 3.0]; n=49)	2.0 ([-1.0 - 3.0]; n=46)
	Difference	-3.5 ([-22.0 - 19.0]; n=30)	-5.0 ([-11.0 - 1.0]; n=2)	-1.5 ([-3.0 to -1.0]; n=4)	0.0 ([-1.0 - 0.0]; n=4)	-	-
LCIG added (all modifications)	Pre	41.0 ([10.0 - 74.0]; n=31)	10.0 ([5.0 to -13.0]; n=10)	1.0 ([0.0 - 3.0]; n=21)	2.0 ([0.0 - 4.0]; n=21)	-	-
	Post	29.0 ([10.0 - 80.0]; n=31)	4.0 ([1.0 to -7.0]; n=10)	1.0 ([0.0 - 2.0]; n=21)	1.0 ([0.0 - 2.0]; n=21)	2.0 ([-3.0 - 3.0]; n=45)	2.0 ([-2.0 - 3.0]; n=42)
	Difference	-10.0 ([-45.0 - 26.0]; n=31)	-6.0 ([-7.0 to -3.0]; n=10)	0.0 ([-2.0 - 2.0]; n=21)	-1.0 ([-3.0 - 1.0]; n=21)	-	-
CSAI added (all modifications)	Pre	31.0 ([14.0 - 82.0]; n=13)	n/a	2.0 ([0.0 - 3.0]; n=7)	2.0 ([0.0 - 4.0]; n=7)	-	-
	Post	29.0 ([14.0 - 37.0]; n=13)	n/a	1.0 ([1.0 - 2.0]; n=7)	1.0 ([0.0 - 3.0]; n=7)	1.0 ([-2.0 - 3.0]; n=30)	2.0 ([-2.0 - 3.0]; n=28)
	Difference	-4.0 ([-49.0 - 14.0]; n=13)	n/a	-1.0 ([-1.0 - 1.0]; n=7)	-1.0 ([-1.0 - 0.0]; n=7)	-	-

eTable 6: Patients affected by side effect groups, stratified by added AT subgroup, before and after the AT modifications (corresponding data to *Figure 4E (main manuscript)*)

n (upper headline): Number of patients in the respective therapy modification group (reference for *percentage* calculations). *n (lower headline)*: Number of patients affected by the respective side effect group. Multiple selections per patient permitted.

	DBS added						**LCIG added**						**CSAI added**					
	n=53						n=49						n=34					
	Pre		**Post**		**Difference**		**Pre**		**Post**		**Difference**		**Pre**		**Post**		**Difference**	
	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*	n	*Percentage*
Neurological	35	*66.0*	24	*45.3*	-11	*-20.8*	32	*65.3*	30	*61.2*	-2	*-4.1*	25	*73.5*	20	*58.8*	-5	*-14.7*
Neuropsychiatric	14	*26.4*	14	*26.4*	0	*0.0*	37	*75.5*	26	*53.1*	-11	*-22.4*	14	*41.2*	12	*35.3*	-2	*-5.9*
Gastrointestinal	3	*5.7*	1	*1.9*	-2	*-3.8*	16	*32.7*	14	*28.6*	-2	*-4.1*	4	*11.8*	1	*2.9*	-3	*-8.8*
Deviceassociated	5	*9.4*	2	*3.8*	-3	*-5.7*	4	*8.2*	11	*22.4*	7	*14.3*	6	*17.6*	2	*5.9*	-4	*-11.8*
Cardiovascular	4	*7.5*	1	*1.9*	-3	*-5.7*	10	*20.4*	10	*20.4*	0	*0.0*	1	*2.9*	2	*5.9*	1	*2.9*
Cutaneous	8	*15.1*	0	*0.0*	-8	*-15.1*	4	*8.2*	4	*8.2*	0	*0.0*	0	*0.0*	1	*2.9*	1	*2.9*
Periprocedural			7	*13.2*	7	*13.2*			13	*26.5*	13	*26.5*			1	*2.9*	1	*2.9*

<u>Supplement 3: Study questionnaire</u>
(German original version)

Klinikum rechts der Isar

Technische Universität München

Klinikum rechts der Isar
Anstalt des öffentlichen Rechts

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Fragebogen zur retrospektiven Studie mit dem Titel

„Combinations of Advanced Therapies in Parkinson´s Disease (CAT-PD)"

der neurologischen Klinik und Poliklinik des Klinikums rechts der Isar der Technischen Universität München

Fragebogen-ID: _____

Klinikum rechts der Isar
Technische Universität München

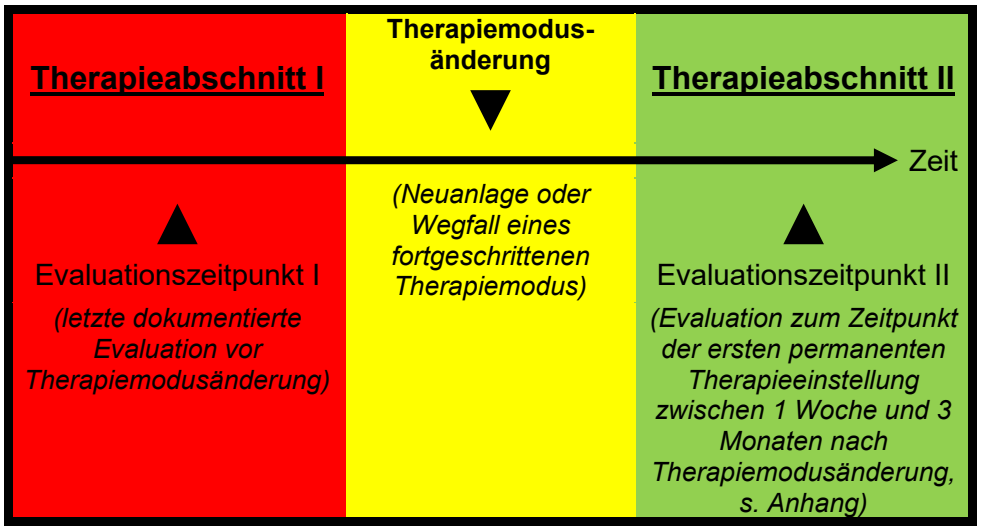
Allgemeine Informationen zum Fragebogen

Grundkonzept der Studie

Klinische und therapeutische Daten zu Patienten mit idiopathischem Parkinson-Syndrom (IPS), die im Laufe ihrer Erkrankung mit **mindestens zwei** fortgeschrittenen Therapiemodi behandelt wurden, sollen erfasst werden. Zu den **fortgeschrittenen Therapiemodi** zählen dabei **Tiefenhirnstimulation (Deep brain stimulation, DBS)**, **Apomorphinpumpe (APO) und Duodopapumpe (Levodopa-carbidopa intestinal gel, LCIG)**. Es sollen hieraus grundlegende Daten zu Parkinsonpatienten gesammelt werden, bei denen trotz bereits erfolgter Therapie mit einem fortgeschrittenen Therapiemodus nur eine unzureichende Parkinsoneinstellung zu erzielen war. Patienten, die im Laufe der Therapie mit insgesamt nur einem fortgeschrittenen Therapiemodus behandelt wurden, werden in der vorliegenden Studie *nicht* berücksichtigt.

Grundkonzept des Fragebogens

Der zur Erfassung o.g. Daten entwickelte Fragebogen ist **modular** aufgebaut, damit nach Möglichkeit alle denkbaren Kombinationen und Konstellationen fortgeschrittener Parkinsontherapien erfasst werden können. Die Datenerhebung beginnt zum Zeitpunkt der Anlage eines zweiten (*nicht des ersten!*) fortgeschrittenen Therapiemodus beim Patienten und endet zum aktuellen (bzw. falls nicht verfügbar letzten dokumentierten) Zeitpunkt. Um den Therapieverlauf nachverfolgen zu können, bitten wir um Erfassung der Daten zum jeweils letzten dokumentierten Zeitpunkt vor der Therapiemodusänderung (= **Evaluationszeitpunkt I**) und zum ersten Zeitpunkt der permanenten Therapieeinstellung nach der Therapiemodusänderung (= **Evaluationszeitpunkt II**, Details siehe Anhang).



Zudem werden wenige allgemeine Daten zu Ihrer Klinik und zum jeweiligen Parkinsonpatienten erfasst.

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Um den Therapieverlauf übersichtlicher modular erfassen zu können, wurden sog. **Meilensteine der Therapiemodusänderung** definiert:

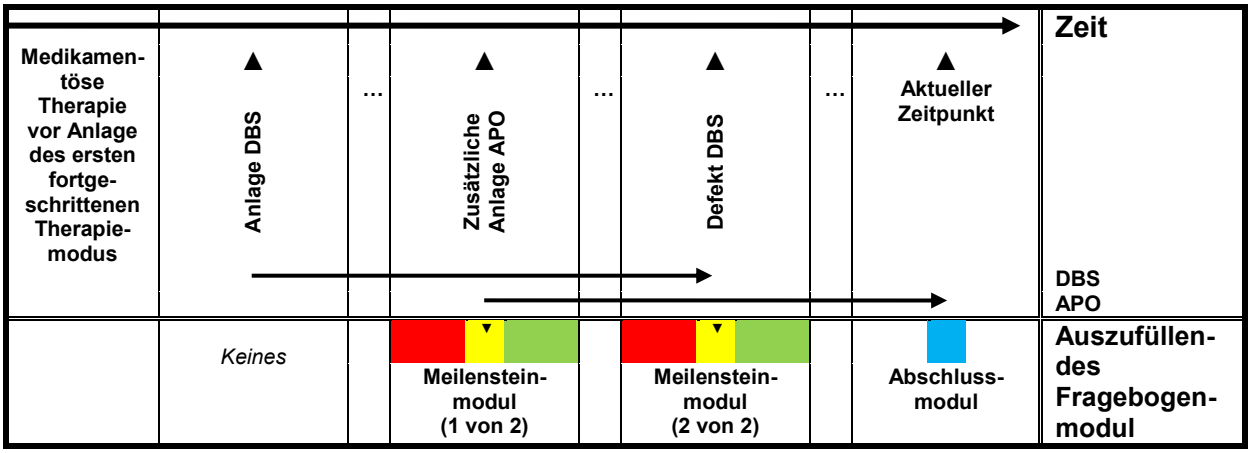
1. **Hinzukommen eines fortgeschrittenen Therapiemodus, z.B. APO zu DBS**

2. **Ersatz eines fortgeschrittenen Therapiemodus durch einen anderen, z.B. APO > LCIG**

3. **Wegfall eines fortgeschrittenen Therapiemodus, z.B. Wegfall DBS bei fortbestehendem LCIG**

Für jeden Meilenstein ist ein entsprechendes vierseitiges **Meilensteinmodul** des Fragebogens auszufüllen *(Farbkonzept rot-gelb-grün)*. Zuletzt wird der aktuelle Therapiestatus (bzw. falls nicht verfügbar der letzte dokumentierte Status) mit einem separaten **Abschlussmodul** erfasst *(Farbkonzept blau)*. Beigelegt sind jeweils 2 Meilensteinmodule und ein Abschlussmodul je Fragebogen. Sollten Sie weitere Meilensteinmodule benötigen, können Sie diese selbstverständlich per Kopie oder PDF-Ausdruck vervielfältigen. Alternativ bitten wir Sie um kurze Kontaktaufnahme per Mail unter Angabe der Fragebogen-ID des Deckblatts; es erfolgt dann eine postalische Zusendung unsererseits.
WICHTIG: Die Therapiekonstellation zum Zeitpunkt der Anlage des ersten fortgeschrittenen Therapiemodus muss *nicht* dokumentiert werden. Der (seltene) komplette Wegfall aller fortgeschrittener Therapiemodi (z.B. DBS-Defekt mit nachfolgend nur noch medikamentöser Therapie) wird in einem Meilensteinmodul dokumentiert. Details zu den Fragebogenmodulen finden sich im Anhang.

<u>Beispiel für die Erfassung eines Therapieverlaufes:</u>



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Allgemeine Informationen zur teilnehmenden Klinik

Anzahl der an Ihrem Zentrum betreuten Parkinsonpatienten (ca.):

_____ pro Jahr

Angebotene fortgeschrittene Therapieoptionen an Ihrem Zentrum (nur Ersteinstellung, nicht Weiterbetreuung):

☐ DBS (ca. _____ Ersteinstellungen pro Jahr)

☐ Apomorphinpumpe (ca. _____ Ersteinstellungen pro Jahr)

☐ LCIG (ca. _____ Ersteinstellungen pro Jahr)

(Dieser Fragebogenteil muss nur bei einem Patientenfragebogen ausgefüllt werden und kann bei allen weiteren an Ihrer Klinik ausgefüllten Patientenfragebögen selbstverständlich leer gelassen werden)

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Allgemeine Patientendaten

Geburtsjahr	_____ (JJJJ)	
Geschlecht	□ männlich	□ weiblich
Anamnestischer Erkrankungsbeginn des IPS = erste motorische Symptome	Ca. ___._____ (MM.JJJJ)	□ unbekannt
Datum Erstdiagnose IPS	Ca. ___._____ (MM.JJJJ)	
Weitere Diagnosen		

Gesamtanzahl n der als Meilensteine gewerteten Therapiemodus-änderungen beim Patienten (entspricht Anzahl der auszufüllenden Meilensteinmodule):

n = _____

(Bitte jeweils auch oben auf den Bögen des Meilensteinmoduls angeben)

CAT-PD: Therapieverlauf

Meilensteinmodul ___ von ___

Fragebogen-ID: _____

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1) Therapieübersicht zum Zeitpunkt des erfassten Meilensteins

		Therapieabschnitt I	Therapie-modus-änderung ▼	Therapieabschnitt II
		Zeit →		
Datum (MM.JJJJ)		___._____ (Letzte dokumentierte Evaluation vor Therapiemodusänderung)	___._____	___._____ (Evaluation zum Zeitpunkt der ersten permanenten Therapieeinstellung zwischen 1 Woche und 3 Monaten nach Therapiemodusänderung, s. Anhang)
Fortge-schrittene Therapie(n)	**DBS**	☐ (Datum Erstanlage: ___._____)		☐
	APO	☐ (Datum Erstanlage: ___._____)		☐
	LCIG	☐ (Datum Erstanlage: ___._____)		☐

2) Angaben zum Therapieverlauf

2.1) Parkinsontherapie vor Therapiemodusänderung *(Letzte dokumentierte Evaluation vor Therapiemodusänderung)*				
☐ Medikation (bitte rechts Präparate und Dosierung der Parkinsonmedikation angeben)				
☐ DBS (Elektrodenort bitte rechts angeben)	☐ Nucleus subthalamicus (STN) ☐ Globus pallidus int. (GPI) ☐ Nucleus ventralis intermedius thalami (VIM) ☐ anderer Elektrodenort (bitte angeben) _____ ☐ unilateral (Seite) _____ ☐ bilateral			
☐ Apomorphinpumpe	Tagesdosis _____mg Laufzeit _____h			
☐ LCIG	Morgendosis _____mg	Erhaltungs-dosis _____mg/h	Zusatzbolus _____mg	Laufzeit _____h

2.2) Grund für Neuanlage bzw. Wegfall des fortgeschrittenen Therapiemodus *(bitte im jeweiligen Freitextfeld rechts näher angeben)*	
☐ unzureichende Wirkung der Vortherapie (z.B. unbefriedigende Wirkung, Fluktuationen)	
☐ Nebenwirkungen der Vortherapie	
☐ geräteassoziiert (z.B. Gerätedefekt)	
☐ ökonomische Gründe (z.B. Wegfall der Erstattung durch die Krankenkasse)	
☐ Versorgungsprobleme (z.B. fehlender Pflegedienst, Handlingprobleme beim Kassettenwechsel)	
☐ andere Gründe	

2.3) Parkinsontherapie nach Therapiemodusänderung *(Evaluation zum Zeitpunkt der ersten permanenten Therapieeinstellung zwischen 1 Woche und 3 Monaten nach Therapiemodusänderung, s. Anhang)*				
☐ Medikation (bitte rechts Präparate und Dosierung der Parkinsonmedikation angeben)				
☐ DBS (Elektrodenort bitte rechts angeben)	☐ Nucleus subthalamicus (STN) ☐ Globus pallidus int. (GPI) ☐ Nucleus ventralis intermedius thalami (VIM) ☐ anderer Elektrodenort (bitte angeben) _____ ☐ unilateral (Seite) _____ ☐ bilateral			
☐ Apomorphinpumpe	Tagesdosis _____mg Laufzeit _____h			
☐ LCIG	Morgendosis _____mg	Erhaltungs-dosis _____mg/h	Zusatzbolus _____mg	Laufzeit _____h

CAT-PD: Therapieverlauf

Meilensteinmodul ___ von ___

Fragebogen-ID: _____

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3) Klinische Angaben

(bitte nach Möglichkeit im ON unter bestmöglicher Therapie angeben (Medikation eingenommen, Aggregat/Pumpe eingeschaltet))

	Vor Therapiemodusänderung *(Letzte dokumentierte Evaluation vor Therapiemodusänderung)*	**Nach Therapiemodus-änderung** *(Evaluation zum Zeitpunkt der ersten permanenten Therapieeinstellung zwischen 1 Woche und 3 Monaten nach Therapiemodusänderung, s. Anhang)*
3.1) Montreal Cognitive Assessment (MoCA)	____/30 Punkten	____/30 Punkten
3.2) Mini Mental Status Test (MMST)	____/30 Punkten	____/30 Punkten
3.3) UPDRS	***Verwendete Version*** ☐ Original-UPDRS ☐ MDS-UPDRS	***Verwendete Version*** ☐ Original-UPDRS ☐ MDS-UPDRS
Teil I (Non-Motor Aspects of Experiences of Daily Living)	_____Punkte	_____Punkte
Teil II (Motor Aspects of Experiences of Daily Living)	_____Punkte	_____Punkte
Teil III (Motor Examination)	_____Punkte	_____Punkte
Teil IV (Motor Complications)	_____Punkte	_____Punkte
Teil IV - Dyskinesie-Zeit	_____Punkte bzw. _____h	_____Punkte bzw. _____h
Teil IV - OFF-Zeit	_____Punkte bzw. _____h	_____Punkte bzw. _____h
3.4) Therapienebenwirkungen *(bitte nach u.g. Kategorien geordnet im jeweiligen Freitextfeld rechts einfüllen)*	*(Leerfeld)*	*(Leerfeld)*
3.4.1) Periprozedural / Geräteassoziiert	*(Leerfeld)*	*(Leerfeld)*
☐ Periprozedural in zeitlichem Zusammenhang mit Neuanlage	*(Leerfeld)*	
☐ Geräteassoziiert		
3.4.2) Neurologisch / Neuropsychiatrisch	*(Leerfeld)*	*(Leerfeld)*

☐ Neurologisch		
☐ Neuropsychiatrisch		
3.4.3) Somatisch / Systemisch	*(Leerfeld)*	*(Leerfeld)*
☐ Kardiovaskulär		
☐ Gastrointestinal		
☐ Kutan		
3.5) Clinical Global Impression - Improvement	*(Leerfeld)*	**Klinischer Gesamteindruck im Vergleich zur Voruntersuchung vor Therapiemodusänderung:** **A) Aus Sicht des Arztes** ☐ sehr viel besser ☐ viel besser ☐ minimal besser ☐ unverändert ☐ minimal schlechter ☐ viel schlechter ☐ sehr viel schlechter **B) Aus Sicht des Patienten** ☐ sehr viel besser ☐ viel besser ☐ minimal besser ☐ unverändert ☐ minimal schlechter ☐ viel schlechter ☐ sehr viel schlechter

4) Weiteres Vorgehen zur Vervollständigung des Fragebogens

Wenn

- ein weiterer Therapiemeilenstein im Therapieverlauf folgte, d.h. ein fortgeschrittener Therapiemodus neuangelegt wurde, durch einen anderen ersetzt wurde bzw. wegfiel > bitte **weiteres Meilensteinmodul** ausfüllen. BITTE PRÜFEN SIE UNBEDINGT, OB

Meilensteinmodul ___ von ___

Fragebogen-ID: _____

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FRAGEBOGEN-ID UND ZAHL DER MEILENSTEINMODULE IN DER KOPFZEILE ALLER MEILENSTEINMODULE AUSGEFÜLLT SIND.

- kein weiterer Therapiemeilenstein im Therapieverlauf folgte, d.h. die Gesamttherapie bis zum aktuellen Zeitpunkt (oder sofern nicht verfügbar zum letzten dokumentierten Zeitpunkt) unverändert geblieben ist bzw. lediglich Geräteeinstellungen oder die Medikation geändert wurden > bitte **Abschlussmodul** ausfüllen

CAT-PD: Therapieverlauf

Abschlussmodul

Fragebogen-ID: _____

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Aktueller Status zum Studienzeitpunkt
(bzw. falls nicht bekannt zum letzten dokumentierten Zeitpunkt)

1) Therapiestatus

Evaluationsdatum: ___._____ (MM.JJJJ)

☐ Medikation (bitte rechts Präparate und Dosierung der Parkinsonmedikation angeben)				
☐ DBS (Elektrodenort bitte rechts angeben)	☐ Nucleus subthalamicus (STN) ☐ Globus pallidus int. (GPI) ☐ Nucleus ventralis intermedius thalami (VIM) ☐ anderer Elektrodenort (bitte angeben) _____ ☐ unilateral (Seite) _____ ☐ bilateral			
☐ Apomorphinpumpe	Tagesdosis _____mg Laufzeit _____h			
☐ LCIG	Morgendosis _____mg	Erhaltungs-dosis _____mg/h	Zusatzbolus _____mg	Laufzeit _____h

2) Klinischer Status

(bitte nach Möglichkeit im ON unter bestmöglicher Therapie angeben (Medikation eingenommen, Aggregate/Pumpen eingeschaltet))

Evaluationsdatum: ___._____ (MM/JJJJ)

2.1) Montreal Cognitive Assessment (MoCA)	____/30 Punkten
2.2) Mini Mental Status Test (MMST)	____/30 Punkten
2.3) UPDRS	***Verwendete Version*** ☐ Original-UPDRS ☐ MDS-UPDRS
Teil I (Non-Motor Aspects of Experiences of Daily Living)	_____Punkte
Teil II (Motor Aspects of Experiences of Daily Living)	_____Punkte
Teil III (Motor Examination)	_____Punkte
Teil IV (Motor Complications)	_____Punkte

Abschlussmodul

Fragebogen-ID: _____

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Teil IV - Dyskinesie-Zeit	_____Punkte bzw. _____h
Teil IV - OFF-Zeit	_____Punkte bzw. _____h
2.4) Therapienebenwirkungen *(bitte nach u.g. Kategorien geordnet im jeweiligen Freitextfeld rechts einfüllen)*	*(Leerfeld)*
2.4.1) Geräteassoziiert	*(Leerfeld)*
☐ Geräteassoziiert	
2.4.2) Neurologisch / Neuropsychiatrisch	*(Leerfeld)*
☐ Neurologisch	
☐ Neuropsychiatrisch	
2.4.3) Somatisch / Systemisch	*(Leerfeld)*
☐ Kardiovaskulär	
☐ Gastrointestinal	
☐ Kutan	

BITTE PRÜFEN SIE ABSCHLIEßEND UNBEDINGT, OB DIE FRAGEBOGEN-ID UND ZAHL DER MEILENSTEINMODULE IN DER KOPFZEILE ALLER MEILENSTEINMODULE SOWIE DIE FRAGEBOGEN-ID IN DER KOPFZEILE DES ABSCHLUSSMODULS AUSGEFÜLLT SIND.

Vielen Dank für Ihre Bemühungen!

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Anhang: Abkürzungen und Erläuterungen zu den Modulen des Fragebogens

1) Abkürzungen

APO	Apomorphinpumpe
DBS	Deep Brain Stimulation, Tiefenhirnstimulation
IPS	Idiopathisches Parkinson-Syndrom
LCIG	Levodopa-carbidopa intestinal gel; Duodopapumpentherapie

2) Meilensteinmodul

Allgemeines:

- Bitte füllen Sie den Fragebogen so weit wie möglich aus. Sofern Daten nicht vorliegen, bitte die entsprechenden Felder einfach leer lassen oder mit n.n. (non notum) kennzeichnen.
- Zutreffende Kästchen (□) bitte jeweils ankreuzen.

Evaluationszeitpunkte:

- **Therapieabschnitt I:** Bitte erfassen Sie die Therapie bzw. die klinischen Daten zum letzten in Ihrer Klinik dokumentierten Zeitpunkt vor der Therapiemodusänderung
- **Therapieabschnitt II:** Bitte erfassen Sie die Therapie bzw. die klinischen Daten möglichst zum Zeitpunkt der ersten permanenten Therapieeinstellung, der nach Möglichkeit zur größeren Datenkonsistenz zwischen 1 Woche und 3 Monaten nach Therapiemodusänderung liegen sollte. Bitte dokumentieren Sie die Daten eines anderen Zeitpunktes nur, wenn im vorgenannten Zeitintervall keine entsprechenden Daten verfügbar sind. Als erste permanente Therapieeinstellung zählen
    - bei DBS: Aggregat vollständig eingeschaltet mit erstmaliger dauerhafter Einstellung nach Einjustierungsphase
    - bei APO und LCIG: Erstmalige dauerhafte Pumpeneinstellung nach Auftitrierungsphase

Klinische Angaben

- **Evaluationszeitpunkte:** s.o.
    - **3.1) MoCA bzw. 3.2) MMST:** Falls ein bzw. beide Scores erhoben wurden, bitte eintragen.
- **3.3) UPDRS:**
    - Bitte vermerken Sie unbedingt, ob die ursprüngliche UPDRS-Version von 1987 oder die revidierte Version der Movement Disorder Society (MDS-UPDRS) verwendet wurde.
    - Dyskinesie- und OFF-Zeit: Angabe in Form der UPDRS-Punkte und / oder in Stunden möglich.
- **3.4) Therapienebenwirkungen: Erläuterungen und Beispiele**
    - **Periprozedural:** in unmittelbarem zeitlichen Zusammenhang mit der Neuanlage des fortgeschrittenen Therapiemodus, z.B.

Schmerz, Wundheilungsstörung, Wundinfekt, Phlegmone, Abszess, Blutung, Peritonitis, Pneumoperitoneum.

- **Geräteassoziiert:** ohne unmittelbaren Zusammenhang mit der Neuanlage / dem Wegfall des fortgeschrittenen Therapiemodus, z.B. Schrittmacherdysfunktion, Schrittmacherinfektion, Schrittmacherdislokation, Sondendislokation, Sondendefekt, Pumpenkomplikation, PEJ-Sondenkomplikation, burried bumper.
- **Neurologisch:** z.B. Dyskinesie, Wirkfluktuationen, Dysarthrie, Dystonie, Freezing, Gangstörung, Stürze, Schwindel, Polyneuropathie, Schmerz.
- **Neuropsychiatrisch:** z.B. Depression, Suizidgedanken, Suizid(-versuch), Antriebsstörung, Impulskontrollstörung, Angst, Insomnie, Somnolenz.
- **Kardiovaskulär:** z.B. Herzerkrankung, Myokardinfarkt, Hypotension, Orthostaseprobleme.
- **Gastrointestinal:** z.B. Reflux, Bauchschmerz, Übelkeit, Obstipation, Flatulenz, Gewichtsänderung, Kolitis.
- **Kutan:** z.B. Erythem, Hautknötchen, Dermatitis, Infektion, Phlegmone.

- **3.5) Clinical Global Impression - Improvement:**
  - Bitte bewerten Sie den generellen klinischen Eindruck des Patienten nach der Therapiemodusänderung im Vergleich zum Vorzustand (sofern vorliegend aus Arzt- und Patientensicht)
  - Genauere Definitionen zu den einzelnen Kategorien finden Sie nachfolgend:

1	= Very much improved—nearly all better; good level of functioning; minimal symptoms; represents a very substantial change
2	= Much improved—notably better with significant reduction of symptoms; increase in the level of functioning but some symptoms remain
3	= Minimally improved—slightly better with little or no clinically meaningful reduction of symptoms. Represents very little change in basic clinical status, level of care, or functional capacity
4	= No change—symptoms remain essentially unchanged
5	= Minimally worse—slightly worse but may not be clinically meaningful; may represent very little change in basic clinical status or functional capacity
6	= Much worse—clinically significant increase in symptoms and diminished functioning
7	= Very much worse—severe exacerbation of symptoms and loss of functioning
Adapted from Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP.*Psychiatry Res* 1997;73(3):159–71.	

(aus: Busner, J und Targum, SD (2007): The Clinical Global Impressions Scale: Applying a Research Tool in Clinical Practice. Psychiatry 4(7):28-37)

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3) Abschlussmodul

Allgemeines:

- Bitte füllen Sie den Fragebogen so weit wie möglich aus. Sofern Daten nicht vorliegen, bitte die entsprechenden Felder einfach leer lassen oder mit n.n. (non notum) kennzeichnen.
- Zutreffende Kästchen (□) bitte jeweils ankreuzen.

Evaluationszeitpunkte:

- Bitte dokumentieren Sie nach Möglichkeit den Status zum aktuellen Zeitpunkt. Nur wenn hierzu keine Daten vorliegen, bitte den letzten dokumentierten Status erfassen.
- Die Evaluationszeitpunkte von Therapie- und klinischem Status sollten nach Möglichkeit identisch sein, können sich aber, sofern dies nicht verfügbar ist, auch unterscheiden.

Klinische Angaben

- Siehe Erläuterungen zum Meilensteinmodul.

Bei Rückfragen bitten wir um Kontaktaufnahme per Email. Vielen Dank!

Supplement 4: Translated study questionnaire

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Technical University of Munich

Klinikum rechts der Isar
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Questionnaire for the retrospective study titled

"Combinations of Advanced Therapies in Parkinson's Disease (CAT-PD)"

of the Department of Neurology of the University Hospital rechts der Isar of the Technical University of Munich

Questionnaire ID: _____

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Technical University of Munich

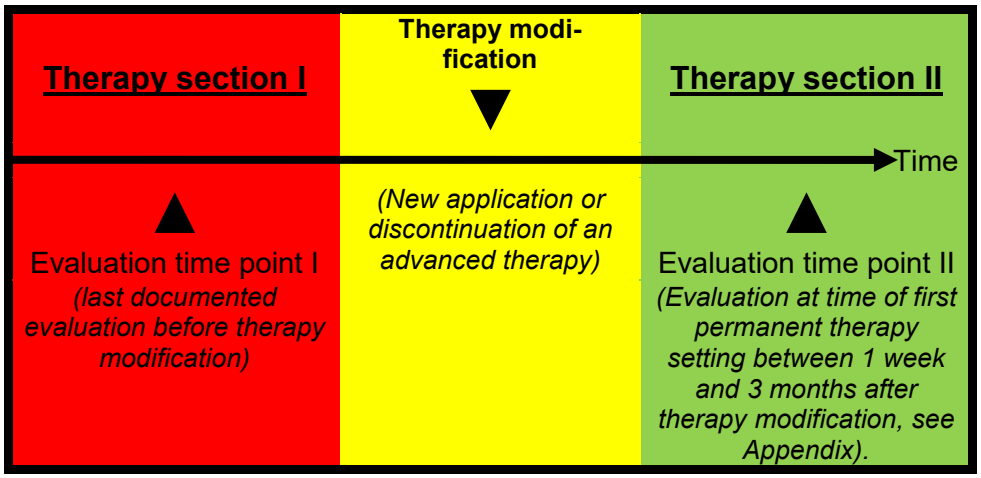
General information about the questionnaire

Basic concept of the study

Clinical and therapeutic data of patients with idiopathic Parkinson's disease (PD) who have been treated with **at least two** advanced therapies during the course of their disease will be collected. **Advanced therapies** include **deep brain stimulation (DBS)**, **apomorphine pump (APO) and duodopa pump (levodopa-carbidopa intestinal gel, LCIG)**. The aim is to collect data on patients with Parkinson's disease in whom only inadequate PD control could be achieved despite having already used an advanced therapy. Patients who were treated with only one advanced therapy during their course of therapy will *not be* considered in the present study.

Basic concept of the questionnaire

The questionnaire developed to collect the above data has a **modular** structure, so that all possible combinations and constellations of advanced PD therapies can be recorded. The data collection starts at the time of the application of a second (*not the first!*) advanced therapy in the patient and ends at the current (or if not available last documented) time. In order to follow the course of therapy, we ask for data collection at the last documented time point before the therapy modification (= **evaluation time point I**) and at the first time point of permanent therapy adjustment after the therapy modification (= **evaluation time point II**, see appendix for details).



In addition, few general data about your hospital and the respective PD patient are collected.

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In order to record the course of therapy in an easily comprehensible way, so-called **milestones of the therapy modifications** were defined:

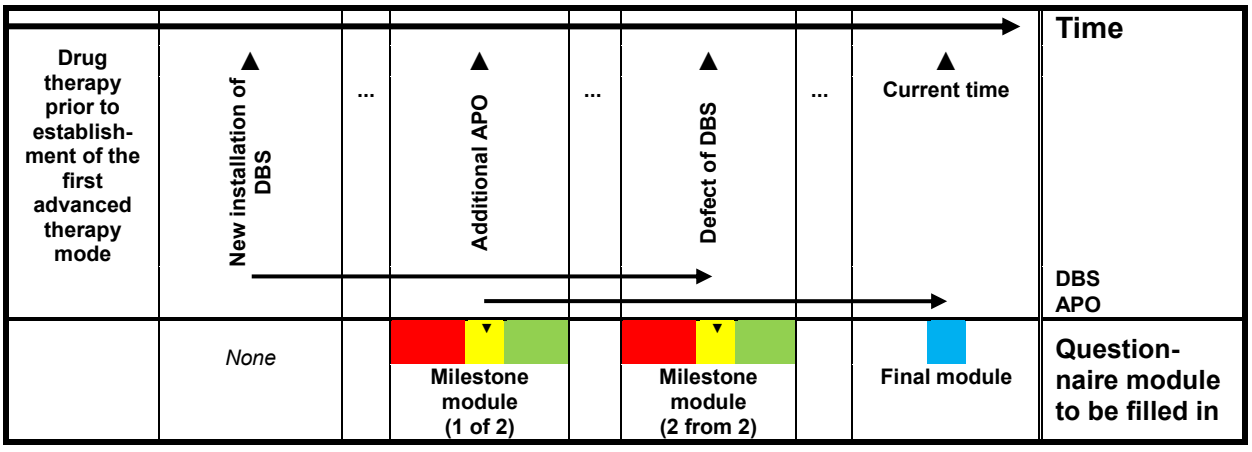
1. **Addition of an advanced therapy, e.g., APO to DBS.**

2. **Replacement of one advanced therapy by another one, e.g., APO > LCIG.**

3. **Omission of an advanced therapy, e.g., omission of DBS if LCIG persists.**

For each milestone, a corresponding four-page **milestone module** of the questionnaire must be completed *(color concept red-yellow-green)*. Finally, the current therapy status (or, if not available, the last documented status) is recorded with a separate **final module** *(color concept blue)*. Enclosed are 2 milestone modules and one final module per questionnaire. If you need further milestone modules, you can of course duplicate them by copy or PDF printout. Alternatively, please contact us by e-mail, stating the questionnaire ID of the cover sheet; we will then send them to you by post.
IMPORTANT: The therapy constellation at the time of establishment of the first advanced therapy does *not* need to be documented. The (rare) complete discontinuation of all advanced therapy modes (e.g., DBS defect with subsequent drug therapy only) is documented in a milestone module. Details on the questionnaire modules can be found in the appendix.

<u>Example of recording a course of therapy:</u>



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General information about the participating hospital

Number of Parkinson's patients cared for at your center (approx.):

_____ per year

Advanced treatment options offered at your center (initial setting only, not continuing care):

☐ DBS (approx. _____ new installations per year)

☐ Apomorphine pump (approx. _____ new installations per year)

☐ LCIG (approx. _____ new installations per year)

(This section only needs to be completed in one patient questionnaire and can of course be left blank for all other patient questionnaires completed at your hospital).

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General patient data

Year of birth	_____ (YYYY)	
Gender	□ male	□ female
Anamnestic onset of PD = first motor symptoms	Approx. ___._____ (MM.YYYY)	□ unknown
Date of PD diagnosis	Approx. ___._____ (MM.YYYY)	
Other diagnoses		

Total number n of therapy modifications of the patient evaluated as milestones (corresponds to number of milestone modules to be completed):

n = _____

(Please also indicate this at the top of the each milestone module).

CAT-PD: Course of therapy

Milestone module ___ from ___

Questionnaire ID: _____

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1) Therapy overview at the time of the recorded milestone.

		Therapy section I	Therapy modi-fication ▼	Therapy section II
		→ *Time*		
Date (MM.YYYY)		___._____ (Last documented evaluation before therapy mode change)	___._____	___._____ (Evaluation at time of first permanent therapy setting between 1 week and 3 months after therapy modification, see Appendix).
Advanced therapy(s)	**DBS**	☐ (Date of first installation: ___._____)		☐
	APO	☐ (Date of first installation: ___._____)		☐
	LCIG	☐ (Date of first installation: ___._____)		☐

2) Information on the course of therapy

2.1) PD therapy before therapy modification *(Last documented evaluation before therapy mode change)*				
☐ Medication (please indicate drugs and dosage of PD medication on the right)				
☐ DBS (please specify electrode location on the right)	☐ Nucleus subthalamicus (STN) ☐ Globus pallidus int. (GPI) ☐ Nucleus ventralis intermedius thalami (VIM) ☐ other electrode location (please specify) _____ ☐ unilateral (side) _____ ☐ bilateral			
☐ Apomorphine pump	Daily dosage _____mg Running time _____h			
☐ LCIG	Morning dosage _____mg	Maintenance dosage _____mg/h	Additional boli _____mg	Running time _____h

2.2) Reason for new application or omission of the advanced therapy *(please specify in more detail in the respective free text field on the right)*	
☐ Insufficient effect of previous therapy (e.g., unsatisfactory effect, fluctuations)	
☐ Side effects of previous therapy	
☐ Device-associated (e.g. device defect)	
☐ Economic reasons (e.g. discontinuation of reimbursement by the health insurance fund)	
☐ Management problems (e.g., lack of care service, handling problems when changing cassettes)	
☐ Other reasons	

2.3) PD therapy after therapy mode change. *(Evaluation at time of first permanent therapy setting between 1 week and 3 months after therapy mode change, see Appendix).*				
☐ Medication (please indicate drugs and dosage of PD medication on the right)				
☐ DBS (please specify electrode location on the right)	☐ Nucleus subthalamicus (STN) ☐ Globus pallidus int. (GPI) ☐ Nucleus ventralis intermedius thalami (VIM) ☐ other electrode location (please specify) _____ ☐ unilateral (side) _____ ☐ bilateral			
☐ Apomorphine pump	Daily dosage _____mg Running time _____h			
☐ LCIG	Morning dosage _____mg	Maintenance dosage _____mg/h	Additional boli _____mg	Running time _____h

3) Clinical data

(If possible, please indicate in ON under best possible therapy (medication taken, aggregate/pump switched on)).

	Before therapy modification *(Last documented evaluation before therapy modification)*	**After therapy modification** *(Evaluation at time of first permanent therapy setting between 1 week and 3 months after therapy modification, see Appendix).*
3.1) Montreal Cognitive Assessment (MoCA)	____/30 points	____/30 points
3.2) Mini Mental Status Test (MMST)	____/30 points	____/30 points
3.3) UPDRS	***Version used*** ☐ Original UPDRS ☐ MDS-UPDRS	***Version used*** ☐ Original UPDRS ☐ MDS-UPDRS
Part I (Non-Motor Aspects of Experiences of Daily Living)	_____Points	_____Points
Part II (Motor Aspects of Experiences of Daily Living)	_____Points	_____Points
Part III (Motor Examination)	_____Points	_____Points
Part IV (Motor Complications)	_____Points	_____Points
Part IV - Dyskinesia Time	_____Points or _____h	_____Points or _____h
Part IV - OFF time	_____Points or _____h	_____Points or _____h
3.4) Side effects of therapy *(please fill in the respective free text field on the right according to the categories mentioned below)*	*(blank field)*	*(blank field)*
3.4.1) Periprocedural / device-associated	*(blank field)*	*(blank field)*
☐ Periprocedural in connection with device installation	*(blank field)*	
☐ Device-associated		
3.4.2) Neurological / Neuropsychiatric	*(blank field)*	*(blank field)*
☐ Neurological		

☐ Neuropsychiatric		
3.4.3) Somatic / Systemic	*(blank field)*	*(blank field)*
☐ Cardiovascular		
☐ Gastrointestinal		
☐ Cutaneous		
3.5) Clinical Global Impression - Improvement	*(blank field)*	**Overall clinical impression compared to examination before therapy modification:** **A) From the physician's point of view** ☐ very much improved ☐ much improved ☐ minimally improved ☐ no change ☐ minimally worse ☐ much worse ☐ very much worse **B) From the patient's point of view** ☐ very much improved ☐ much improved ☐ minimally improved ☐ no change ☐ minimally worse ☐ much worse ☐ very much worse

4) Further procedure for the completion of the questionnaire

If

- another therapy milestone followed in the course of therapy, i.e. an advanced therapy was newly installed, replaced by another or omitted > please fill in another **milestone module**. PLEASE BE SURE TO CHECK THAT QUESTIONNAIRE ID AND NUMBER OF MILESTONE MODULES ARE FILLED IN THE HEADER OF ALL MILESTONE MODULES.
- no further therapy milestone followed in the course of therapy, i.e. the overall therapy has remained unchanged up to the current point in time

(or, if not available, at the last documented point in time) or only device settings or medication have been changed > please fill in the **final module**

CAT-PD: Course of therapy

Final module

Questionnaire ID: _____

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Current status at the time of the study
(Or, if not known, at the last documented time)

1) Therapy status

Evaluation Date: ___._____ (MM.YYYY)

☐ Medication (please indicate drugs and dosage of PD medication on the right)				
☐ DBS (please specify electrode location on the right)	☐ Nucleus subthalamicus (STN) ☐ Globus pallidus int. (GPI) ☐ Nucleus ventralis intermedius thalami (VIM) ☐ other electrode location (please specify) _____ ☐ unilateral (side) _____ ☐ bilateral			
☐ Apomorphine pump	Daily dosage _____mg Running time _____h			
☐ LCIG	Morning dosage _____mg	Maintenance dosage _____mg/h	Additional boli _____mg	Running time _____h

2) Clinical status

(If possible, please indicate in ON under best possible therapy (medication taken, aggregates/pumps switched on)).

Evaluation Date: ___._____ (MM/YYYY)

2.1) Montreal Cognitive Assessment (MoCA)	____/30 points
2.2) Mini Mental Status Test (MMST)	____/30 points
2.3) UPDRS	***Version used*** ☐ Original UPDRS ☐ MDS-UPDRS
Part I (Non-Motor Aspects of Experiences of Daily Living).	_____Points
Part II (Motor Aspects of Experiences of Daily Living)	_____Points
Part III (Motor Examination)	_____Points
Part IV (Motor Complications)	_____Points

CAT-PD: Course of therapy

Final module

Questionnaire ID: _____

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Part IV - Dyskinesia Time	_____Points or _____h
Part IV - OFF time	_____Points or _____h
2.4) Side effects of therapy *(please fill in the respective free text field on the right according to the categories mentioned below)*	*(blank field)*
2.4.1) Device associated	*(blank field)*
☐ Device-associated	
2.4.2) Neurological / Neuropsychiatric	*(blank field)*
☐ Neurological	
☐ Neuropsychiatric	
2.4.3) Somatic / Systemic	*(blank field)*
☐ Cardiovascular	
☐ Gastrointestinal	
☐ Kutan	

Finally, please be sure to check that the questionnaire ID and number of the milestone modules are filled in in the header of all milestone modules as well as the questionnaire ID in the header of the final module.

Thank you very much for your efforts!

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Appendix: Abbreviations and explanations for the modules of the questionnaire

1) Abbreviations

APO	Apomorphine pump
DBS	Deep Brain Stimulation
PD	Idiopathic Parkinson Syndrome
LCIG	Levodopa-carbidopa intestinal gel; duodopa pump therapy.

2) Milestone module

General:

- Please complete the questionnaire as far as possible. If data are not available, please simply leave the corresponding fields blank or mark them with n.n. (non notum).
- Please tick the appropriate boxes (□).

Evaluation time points:

- **Therapy section I:** Please record therapy or clinical data as of the last time documented in your hospital prior to the therapy modification.
- **Therapy section II:** If possible, please record therapy or clinical data at the time of the first permanent therapy setting, which should be between 1 week and 3 months after therapy mode change for greater data consistency. Please document data from a different time point only if no corresponding data are available in the aforementioned time interval. The following count as the first permanent therapy setting
    - For DBS: Implanted pulse generator completely switched on with initial permanent setting after adjustment phase.
    - For APO and LCIG: Initial permanent pump setting after uptitration phase.

Clinical data

- **Evaluation dates:** see above.
    - **3.1) MoCA or 3.2) MMST:** If one or both scores were collected, please fill them in.
- **3.3) UPDRS:**
    - Please be sure to note whether the original 1987 UPDRS version or the revised Movement Disorder Society (MDS-UPDRS) version was used.
    - Dyskinesia and OFF time: documentation possible in UPDRS points and / or hours.
- **3.4) Therapy side effects: Explanations and examples**
    - **Periprocedural:** in immediate temporal relation to the new installation of the advanced therapy, e.g., pain, wound healing disorder, wound infection, phlegmone, abscess, hemorrhage, peritonitis, pneumoperitoneum.

- **Device-associated:** not directly related to new device installation / discontinuation of advanced therapy, e.g., pacemaker dysfunction, pacemaker infection, pacemaker dislocation, electrode dislocation, electrod defect, pump complication, PEJ complication, burried bumper.
- **Neurological:** e.g., dyskinesia, effect fluctuations, dysarthria, dystonia, freezing, gait disturbance, falls, dizziness, polyneuropathy, pain.
- **Neuropsychiatric:** e.g., depression, suicidal ideation, suicide (attempt), lack of drive, impulse control disorder, anxiety, insomnia, somnolence.
- **Cardiovascular:** e.g., heart disease, myocardial infarction, hypotension, orthostasis problems.
- **Gastrointestinal:** e.g., reflux, abdominal pain, nausea, constipation, flatulence, weight change, colitis.
- **Cutaneous:** e.g., erythema, skin nodules, dermatitis, infection, phlegmone.

- **3.5) Clinical Global Impression - Improvement:**
  - Please rate the patient's general clinical impression after the therapy modification compared to the previous condition (if available from the physician's and patient's perspective)
  - More detailed definitions of each category can be found below:

1 = Very much improved—nearly all better; good level of functioning; minimal symptoms; represents a very substantial change
2 = Much improved—notably better with significant reduction of symptoms; increase in the level of functioning but some symptoms remain
3 = Minimally improved—slightly better with little or no clinically meaningful reduction of symptoms. Represents very little change in basic clinical status, level of care, or functional capacity
4 = No change—symptoms remain essentially unchanged
5 = Minimally worse—slightly worse but may not be clinically meaningful; may represent very little change in basic clinical status or functional capacity
6 = Much worse—clinically significant increase in symptoms and diminished functioning
7 = Very much worse—severe exacerbation of symptoms and loss of functioning
Adapted from Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP.*Psychiatry Res* 1997;73(3):159–71.

(from: Busner, J and Targum, SD (2007): The Clinical Global Impressions Scale: Applying a Research Tool in Clinical Practice. Psychiatry 4(7):28-37)

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3) Final module

General:

- Please complete the questionnaire as far as possible. If data are not available, please simply leave the corresponding fields blank or mark them with n.n. (non notum).
- Please tick the appropriate boxes (□).

Evaluation time point:

- If possible, please document the status at the current time. Only if no data is available for this, please record the last documented status.
- Evaluation time points of therapeutic and clinical status should be identical if possible, but may differ if not available.

Clinical data

- See explanations for the milestone module.

If you have any questions, please do not hesitate to contact us by email. Thank you very much!