Movement Disorders
CLINICAL PRACTICE

BRIEF REPORT

# Long-Term Medication Profiles in Parkinson's Disease under Subthalamic Deep Brain Stimulation: A Controlled Study

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**Abstract:** Background: Subthalamic deep brain stimulation (STN-DBS) reduces antiparkinsonian medications in Parkinson's disease (PD) compared with the preoperative state. Longitudinal and comparative studies on this effect are lacking.

Objective: To compare longitudinal trajectories of antiparkinsonian medication in STN-DBS treated patients to non-surgically treated control patients.

Methods: We collected retrospective information on antiparkinsonian medication from PD patients that underwent subthalamic DBS between 1999 and 2010 and control PD patients similar in age at onset and baseline, sex-distribution, and comorbidities.

Results: In 74 DBS patients levodopa-equivalent daily dose (LEDD) were reduced by 33.9–56.0% in relation to the preoperative baseline over the 14-year observational period. In 61 control patients LEDDs increased over approximately 10 years, causing a significant divergence between groups. The largest difference amongst single drug-classes was observed for dopamine agonists.

Conclusion: In PD patients, chronic STN-DBS was associated with a lower LEDD compared with control patients over 14 years.

Parkinson's disease (PD) is a relentlessly progressive neurodegenerative disorder leading to increasingly disabling motor and non-motor symptoms (NMS) with a substantial risk for dependency and reduced life expectancy.[1] Levodopa and other dopaminergic therapies can effectively control motor symptoms,[2] but these treatments do not modify underlying disease progression or normalize life expectancy.[3,4] Deep brain stimulation (DBS) of the nucleus subthalamicus (STN) is effective in reducing levodopa related motor complications and improving quality of life in moderately advanced PD with benefits persisting for 5–10 years and even longer.[5] Moreover, treatment with STN-DBS allows marked reductions in levodopa and other antiparkinsonian medications with LEDDs decreases of around 40% after implantation as reported in large randomized controlled trials.[6] Additionally, observational long-term studies suggest that the LEDD lowering effect of STN-DBS ranging between 40% and 60% is sustained for up to 10 years in comparison to the presurgical baseline.[7–12] However, these studies have not serially monitored antiparkinsonian medication in STN-DBS treated patients and only compared presurgical baseline with last follow-up data. No long-term study has compared antiparkinsonian medication of PD patients with STN-DBS to those without and the longitudinal trajectories of LEDDs over long periods are unknown.

Hence, in the present study we serially assessed detailed antiparkinsonian medication in our previously described long-term cohort of STN-DBS treated PD patients[13] and compared

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their medical treatment trajectories to those of a purely medically managed cohort.

# Methods

## Cohort

The details of our long-term PD cohort under STN-DBS and the control group have been reported previously.[13] In brief, all 77 PD patients with STN-DBS implanted between 1999 and 2010, more than 10 years before data collection (January 2022), at our center were screened. Standard (exclusion) criteria for surgery have been used.[14] Patients were followed at least annually from surgery until December 2021 or until death. A control group of purely medically managed PD patients was extracted from a registry study (EuroPa),[15] a random prospective outpatient sample of PD patients entered in 2004 for whom data on corresponding long-term medications could be obtained. Baseline was defined as last visit before surgery for the DBS group and the index date in the middle of the EuroPa study period for the control group. Out of the 113 patients entered in the EuroPa registry at our site we went ahead with data extraction for all that were similar in age at onset and age at baseline (n = 69; See Fig. S1 for a flow chart of study participants). This retrospective study was approved by the local ethics committee of the Medical University of Innsbruck and performed in accordance with the declaration of Helsinki.

## Data Extraction

Baseline data were retrospectively extracted from clinical records (hospital discharge letters and outpatient reports). They included age at onset, age at baseline, sex, comorbidities and detailed medications. Subsequently, information on medication was extracted from follow-up visits every 2 years (+/− 6 months). Source data from all patients were systematically screened by two authors (PM and CT). LEDDs were calculated through a previously published and generally accepted conversion formula.[16] In addition to antiparkinsonian medication, information on use of antidepressant and neuroleptic medication was extracted.

## Statistical Analysis

For comparisons between groups, the chi-square test for categorical variables and the Mann–Whitney U test for continuous variables were used, as non-normal distributions were shown by the Kolmogorov–Smirnov test. The association between LEDD and group (DBS and control) over time was investigated using a generalized additive model to allow for nonlinear associations (R package mgcv, version 1.8–40). The base model was given by the formula LEDD $\sim$ Group + s(Time, by = Group, $k = 3$) + s(Patient, bs = 're') + s(Patient, Time, bs = 're') + DiseaseDuration, where $s()$ are smooth terms with k indicating the basis dimension, and bs = 're' indicating random effects. The basis dimension of the smooth term ($k = 3$) was selected as the smallest basis dimension which did not statistically improve the model fit. Age, sex, and voltage stimulations means were additionally considered as covariates and models' comparison was performed using the function compareML (itsadug, v 2.4.1). SPSS 29.0 (IBM Corp., Armonk, NY, USA) and R software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. The significance level was set at a 2-sided $P$-value of <0.05.

# Results

As reported in the original publication of our long-term series, 74 patients in the DBS group and 61 patients in the control group had been included[13] and followed for up to 16 years (see Fig. S1 and S2). Patient characteristics are summarized in Table 1.

The mean longitudinal LEDD trajectories for the DBS and control groups and their differences are shown in Fig. 1A,B. Baseline LEDDs were significantly higher in the DBS group in comparison to the control group, but dropped by 56% upon initiation of stimulation. Thereafter, the average LEDD was significantly lower in the DBS group compared to the controls. In the DBS group relative LEDD changes ranged from 33.9 to 56.0% below presurgical values, while in the control group LEDD rose by up to 50% compared to baseline over the study period (Fig. 1A, B). The average LEDD trajectory for the DBS group was approximately linear over the observation period, whereas for the controls it rose for the first 10 years and then gradually declined.

The biggest difference regarding LEDD was seen at the 10-year visit with a mean LEDD of 600 mg (IQR: 400–988 mg) in the DBS cohort and 1316 mg (IQR: 963–1475 mg) in the control cohort ($P < 0.001$). Compared to baseline values, after 10 years LEDDs were approximately 600 mg (IQR: 175–900 mg; 49.6% decrease) lower in the stimulated patients and 395 mg (IQR: 13–688 mg; 43.9% increase) higher in the control patients.

In the DBS group, mean stimulations voltages steadily rose from around 2.8 V and plateaued at around 3.4 V (Appendix S1 and Fig. S3). Mean stimulations voltages, age and sex did not significantly improve the model's prediction of LEDD and were thus not included as covariates in the model.

Assessment of the different PD medication classes showed a significantly lower number of patients taking dopamine agonists (DA) after stimulation in the DBS cohort (Fig. 1C,D). Also, COMT-Inhibitors and apomorphine were less frequently used in the stimulated patient cohort. There was no significant difference between the groups regarding use of antidepressants (range: 23.0–66.7% in DBS cohort; Fig. S4) or neuroleptics (range: 11.8–29.7% in DBS cohort; Fig. S5).

# Discussion

In the present study, we retrospectively analyzed trajectories of antiparkinsonian medications in PD patients with chronic subthalamic neurostimulation versus patients under medical

**TABLE 1** *Group characteristics as % (n) or median (25th–75th percentile)*

| | STN-DBS (n = 74) | Controls (n = 61) | *P*-value |
|---|---|---|---|
| Baseline characteristics | | | |
| Female | 32.4% (n = 24) | 32.8% (n = 20) | 0.56 |
| Age at baseline, years | 62.6 (56.7–68.8) | 63.4 (55.4–70.0) | 0.53 |
| Age at onset, years | 49.2 (41.0–55.0) | 50.9 (46.1–57.1) | 0.095 |
| Disease duration | 11.9 (9.3–15.8) | 8.4 (5.3–15.1) | 0.014 |
| No. of comorbidities[a] | 0 (0–0) | 0 (0–0.5) | 0.97 |
| LEDD Baseline (mg) | 1210 (930–1563) | 900 (600–1325) | <0.001 |
| LEDD post-DBS (mg)[b] | 532 (288–900) | | <0.001 |
| H&Y baseline | 2.0 (2.0–2.5) | 2.0 (1.5–2.0) | 0.001 |
| Baseline intake of medication | | | |
| Levodopa[c] | 100% (n = 74) | 80.3% (n = 49) | <0.001 |
| Dopamine-Agonists[c] | 82.4% (n = 61) | 67.2% (n = 41) | 0.041 |
| COMT-Inhibitors[c] | 41.9% (n = 31) | 29.5% (n = 18) | 0.14 |
| MAO-B-Inhibitors[c] | 13.5% (n = 10) | 3.3% (n = 2) | 0.038 |
| Amantadine[c] | 36.5% (n = 27) | 19.7% (n = 12) | 0.032 |
| Apomorphine[c] | 2.7% (n = 2) | 4.9% (n = 3) | 0.50 |
| Neuroleptics[c] | 17.6% (n = 13) | 13.1% (n = 8) | 0.48 |
| Antidepressants[c] | 31.1% (n = 23) | 26.2% (n = 16) | 0.54 |
| Follow-up characteristics | | | |
| Duration of follow-up, years | 9.6 (6.1–12.0) | 8.2 (4.2–13.1) | 0.61 |
| Duration from Baseline until end of study period, years | 16.4 (13.8–19.7) | 17.7 (17.7–17.7) | 0.094 |
| LEDD 10 years after Baseline (mg) | 600 (400–988) | 1316 (963–1475) | <0.001 |

*Note*: Metric and ordinal variables are given in medians (25th–75th percentile). LEDD for the 10 year FU is given as an example; for a graphical depiction of LEDDs over time please see Fig. 1, and for the values over time please Appendix S1.
[a]According to the Charlson comorbidity index.
[b]Post DBS refers to a visit undertaken ~3 (range 2–4) months after DBS implantation.
[c]Data indicates the relative proportion of patients taking this class of substances, total amount in brackets.
Abbreviations: COMT-Inhibitors, catechol-O-methyltransferase Inhibitors; H&Y, Hoehn and Yahr stages; LEDD, levodopa equivalent daily dose; MAO-B-Inhibitors, monoamine-oxidase type B inhibitors; STN-DBS, subthalamic nucleus deep brain stimulation.

management alone. In line with previous uncontrolled long-term studies[6–12] we found that LEDDs are reduced by 56% after commencement of stimulation in comparison to the presurgical baseline and remained stable thereafter. While previous long-term follow-up studies had no control groups, we have also shown that LEDD in medically managed patients continue to increase such that LEDD trajectories diverge until 10 years of follow-up (~15–25 years into the disease) with a maximal relative LEDD change in relation to baseline of up to 96.6% in favor of the DBS cohort. Beyond 10 years LEDD in the control group plateaued or even decreased until last follow-up. In clinical practice, reductions of antiparkinsonian medications in the very late stages of PD are often necessary to address neuropsychiatric complications such as hallucinations, confusion, but also falls (eg, due to orthostatic hypotension) and may also serve to reduce polypharmacy in elderly frail patients.[17]

It would be tempting to speculate that subthalamic DBS has a disease-modifying property indicated by the divergent LEDD trajectories of the two groups, as LEDD has been used in past clinical trials as a surrogate for such effects.[18–20] However, this is not conclusive from our data as (1) LEDDs differed between the two groups at baseline and (2) the divergent trajectories were only observed up to 10 years of follow-up.

The evaluation of the different subclasses of antiparkinsonian medications showed a significant reduction for DA compared to baseline and the control cohort. Previous longitudinal studies showed a reduction mostly for MAO-B inhibitors and COMT inhibitors.[7,21] In addition to a site-policy of lowering or stopping DA therapy with surgery (for successful intraoperative clinical testing), it has to be considered DA use generally decreased during the study period, because of growing concerns around the induction of impulse control disorders.[22] Contrary to what might

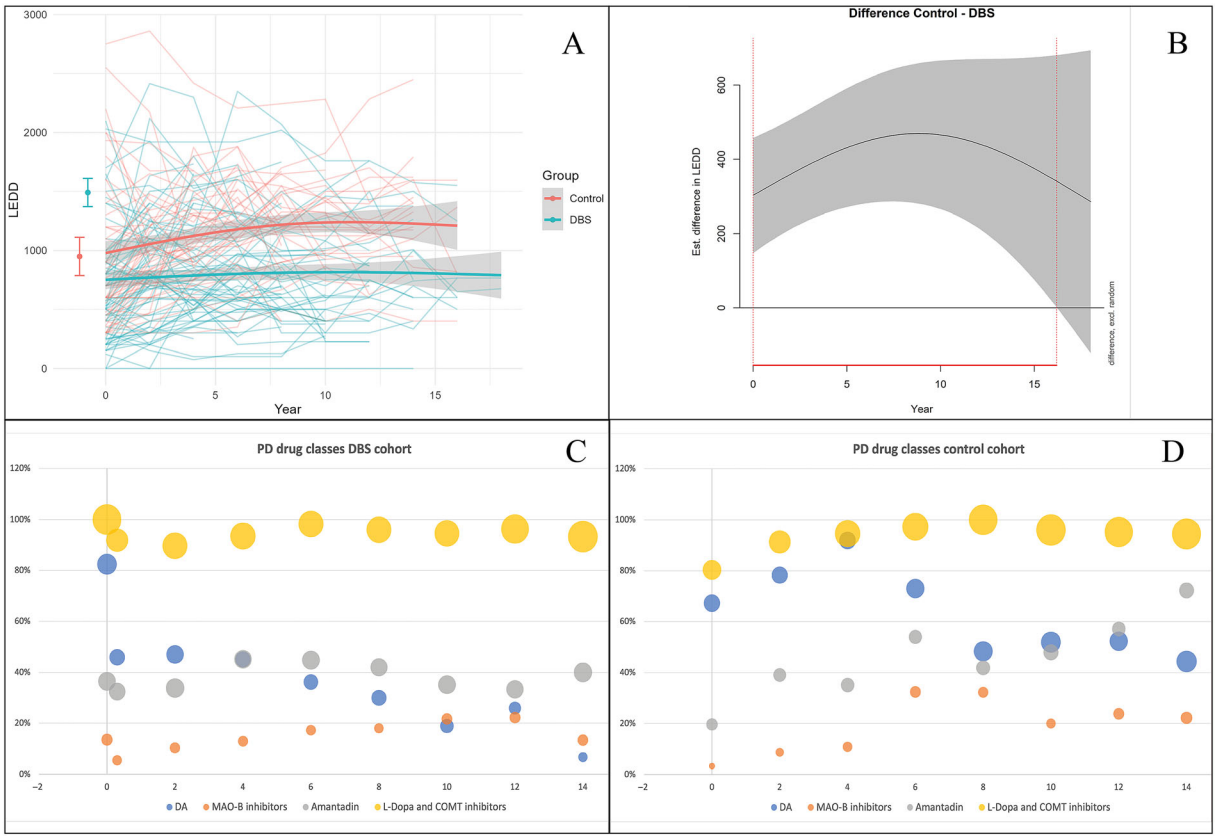


**Figure 1.** Raw individual trajectories of levodopa equivalent daily dose (LEDD) in the deep brain stimulation (DBS) and control group, with group means and 95% confidence intervals represented by bold lines and gray areas, respectively. The distribution of baseline LEDD for the controls and DBS group, respectively, are displayed on the left side as boxplots (**A**). Estimated difference in average LEDD between DBS and control patients over time, starting with the first post-DBS visit for the DBS group. The interval significantly different than 0 is indicated by the vertical and horizontal red lines (**B**). Usage of different antiparkinsonian drugs in the two cohorts over time; Percent users on the *x*-axis, the size of each circle is proportionate to the mean LEDD for that medication class in relation to the baseline values (**C, D**).

be expected, amantadine was not significantly reduced after initiation of stimulation. Similar findings were also made by a long-term study on medication use before and after STN-DBS.[7]

Beyond changes in LEDD the relative use of antidepressants and neuroleptics in our cohorts followed a similar pattern as previous studies[21] with no significant differences between the two cohorts.

There are a number of limitations that need consideration. First, this is a retrospective and single center study such that patient numbers are smaller and the control cohort might not fully represent DBS candidates. However, they were carefully selected according to age at onset and age at baseline and were also not different regarding sex distribution and comorbidities at baseline. Furthermore, we investigated potential confounders including age, sex, disease duration, and stimulation amplitudes. With a mean age at surgery of 63 at mean disease durations of 12 years our cohort compares well to typical DBS patients in other long-term cohorts.[13] Also, baseline LEDD was higher in DBS patients, a fact that is in line with a recent study in the PPMI cohort finding faster LEDD increase in early PD patients as a predictor of future DBS treatment.[23] For these reasons and as LEDD was investigated mainly in relation to change versus baseline compared with the control group, we did not adjust analysis for baseline LEDD. Missing data due to dropouts with increasing follow-up time (e.g., ~50% at 8 years of FU) rendered the model fit increasingly less precise. This is readily visible with widening confidence interval in Fig. 1A,B in the later years.

In conclusion, we found that antiparkinsonian medication was significantly reduced in our DBS patients versus the control patients, who remained on medications only. This effect was sustained until last follow-up.

# Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution,

C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

C.T.: 1A, 1B, 1C, 2A, 2B, 3A
V.B.: 2A, 2B, 3B
F.K.: 2A, 2B, 3B
M.P.: 1C, 2C, 3B
K.M.: 2C, 3B
B.H.: 2C, 3B
A.D.: 2C, 3B
S.K.: 2C, 3B
W.E.: 1C, 2C, 3B
S.E.: 2C, 3B
G.K.W.: 2C, 3B
P.W.: 1A, 2C, 3B
K.S.: 1A, 2C, 3B
W.P.: 1A, 2C, 3B
P.M.: 1A, 1B, 1C, 2A, 2C, 3A, 3B

# Disclosures

**Ethical Compliance Statement:** We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. This retrospective study was approved by the local ethics committee of Medical University of Innsbruck and performed in accordance with the declaration of Helsinki. Informed patient consent was not necessary for this retrospective work.

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# References

1. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Prim* 2017;3:1–21.
2. Poewe W, Mahlknecht P. Pharmacologic treatment of motor symptoms associated with Parkinson disease. *Neurol Clin* 2020;38:255–267. http://www.ncbi.nlm.nih.gov/pubmed/32279709.
3. Macleod AD, Taylor KSM, Counsell CE. Mortality in Parkinson's disease: a systematic review and meta-analysis. *Mov Disord* 2014;29:1615–1622. http://www.ncbi.nlm.nih.gov/pubmed/24821648.
4. Verschuur CVM, Suwijn SR, Boel JA, et al. Randomized delayed-start trial of levodopa in Parkinson's disease. *N Engl J Med [online serial]* 2019;380:315–324. http://www.ncbi.nlm.nih.gov/pubmed/30673543.
5. Deuschl G, Agid Y. Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits. *Lancet Neurol* 2013;12:1025–1034.
6. Mahlknecht P, Foltynie T, Limousin P, Poewe W. How does deep brain stimulation change the course of Parkinson's disease? *Mov Disord* 2022;37:1581–1592. http://www.ncbi.nlm.nih.gov/pubmed/35560443.
7. Ng JH, See AAQ, Xu Z, King NKK. Longitudinal medication profile and cost savings in Parkinson's disease patients after bilateral subthalamic nucleus deep brain stimulation. *J Neurol* 2020;267:2443–2454. https://doi.org/10.1007/s00415-020-09741-3.
8. Lau B, Meier N, Serra G, et al. Axial symptoms predict mortality in patients with Parkinson disease and subthalamic stimulation. *Neurology* 2019;92:e2559–e2570. http://www.ncbi.nlm.nih.gov/pubmed/31043471.
9. Rizzone MG, Fasano A, Daniele A, et al. Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: from the advanced phase towards the late stage of the disease? *Park Relat Disord* 2014;20:376–381. https://doi.org/10.1016/j.parkreldis.2014.01.012.
10. Zibetti M, Merola A, Rizzi L, et al. Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. *Mov Disord* 2011;26:2327–2334. http://www.ncbi.nlm.nih.gov/pubmed/22012750.
11. Castrioto A, Lozano AM, Poon Y-Y, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol* 2011;68:1550–1556. http://www.ncbi.nlm.nih.gov/pubmed/21825213.
12. Fasano A, Romito LM, Daniele A, Piano C, Zinno M, Bentivoglio AR, Albanese A. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain* 2010;133:2664–2676. http://www.ncbi.nlm.nih.gov/pubmed/20802207.
13. Mahlknecht P, Peball M, Mair K, et al. Has deep brain stimulation changed the very long-term outcome of Parkinson's disease? A controlled longitudinal study. *Mov Disord Clin Pract* 2020;7:782–787. http://www.ncbi.nlm.nih.gov/pubmed/33033735.
14. Limousin P, Foltynie T. Long-term outcomes of deep brain stimulation in Parkinson disease. *Nat Rev Neurol* 2019;15:234–242. https://doi.org/10.1038/s41582-019-0145-9.
15. Peralta CM, Frauscher B, Seppi K, Wolf E, Wenning GK, Högl B, Poewe W. Restless legs syndrome in Parkinson's disease. *Mov Disord* 2009;24:2076–2080. http://www.ncbi.nlm.nih.gov/pubmed/19691124.
16. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010;25:2649–2653.
17. Coelho M, Ferreira JJ. Late-stage Parkinson disease. *Nat Rev Neurol* 2012;8:435–442. https://doi.org/10.1038/nrneurol.2012.126.
18. Kieburtz K, Tilley BC, Elm JJ, et al. Effect of creatine monohydrate on clinical progression in patients with Parkinson disease: a randomized clinical trial. *JAMA* 2015;313:584–593. http://www.ncbi.nlm.nih.gov/pubmed/25668262.
19. Parkinson Study Group STEADY-PD III Investigators. Isradipine versus placebo in early Parkinson disease: a randomized trial. *Ann Intern Med* 2020;172:591–598. http://www.ncbi.nlm.nih.gov/pubmed/32227247.

20. Gonzalez-Robles C, Weil RS, van Wamelen D, et al. Outcome measures for disease-modifying trials in Parkinson's disease: consensus paper by the EJS ACT-PD multi-arm multi-stage trial initiative. *J Parkinsons Dis* 2023;13:1011–1033. http://www.ncbi.nlm.nih.gov/pubmed/37545260.

21. Alexoudi A, Shalash A, Knudsen K, Witt K, Mehdorn M, Volkmann J, Deuschl G. The medical treatment of patients with Parkinson's disease receiving subthalamic neurostimulation. *Parkinsonism Relat Disord* 2015;21:555–560; discussion 555. https://doi.org/10.1016/j.parkreldis.2015.03.003.

22. Corvol J-C, Artaud F, Cormier-Dequaire F, et al. Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology* 2018;91:e189–e201. http://www.ncbi.nlm.nih.gov/pubmed/29925549.

23. Lang S, Vetkas A, Conner C, Kalia LV, Lozano AM, Kalia SK. Predictors of future deep brain stimulation surgery in de novo Parkinson's disease. *Mov Disord Clin Pract* 2023;10(6):933–942. https://doi.org/10.1002/mdc3.13747.

# Supporting Information

Supporting information may be found in the online version of this article.

**Figure S1.** Flow chart of participants.

**Figure S2.** Data availability over time.

**Figure S3.** Mean voltage trajectories in DBS patients over time.

**Figure S4.** Neuroleptics use over time.

**Figure S5.** Antidepressant use over time.

**Appendix S1.** Stimulation parameters and their changes of time are given in the text of the supplementary appendix (page 3).