

Treatment Outcomes in Aspirin-Exacerbated Respiratory Disease Based on the 12-Item Short Form Survey

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Abstract

Background: Aspirin-exacerbated respiratory disease (AERD) is optimally managed by endoscopic sinus surgery (ESS) followed by aspirin therapy after desensitization (ATAD). Most AERD quality of life (QOL) studies use the 22-item Sinonasal Outcomes Test (SNOT-22), which focuses predominantly on sinonasal outcomes.

Objective: This study seeks to assess QOL outcomes in AERD patients after ESS and ATAD via the 12-item Short Form Survey (SF-12), a well-validated QOL measure for general health status of chronic conditions.

Methods: Retrospective review of 112 AERD patients who underwent ESS followed by ATAD at our institution between 2016 and 2019. SF-12 was collected preoperatively, postoperatively/pre-AD, and serially post-AD (1–3, 4–6, 7–12, and >12 months). Optum[®] PRO CoRE software was used to compare data to national norms. ANOVA was performed comparing physical component summary (PCS), mental component summary (MCS) and eight health domains (physical functioning, role physical, general health, bodily pain, vitality, social functioning, role emotional, and mental health).

Results: AERD patients showed improvement in PCS scores across all timepoints after ESS and ATAD ($p = 0.004$). When stratified by gender, women demonstrated an improvement in PCS scores ($p = 0.004$). Within the domains, there were significant improvements in social functioning (SF), role physical (RP), and bodily pain (BP) at all timepoints (SF: $p = 0.006$; RP: $p = 0.005$; BP: $p < 0.001$).

Conclusions: AERD patients undergoing ESS and ATAD show improvement in physical QOL and 3 of the 8 health domains as measured by the SF-12. Future studies can use the SF-12 to study the impact of AERD treatment versus other chronic diseases and health demographics.

Keywords

aspirin-exacerbated respiratory disease, quality of life, endoscopic sinus surgery, aspirin desensitization, 12-item Short Form survey

Introduction

Aspirin-exacerbated respiratory disease (AERD) consists of a triad of chronic rhinosinusitis with nasal polyps (CRSwNP), adult-onset asthma, and airway hypersensitivity to acetylsalicylic acid (ASA) and cyclooxygenase-1 (COX-1) inhibitors.^{1,2} When compared to patients with chronic rhinosinusitis (CRS), AERD patients have worse disease severity and are

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often recalcitrant to conventional therapies, including surgery.³ The disease is optimally managed by a combination of endoscopic sinus surgery (ESS) followed by aspirin therapy after desensitization (ATAD).^{4–6}

The goal of any treatment is to address the disease and improve quality of life. Disease-specific instruments and health-related quality of life (HRQL) tools have been developed to evaluate the impact of treatment on AERD patients. The majority of AERD quality of life (QOL) studies use the 22-item Sinonasal Outcomes Test (SNOT-22).^{4,7,8} The disease-specific SNOT-22 excels at evaluating the impact of treatment on AERD at an individual level due to its focus on sinonasal symptoms, however it does not allow for direct comparisons with other chronic conditions. There are several generic HRQL assessment tools, including the Health Utility Index (HUI),⁹ the Short Form 36 (SF-36)¹⁰ and its abridged versions, the 12-item Short Form Survey (SF-12)¹¹ and Short Form Six-Dimension (SF-6D), which allow for comparison of diseases at both a functional level and as a burden to society. Both the SF-12 and SF-36 have been used to analyze quality of life in patients with chronic rhinosinusitis, including after ESS.^{12–14} CRSwNP patients have lower QOL when compared to population norms and other chronic conditions, like congestive heart failure and chronic obstructive pulmonary disease.^{14,15}

Aside from improvements in quality of life, it is important to ensure that interventions are simultaneously cost-effective. The estimated average annual health care cost of CRS is 8.6 – 13 billion dollars per year in the United States, with the majority of costs stemming from medical management and ambulatory care.^{16–18} AERD patients incur higher treatment costs compared to CRS patients alone due to a higher number of inpatient visits, procedures, and prescriptions.^{19,20} The SF-12 scoring software via QualityMetric incorporates a predictive model for future medical expenditures, allowing physicians to identify patients at risk for increased medical cost or evaluate cost-effectiveness of certain interventions.¹¹ Currently, no study has used the SF-12 to evaluate AERD patients. This study seeks to assess QOL outcomes in AERD patients after ESS and ATAD via the SF-12, a well-validated QOL measure for general health status of chronic conditions.

Methods

This research was approved by the Institutional Review Board at the University of Pennsylvania. A retrospective review was performed of all ASA-challenge proven AERD patients in the Division of Rhinology and Skull Base Surgery at the University of Pennsylvania between July 2016 and November 2019. Patients were included if they underwent endoscopic sinus surgery (ESS) by one

of two senior attending rhinologists (JNP or NDA) followed by aspirin desensitization (AD) and ongoing aspirin therapy after desensitization (ATAD) by the senior allergist (JVB). SF-12 questionnaires were collected and included in the analysis at the following timepoints: pre-operative (timepoint 1), postoperative (timepoint 2), and serially post-AD at 1–3, 4–6, 7–12, and over 12 months (timepoints 3, 4, 5, and 6 respectively). Patients were excluded if they were under the age of 18 years, failed ATAD, or did not complete an SF-12 form. Demographic data including age, sex, and smoking status were additionally collected.

The SF-12 survey is a 12-item patient-reported health outcomes questionnaire developed by Ware et al. as part of the Medical Outcomes Study (Figure 1).¹¹ Patient responses are quantified and converted into eight separate health domains (physical functioning (PF), role physical (RP), general health (GH), bodily pain (BP), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH)) with two validated scores, the physical component summary (PCS) and the mental component summary (MCS), all of which are provided as *T* scores. The health domain and component scores are calculated using a norm-based scoring algorithm and compared to United States (U.S.) national norms where 50 indicates the mean response of a healthy U.S. adult, with a standard deviation of 10. Each 1-point difference or change in *T* score is equivalent to one-tenth of a standard deviation. A score over 50 indicates better health than the average adult whereas a score lower than 50 indicates worse health. As a general rule, when evaluating group-level data, scores within 0.3 standard deviation are considered to be within the “normal” range for the U.S. general population. In other words, a group mean score of less than 47 would suggest impaired functioning within that specific domain or component summary score.²¹

One-way analysis of variance (ANOVA) was performed comparing PCS, MCS, and the eight health domains (PF, RP, GH, BP, VT, SF, RE, MH) to national norms. Univariate, single-variable regression was performed comparing PCS, MCS, and smoking status to SNOT-22 scores. Health care expenditures were analyzed using a two-tailed *T*-test comparing medical expenditures across timepoints to national means. This was further subcategorized by gender and age as evaluated by a one-way ANOVA. Health survey responses were compiled and categorized using Optum[®] PRO CoRE (Optum, Inc., Eden Prairie, MN) software. Statistical analysis was performed using Stata Version 15.1 (StataCorp, 2017. *Stata Statistical Software*. College Station, TX: StataCorp LP).

Results

There were 197 patients with AERD who were seen at our institution during the study period. Eight-five

Your Health and Well-Being				
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1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Yes, limited a lot	Yes, limited a little	No, not limited at all
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 - a Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf..... ☐ 1 ☐ 2 ☐ 3
 - b Climbing several flights of stairs..... ☐ 1 ☐ 2 ☐ 3
3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
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 - a Accomplished less than you would like..... ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
 - b Were limited in the kind of work or other activities..... ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
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 - a Accomplished less than you would like..... ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
 - b Did work or other activities less carefully than usual..... ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
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 - a Have you felt calm and peaceful? ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
 - b Did you have a lot of energy? ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
 - c Have you felt downhearted and depressed? ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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 (SF-12v2® Health Survey Standard, United States (English))

Figure 1. 12-item Short Form Survey.

patients were excluded due to: 1) lack of SF-12 survey ($n=74$), 2) inability to tolerate aspirin therapy ($n=2$), and 3) did not have ESS or had ESS at an outside institution ($n=9$). A total of 112 patients were identified who met inclusion criteria, 53 (47.3%) of whom were male with a median age of 51.5 years (interquartile range 40.8–62.3). The mean SNOT-22 score at pre-op and 6 months post-AD were 48.8 ± 20.7 and 18.4 ± 16.0 . Assessment of SF-12 survey responses from all timepoints showed an increase in PCS following ESS and ATAD (ANOVA $F=3.46$; $p=0.004$) (Table 1). There was no significant difference in MCS across survey timepoints (ANOVA $F=1.16$; $p=0.32$) (Table 2). When stratified by gender, females demonstrated an improvement in PCS scores from baseline (ANOVA $F=3.60$; $p=0.04$) (Table 3), however this was not significant for males

Table 1. PCS Scores Versus General Population Norms.

Timepoint	N	Mean	SD	P-value
Pre-op	77	48.73	7.64	0.38
Post-op/Pre-AD	74	47.79	7.14	0.12
1–3 mo post-AD	52	49.89	7.71	0.23
4–6 mo post-AD	35	51.78	8.12	0.41
7–12 mo post-AD	36	52.62	6.01	0.18
>12 mo post-AD	32	51.84	7.32	0.40
Between all timepoints (single institution) $F=3.46$				0.004*

AD: Aspirin Desensitization; PCS: physical component summary; SD: standard deviation; *denotes statistical significance at 0.05 level.

Table 2. MCS Scores Versus General Population Norms.

Timepoint	N	Mean	SD	P-Value
Pre-op	77	50.85	10.07	0.60
Post-op/Pre-AD	74	52.32	8.28	0.12
1–3 mo post-AD	52	53.59	7.49	0.04
4–6 mo post-AD	35	52.24	7.62	0.14
7–12 mo post-AD	36	54.33	6.81	0.04
>12 mo post-AD	32	51.49	8.93	0.26
Between all timepoints (single institution) $F=1.16$				0.32

AD: Aspirin Desensitization; MCS: mental component summary; SD: standard deviation.

Table 3. Comparison of PCS Scores by Sex (Mean $\pm$ SD).

Timepoint	Female	Male	P-Value
Pre-op	48.59 ± 6.98	48.87 ± 8.36	0.87
Post-op/Pre-AD	46.53 ± 6.87	48.67 ± 7.33	0.21
1–3 mo post-AD	49.59 ± 7.77	50.94 ± 7.76	0.54
4–6 mo post-AD	51.40 ± 8.22	51.27 ± 8.25	0.69
7–12 mo post-AD	53.52 ± 5.15	51.56 ± 6.92	0.34
>12 mo post-AD	52.37 ± 6.80	51.19 ± 8.30	0.79

(ANOVA $F=0.72$; $p=0.61$), or when evaluating MCS (females, ANOVA $F=0.78$ $p=0.56$; males, ANOVA $F=1.18$; $p=0.28$) (Table 4).

When stratifying by health domains, there were significant improvements in social functioning (SF), role physical (RP), and bodily pain (BP) between the baseline timepoint and subsequent follow-up points (SF, ANOVA $F=3.33$; $p=0.006$; RP, ANOVA $F=3.41$; $p=0.005$; BP, ANOVA $F=4.31$; $p<0.001$) (Table 5). SF domain measures the frequency at which physical health or emotional problems interfere with normal social activities. RP domain assesses role limitations due to physical health, specifically 1) limitations in the kind of work performed and 2) achieving less than the respondent would have liked. BP domain evaluates the extent of interference with normal work activity due to

Table 4. Comparison of MCS Scores by Sex (Mean $\pm$ SD).

Timepoint	Female	Male	P-value
Pre-op	50.91 ± 9.31	50.79 ± 10.79	0.96
Post-op/Pre-AD	49.63 ± 10.27	54.39 ± 7.64	0.015*
1–3 mo post-AD	53.15 ± 7.16	54.07 ± 7.30	0.67
4–6 mo post-AD	50.33 ± 7.71	53.83 ± 7.01	0.19
7–12 mo post-AD	53.35 ± 8.43	55.49 ± 5.34	0.36
>12 mo post-AD	50.04 ± 8.08	52.89 ± 6.36	0.40

*denotes statistical significance at 0.05 level.

Table 5. Health Domain Scores Across Timepoints.

Timepoint	Mean
Social Functioning (SF) score	
Pre-op	79.60
Post-op/Pre-AD	77.08
1–3 mo post-AD	90.20
4–6 mo post-AD	85.60
7–12 mo post-AD	90.97
>12 mo post-AD	83.06
ANOVA (between timepoints): $F=3.33$, $P=0.006^*$	
Role Physical (RP) score	
Pre-op	77.11
Post-op/Pre-AD	69.11
1–3 mo post-AD	81.12
4–6 mo post-AD	83.09
7–12 mo post-AD	85.76
>12 mo post-AD	85.08
ANOVA (between timepoints): $F=3.41$, $P=0.005^*$	
Bodily Pain (BP) score	
Pre-op	77.59
Post-op/Pre-AD	71.83
1–3 mo post-AD	84.50
4–6 mo post-AD	87.85
7–12 mo post-AD	92.36
>12 mo post-AD	82.25
ANOVA (between timepoints): $F=4.31$, $P<0.001^*$	

*denotes statistical significance at 0.05 level.

pain.²¹ There was no significant difference in PCS or MCS when patients were stratified by age (PCS $p=0.72$, MCS $p=0.18$). Subjects were further categorized by smoking status. There was no difference between MCS and PCS scores among current smokers versus non-smokers. When PCS and MCS scores were compared with SNOT-22 scores, scores were inversely correlated at 6 months (MCS, univariate regression, coefficient = -1.69 ; $p=0.001$; PCS, coefficient = -0.17 ; $p=0.03$). This result corresponds to both surveys reporting improved QOL (where higher score on SF-12 indicates higher QOL, lower score on SNOT-22 indicates higher QOL) (Table 6).

There was a significant difference across all timepoints between the cohort monthly expenditure and national mean monthly expenditure (Table 7). However, when compared to baseline, there was an observed gradual decrease in the cohort monthly expenditure through timepoint 5. When patients were stratified by sex, mean medical expenditures were higher for men than for women at timepoint five (t-test, $\$277.96 \pm \$15.99$ vs $\$186.19 \pm \$34.88$; $p=0.02$). There were no significant differences in expenditures based on age group at any timepoint.

Discussion

This is the first publication evaluating SF-12 scores in patients diagnosed with AERD. At baseline, the average

Table 6. Univariate Regression Comparing PCS and MCS Versus SNOT-22 Scores.

Timepoint (PCS)	SNOT-22 (SD)	Coefficient	P-Value
1 (pre-op)	48.8 (20.7)	0.03	0.47
4 (6 month post-AD)	18.4 (16.0)	-0.17	0.03*
Timepoint (MCS)	SNOT-22 (SD)	Coefficient	P-Value
1 (pre-op)	48.8 (20.7)	-0.317	0.335
4 (6 month post-AD)	18.4 (16.0)	-1.69	0.001*

SNOT-22: Sinonasal Outcome Test; AD: aspirin desensitization; SD: standard deviation; *denotes statistical significance at 0.05 level.

Table 7. Medical Expenditures Versus National Mean Across Timepoints.

Timepoint	Mean $\pm$ SD	Cost Above National Mean (\$137)	P-Value
Pre-op	\$260.96 $\pm$ 158.60	+ \$123.96	<0.001
Post-op/Pre-AD	\$262.37 $\pm$ 126.22	+ 125.37	<0.001
1-3 mo post-AD	\$246.32 $\pm$ 160.35	+ 109.32	<0.001
4-6 mo post-AD	\$243.65 $\pm$ 167.96	+ \$106.65	<0.001
7-12 mo post-AD	\$228.14 $\pm$ 115.37	+ 91.14	0.006
>12 mo post-AD	\$284.75 $\pm$ 279.28	+ 147.75	<0.001

PCS and MCS scores of our AERD patients were not significantly different when compared to the general U.S. population based on survey definition. However, it is important to note that the average PCS score was relatively lower compared to the general norm preoperatively. Furthermore, by 12 months post-ESS and -AD, there was an overall significant improvement in PCS score by over 0.3 standard deviations within our cohort (Table 1), with a marked improvement in the female cohort (Table 3). Within the individual health domains, there were significant improvements in social functioning (SF), role physical (RP), and bodily pain (BP) after ESS and ATAD (Table 5).

These findings are consistent with previous studies utilizing the Short Form surveys for CRS.^{14,15,22,23} For example, using the SF-36, Metson et al. showed that CRS patients had worse function in the BP and SF sub-scores when compared to national norms.¹⁵ In addition, when CRS patients were compared pre- and post-FESS, there was a significant improvement in PF, RP, BP, SF, VT, and MH.

It is well known that surgery and subsequent aspirin desensitization improves respiratory symptoms and sense of smell, slows polyp regrowth, reduces need for revision surgery, and decreases topical and oral corticosteroid use.^{4-6,24,25} In combination with previously published data on improved sinonasal outcomes,^{4,25-27} this SF-12 study highlights how ESS and AD can also lead to an improvement in overall physical burden and social function for AERD patients. The improvements in the SF-12 scores within our AERD cohort are mirrored by their SNOT-22 scores. In addition, the mean pre-operative SNOT-22 score was 48.8, which is comparable to other cohorts of AERD patients prior to treatment.^{3,28,29}

An emerging number of studies have sought to evaluate non-sinonasal related disease burden of AERD, including disruptions in eating-related QOL³⁰ and depression.³¹⁻³⁴ Using disease specific tools, these studies show that AERD patients tend to perform the same or better in regards to overall physical and psychological issues when compared to other chronic illnesses. For instance, using the Beck Depression Inventory and Mini Asthma Quality of Life Questionnaire, Feldman et al. showed that AERD patients reported fewer depression symptoms, better asthma-related QOL, and subjectively less asthma-related impairment when compared to asthma-only patients.³¹ Our baseline SF-12 data further corroborates these studies, demonstrating that AERD patients are generally on par with the general population when it comes to the physical and mental domains.^{31,32} When analyzing overall physical and health domains, use of a general QOL tool can provide a broader, more beneficial overview of the effects of various interventions.

Aside from providing general health related QOL information, the SF-12 offers unique insight into the

economic burden of AERD. While the economic burden of CRS, which is estimated at \$8.6 billion per year, has been studied, the economic burden among AERD patients has not been fully investigated.^{16,35,36} Rudmik et al. demonstrated that early intervention with ESS versus continued medical therapy was cost-effective for patients with refractory CRS.³⁷ A recent study by Bhattacharyya et al. showed that patients with CRSwNP had higher annual healthcare costs and resource utilization when compared to CRS without nasal polypsis (CRSsNP).¹⁶ Furthermore, CRSwNP patients who had co-morbid asthma or were on corticosteroids or macrolides had higher costs when compared to CRSwNP patients without these additional factors. Based on the SF-12 data, AERD patients have a significantly higher monthly healthcare expenditure compared to the general U.S. population (\$137/month). Our study shows a gradual decrease in monthly medical expenditure, up to 12 months post-ESS and -AD (Table 7). This finding supports a previous study utilizing an economic model to demonstrate the cost-effectiveness of aspirin desensitization in AERD.³⁸ Further studies on the cost-effectiveness of various interventions for AERD are required and could potentially be performed utilizing the SF-12 survey.

The use of a general health questionnaire, like the SF-12, is relatively novel for the study of AERD. Currently, the vast majority of outcomes studies in AERD patients utilize disease-specific QOL metrics such as the SNOT-22, Asthma Control Test (ACT), or the Rhinosinusitis Disability Index (RSDI).^{4,26,27,30,39} The SNOT-22 is characterized into five distinct domains – rhinologic, extra-rhinologic, ear/facial, psychosocial, and sleep – which allow physicians to evaluate outcomes of interventions for CRS.⁴⁰ Similar to the SNOT-22, the RSDI, which is comprised of 30-questions on a Likert-scale, provides information within 3 areas: physical, functional, and emotional. However, the additional data comes at the expense of increased patient burden, requiring about 5–7 mins to complete.^{41,42} While these questionnaires are useful at evaluating specific disease outcomes, they lack the ability to compare QOL in CRS patients to QOL in other chronic diseases.⁴²

Realistically, many of these QOL instruments are complementary and together can improve evaluation of treatment outcomes, particularly for AERD. The SF-36 offers a sensitive, comprehensive evaluation of various chronic illnesses, and due to its widespread use, provides the ability to compare chronic diseases to one another.⁴³ The SF-12 survey offers a representative sampling of the SF-36 and eliminates the constraints of time burden and questionnaire length.¹¹ Ultimately, the combined use of a disease-specific instrument, like the SNOT-22, and a general QOL tool, like the SF-12, can provide a better evaluation of the patient and the outcomes following interventions and thereby help guide

treatment choices moving forward. The ease and brevity of the SF-12 survey makes it ideal as a general QOL tool in the clinical setting.

There are some limitations to this study that need to be considered, including the modest sample size. As this is a survey-based study at a tertiary center, it is difficult to perform a prospective longitudinal study due to practice referral patterns and subject attrition at long-term follow-up. Some of our patients who are doing well choose to follow-up with their local otolaryngologist after 3–6 months post-ESS. The reduction in sample size may skew the survey results at later timepoints. In addition, as patients presented to a tertiary rhinology clinic, there may be more severe disease at baseline. Other limitations of our study design include non-response as some participants missed follow-up appointments and failed to fill out the survey completely at each of the timepoints. Finally, the Optum® PRO CoRE software may have presented a limitation to our study, as the software developer's proprietary intellectual property rights prevented us from accessing the data comprising the U.S. national norms used for comparison.

Despite the above limitations, this is the first study using the SF-12, a general QOL tool, to evaluate the effects of ESS and ATAD in AERD patients. Future studies will use the SF-12 to examine the disease burden and economic impact of AERD versus other chronic diseases and health demographics.

Conclusions

ESS followed by ATAD for AERD patients results in an improvement in physical QOL and three of the eight health domains as measured by the SF-12. This is consistent with previous quality of life studies evaluating treatment outcomes in CRS. This study highlights the potential use of the SF-12 to compare various interventions and their effectiveness for AERD patients and to perform a comparative analysis of AERD versus other chronic illnesses.

Authors' Note

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: D. W. K. is a consultant for GSK, Fiagon, Medtronic, and NeurENT. The remaining authors declare no relevant conflicts of interest.

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