Research article

Anti-seizure medications and quality of life in person with epilepsy

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ABSTRACT

Objective: The goal of this study was to determine the effects of mono-, bi-, and polytherapy anti-seizure medications (ASMs) in terms of seizure reduction and quality of life (QOL) in persons with epilepsy (PWE).

Methods: A cross-sectional observational study was conducted. All PWE with age <75 years were recruited and further classified into two groups: responders and non-responders, based on the response of the ASMs to the treatments for reduced seizure frequency since the last one year. Other demographic and clinical data such as seizure frequency, type of seizures, age at onset of seizures, and information about ASMs with their daily doses were assessed for the descriptive analysis. The quality of life was assessed in randomly selected PWE (n = 100) using the quality of life in epilepsy inventory-31 (QOLIE-31) in adults.

Results: With a total of 486 PWE, the median age (years) was comparable in both groups. Out of these the non-responders group was found to be significantly higher (77.8%) than the responders group (22.2%). In the responders group, the percentage of PWE who were on monotherapy was significantly higher (51.85%) than those who were on polytherapy (17.59%), whereas in the non-responders group, 21.16% of PWE were on monotherapy and 44.86% were on polytherapy. The duration of epilepsy was similar in both groups, but the average seizure frequency was significantly higher in the non-responders. In QOL assessments, 43% of PWE were observed in the responders group, whereas 57% of PWE were found in the non-responders group. The overall comparative QOL scores were also significantly higher (p < 0.0001) in the responders group as compared to the non-responders group.

Conclusion: Our findings revealed that those PWE who were on monotherapy showed better reduction in seizure frequency and improved QOL in responder groups as compared to non-responders group.

1. Introduction

Recurrent seizures characterize epilepsy, a neurological disorder. It affects approximately 50 million people worldwide, with 40 million receiving no treatment and 85 percent living in developing countries [1, 2]. This prevalence may be related to concerns about epilepsy diagnosis and drug management strategies at tertiary care centers. The prevalence rate in India was reported to be 3.0 to 11.9 people per 1000 people, with an annual incidence of 0.2–0.6 people per 1000 people [3]. Despite the availability of different anti-seizure medications (ASMs), approximately 30% of epilepsy patients are resistant to drug treatment [4]. Other non-pharmacological therapies, such as resective surgery, vagus nerve stimulation, and dietary therapy are used to treat persons with epilepsy (PWE) or drug resistance patients [5]. In recent years, ~20 ASMs have been found to treat PWE and each has unique pharmacokinetic features for controlling seizure frequency. Based on the diagnosis of epilepsy types and frequencies of seizures, these ASMs are usually recommended in doses of either mono- or bi-, or polytherapy. Phenytoin (PHT), carbamazepine (CBZ), and sodium valproate (VPA) are the first-generation ASMs that are widely used for the treatment of epilepsy [6, 7]. However, in combination therapy is also recommended with a combination of first-generation ASMs and newer ASMs such as Clobazam (CLB), gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (Ox-CBZ), topiramate (TPM), and Zonisamide (ZNS). These recommendations is usually based on the seizure severity or seizure frequency in PWE [8, 9]. Furthermore, these doses and numbers of prescribed ASMs are considered in view of minimizing the side effects of ASMs and followed by maintaining or improving the quality of life (QOL) [10]. Currently, various studies have been conducted to evaluate the pharmacological effects and their interactions by using either first-generation

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ASMs or their combinations with newer-generation ASMs, that might be associated with reducing seizure frequency or improving the quality of life and also minimizing the adverse effects in PWE [11]. In the previous reports, the effects of ASMs were associated with modulating the seizure frequency as well as QOL and these studies were performed in different ethnic regions which have shown the variations with ethnicity. Anxiety and depression are substantially more common in epilepsy patients than in the healthy population, which shows that patients exhibiting symptoms of anxiety and/or depression are not receiving standard care in the epilepsy management [12, 13]. In terms of ASMs, it has also been demonstrated that initial prescription of monotherapy and further addition of newer regimens was more effective in controlling seizures and reduced the seizure frequency significantly in PWE [14, 15, 16]. However, the use of these bi or polytherapy ASMs has been found to cause drug resistance and showed adverse effects in PWE. These phenomenal changes may be impacted due to drug-drug interactions or other pharmacologically or physiologically unknown mechanisms that may be attributed to disease pathogenicity and affect to the treatments [17]. Detrimental ASMs side effects and depression were found to have a significant negative impact on a person’s perception of their present health status. Additionally, the subsequent selection of appropriate antiepileptic medications and the early identification and treatment of depression may result in considerable improvements in the general health of epilepsy patients [18]. It has been shown that the numbers and doses of ASMs can modulate the seizure frequency and effects on the QOL to cause multiple psychological disorders like abnormal behavior, stigma, physical impairments, or other mental co-morbidities like social, behavioral, psychological, or psychological well-being. In a study, stigma was found to be associated with seizure severity and it showed a poorer quality of life [19, 20]. The effect of ASMs in PWE resulted in a worse quality of life due to enriched seizure episodes, adverse effects, psychological issues, and various etiological aspects that may lead to medical co-morbidities. These limitations provide an urgency to conduct more studies to address the concerns which may be impacted by ASMs in seizure frequency and QOL for disease management in PWE of different ethnic regions [21].

Therefore, in our study, we performed a cross-sectional descriptive cohort study in order to assess the effect of mono-, bi-, and polytherapy in two groups: responders versus non-responders group in the Indian population. In addition, we have evaluated the effect of these ASMs on the quality of life (QOL) with randomly selected PWE in both groups.

2. Methods

2.1. Study design and recruitment

This was a cross-sectional, observational, prospective study that was carried out at the All India Institute of Medical Sciences (AIIMS), New Delhi, India. This study was approved by institutional ethics committee, AIIMS, New Delhi. All eligible PWE were recruited from the epilepsy clinic in the Out-Patients Department (OPD) of neurology. Written consent was requested from the subjects or their parents/guardians. PWE who were clinically diagnosed with epilepsy, aged <75 years old, and had on either mono-, bi-, or polytherapy of first-generation ASMs or a combination of newer ASMs in the last three months were included in the study. Patients who were unable to give consent or who had a history of other illnesses such as stroke, tuberculosis, diabetes, endocrine disorders, AIDS, or who presented with non-epileptic seizures or pseudo-seizures were excluded from the study (14). The diagnosis of epilepsy was made according to ILAE (International League Against Epilepsy) guidelines [22].

2.2. Data collection and estimation of ASMs on seizure control

In PWE, clinical and demographic data were recorded in the standard clinical peroma at the time of recruitment, including age, gender, seizures frequency and type, age at onset, seizures control, clinical investigation details, and prescription of ASMs. The scalp electroencephalography (EEG) records were collected to support epilepsy diagnosis and classification. PHT, CBZ, VPA, PHB, LEV, CLB, LTG, OxCBZ, Clonazepam (CLZ), TPM and ZNS were among the ASMs recommended to PWE. Based on the number of medication intake, all enrolled patients were divided into three groups: (i) monotherapy included individual ASM; (ii) bitherapy included a combination of two ASMs; and (iii) polytherapy included a combination of three or more ASMs. The effectiveness of ASMs was divided into two groups: A) responders group: those who had no seizure since last one year and controlled by ASMs. B) non-responders group: those who had at least one or more seizures occurring daily, weekly, monthly, or yearly and not controlled by ASMs.

2.3. Assessment of quality of life

A total of 100 PWE (>18 years of age) were evaluated for their QOL. These subjects were randomly screened using random sampling methods in both groups. The quality of life in epilepsy inventory-31 (QOLIE-31) scale was used to assess the overall QOL. It is an individual and self-administered questionnaire that consists of 31 questions. It is related to health (physical and mental) and routine activities, and it takes around 10–15 min for the administration of each patient. These questionnaires were evaluated by either subjects or caregivers (in the cases of participants who were not able to complete the form). The responses to the questionnaire were recorded in our datasheet. These responses were measured using a Likert scale and translated into a linear scale (ranging from 0 to 100) and rated as per the standard recommendations of the scores [23].

2.4. Statistical analysis

The dataset was analyzed using STATA version 14.0. The descriptive statistics were represented in terms of mean, standard deviation (SD), and, wherever appropriate, number and percentage. Discrete variables were tested using the Wilcoxon rank-sum method. The chi-square test was used to compare the frequency of individual ASMs between each group. To compare the means of QOL scores and medication therapies between the two groups, the unpaired t-test or one-way analysis of variance (ANOVA) was utilized. A p-value of <0.05 was used to determine the degree of significance.

3. Results

3.1. Demographic and clinical characteristics

A total of 490 PWE were screened for this study, and out of these, a total of 486 PWE were studied. Two subjects had neuropathy and two declined to participate, henceforth excluded from the study. In these, 22.22% and 77.78% of PWE were found in the responders group and the non-responders group, respectively. The distribution of gender (male and female), median age and the duration of epilepsy were comparable in both groups. Age at onset of seizures was significantly higher (p = 0.036) in the responders as compared to the non-responders. As expected, the average seizure frequencies (in a year) were higher (326.85 ± 1360.99) in PWE of the non-responders group whereas the responders group showed controlled seizure frequency or no seizures. The number of seizures was observed as daily (18.52%), weekly (10.05%), monthly (47.09%) and yearly (24.34) basis in the non-responders group. A total of 1360.99)

In the responders group, both the generalized seizures (49.47%) and focal seizures (50.53%) were quite similar. The detailed demographic and clinical characteristics of the enrolled PWE are stipulated in Table 1.

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Table 1. Demographic and clinical characteristics of PWE (n = 486).

| Variables                      | Responders group N (%) | Non-responders group N (%) |
|--------------------------------|-------------------------|-----------------------------|
| Total subjects                 | 108 (22.22)             | 378 (77.78)                 |
| Age (mean ± SD)                | 26.38 ± 13.59           | 22.51 ± 11.97               |
| Median (Range)                 | 23 (7-63)               | 20 (2-70)                   |
| Type of seizures               |                         |                             |
| Generalized seizures           | 68 (62.96)              | 191 (50.53)                 |
| Focal seizures                 | 40 (37.04)              | 191 (50.53)                 |
| Gender                         |                         |                             |
| Male                           | 65 (60.19)              | 253 (66.93)                 |
| Female                         | 43 (39.81)              | 125 (33.07)                 |
| Age at onset of seizures (in yrs) | 16.25 ± 13.40           | 13.12 ± 11.16               |
| Median (Min-Max)               | 14 (0.1-55)             | 11 (1.01-66)                |
| Duration of Epilepsy (in years) | 10.12 ± 7.6716          | 9.39 ± 8.47                 |
| Median (Min-Max)               | 8.95 (1-43)             | 7 (0.5-49)                  |
| Average Seizure frequency in last one year (mean ± SD) | 326.85 ± 1360.99 | 0 |
| At least one seizures:         |                         |                             |
| Daily                          | -                       | 70 (18.52%)                 |
| Weekly                         | -                       | 38 (10.05%)                 |
| Monthly                        | -                       | 178 (47.09%)                |
| Yearly                         | -                       | 92 (24.34%)                 |
| >1 year                        | 108 (100%)              | -                           |

(Data are represented as mean ± SD, number (percentage).

3.2. ASM treatment outcomes

51.85% of PWE in the responders group were on monotherapy, which was significantly higher than PWE in the non-responders group (21.16%). However, those subjects who were on bitherapy found slightly higher in the non-responders group (35.08%) than the responders group (30.56%) and this trend was more prominent in those PWE who had on polytherapy and found to be significantly higher in the non-responders group (42.86%) than the responders group (17.59%). PWE who had been on monotherapy or a combination of bi or polytherapy in both groups, were included as VPA, CLB, CBZ, LEV, and PHT. The decreasing pattern of PWE distribution in both groups was included in PHT, CBZ, VPA, LEV, ZNS, and Ox-CBZ, and then recommended other monotherapies as shown in Figure 1. In both groups, a maximum of six ASMs were prescribed. The daily doses of prescribed ASMs were included as LEV, VPA, Ox-CBZ, CBZ, PHT, ZNS, TPM, LTG, PHB, CLB, and CLZ in decreasing order. The detailed ASM profile and doses are described in Table 2.

3.3. Effect of ASMs in quality of life

The QOL was assessed using a random sampling procedure on a total of 100 PWE subjects. In both groups, the mean age and age at the onset of epilepsy were almost similar. Both groups had a higher percentage of males than females. Similarly, the prevalence of generalized seizures was found to be higher than focal seizures. 51.16% of the responders group was on monotherapy, whereas 47.37% of the non-responders group was on bitherapy. We found that the responders group showed a significantly improved overall QOL (p < 0.0001) as compared to the non-responders group in PWE. The other sub-domains like seizure worry, overall quality of life, emotional wellbeing, energy/fatigue, cognitive function, medication effects, social functioning, and overall weighted average health-related quality of life were quietly similar in both groups. Also, the responders group showed higher overall and sub-domain QOL scores for those subjects who were on monotherapy as compared to the non-responders group. The overall total QOL scores ranged from 34.0 to 62.0, with the lowest score of 34.0 and the highest score of 62.0. In more details, the overall QOL scores and subscale scores for both groups are represented in Table 2.

In addition, we also evaluated the individualized effects of monotherapy, bitherapy, and polytherapy on QOL. The overall QOL score in both groups was significantly higher (p = 0.0009 & p = 0.0042) when compared to mono-, bi-, or polytherapy separately. However, frequency was observed in a similar manner. In both groups, the total mean scores of all sub-domains were significantly higher (p < 0.0001) in those PWE who had on monotherapy as compared to bi- or polytherapy. In addition, the overall individual sub-domain subset mean scores of the responders group were higher than those of the non-responders group. Table 4 represents the individualized effect of ASMs using QOL domains.

4. Discussion

As a result of the current increasing cases of PWE, there is a need to focus on attaining seizure freedom and achieving optimal QOL by the use of appropriate ASMs. The use of first generation medications either alone or in combination with newer medications is widely prescribed to manage epilepsy. The continuous uses of these ASMs (mono, bi- or polytherapy) were resulted in the form of uncontrolled seizures, generated...
the adverse effects and may cause drug resistance and further deteriorate the quality of life [24, 25]. Therefore, the uses of appropriate therapeutic doses of ASMs to control seizure frequency and improve quality of life are critically needed to be evaluated. In this study, we designed to evaluate the impact of ASMs (monotherapy, bi- or polytherapy) on seizure control in the responders and the non-responder groups and further evaluated the QOL for selected PWE in adults. According to earlier reports, the gender (male and female) distributions were quiet similar and have been observed in both adults and children [24, 26, 27]. However, the number of male subjects in both groups was comparatively higher than females and this could be attributed to availability in the tertiary care centre during recruitment [21, 24, 28]. The age at the onset of seizures was found to be a year and comparable in both group which was accordance to the previous reports [24, 29]. Furthermore, the common types of seizures were found to be generalized seizure as compared to focal seizures which were quiet similar in the both groups and were accordance with the earlier reports. In the non-responders group, we observed higher numbers of seizure frequencies in the last one year and they were maximally recorded at a monthly duration when we compared them to daily, weekly or yearly intervals. These results were consistent with previous findings and highlighted the poor patient outcome related to uncontrolled seizures in the non-responders group [30].

Further, to see the effect of mono, bi, or polytherapy, percentage of the responders group who were on monotherapy and found to be significantly higher than those who were on bi-or polytherapy. In contrast to responders group, the percentage of non responders group who were on polytherapy was significantly higher than those who were on monotherapy. These results implicate that it could be due to either non-adherence to ASMs or number or doses of recommended ASMs, or seizure recurrence, or some unknown reason that might be affecting the pathological activity of the PWE or some unknown pharmacological parameters that need to be evaluated in future studies. However, this is the first study that compared the effects of ASMs as mono-, bi-, or poly-therapy for the responders group versus non-responders group in PWE of Indian population [31, 32]. Previously, it was reported that monotherapy can be used as a gold standard therapy for epilepsy treatment and most of the PWE responded well to use of monotherapy. However, if monotherapy did not respond well, then it may have increased the disease severity in terms of increased seizure frequency and further need to recommend a combination therapy of first-generation ASMs with a combination of newer medications to treat the uncontrolled seizures, either as bi- or polytherapy [33, 34]. As previously reported PHT, VPA, and CBZ are the most commonly prescribed first-generation ASMs and were used to treat large numbers of PWE. Furthermore, CLB and LEV are the most commonly prescribed new medications in both groups. The usage of PHB has been demonstrated to cause cognitive side effects. Its recommendation is made whenever critically needed in the PWE. Therefore, it has to be avoided in most cases. It has been shown that the use of newer ASMs in combination with first-generation ASMs results in a significant impact on controlling the seizure and may reveal distinct mechanisms of action in PWE. Therefore, future studies are needed to evaluate the drug-drug interaction or modulatory mechanism with adverse effects of this prescribed monotherapy or polytherapy in a

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**Table 2. Distribution of ASMs in responders group and non-responders group (n = 486).**

| Epilepsy treatment regimen | Responders group (N = 108) | Non-responders group (N = 378) |
|---------------------------|-----------------------------|-------------------------------|
| Mono-therapy              | 56 (31.85)                  | 80 (21.16)                    |
| bi-therapy                | 33 (30.56)                  | 136 (35.98)                   |
| Poly-therapy              | 19 (17.59)                  | 162 (42.86)                   |

**Anti-seizures medication profile: First generation anti-seizure medications**

- PHT (130) 32 (24.62) 98 (75.38)
- CBZ (168) 31 (18.45) 137 (81.55)
- VPA (251) 41 (16.33) 210 (83.67)
- PHB (14) 2 (14.29) 12 (85.71)

**Newer medications:**

- CLB (195) 28 (14.36) 167 (85.64)
- LEV (151) 22 (14.57) 129 (85.43)
- CLNZ (26) 8 (30.77) 18 (69.23)
- LTG (48) 8 (16.67) 40 (83.33)
- ZNS (24) 3 (12.50) 21 (87.50)
- TPM (28) 3 (10.71) 25 (89.29)
- OxCRZ (31) 5 (16.13) 26 (83.87)
- PGB (1) 0 (0.0) 1 (100)
- GBP (1) 0 (0.0) 1 (100)

**Medications Doses (mg/day) - First generation anti-seizure medications**

- PHT 272.65 ± 75.49 261.6327 ± 114.07
- CBZ 633.87 ± 254.09 758.03 ± 295.19
- VPA 925.61 ± 349.48 987.1429 ± 388.01
- PHB 37.5 ± 31.81 87.08 ± 49.28

**Newer medications:**

- CLB 11.10 ± 4.97 15.11 ± 6.98
- LEV 1931.81 ± 707.87 2140.31 ± 934.51
- CLNZ 1 ± 1.26 0.53 ± 0.29
- LTG 131.25 ± 81.00 199.825 ± 184.43
- ZNS 250 ± 50 488.09 ± 398.40
- TPM 233.33 ± 152.75 160 ± 86.60
- OxCRZ 870 ± 268.32 1050 ± 384.44
- PGB 0 600
- GBP 0 225

(Data are represented as number (percentage). PHT = phenytoin, CBZ = carbamazepine, VPA = valproic acid, PHB = phenobarbitol, CLB = clabazam, LEV = levetiracetam, CLNZ = clonazepam, LTG = lamotrigine, ZNS = zonisamide, TPM = topiramate, Ox-CBZ = oxcarbazepine, PGB = pregabalin, GBP = gabapentin.)

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**Table 3. QOL in responders group and non-responders group (n = 100).**

| Variables            | Responders group (n = 43) | Non-responders group (n = 57) | p-value  |
|----------------------|---------------------------|-------------------------------|----------|
| Age                  | 32.23 ± 13.00             | 28.40 ± 9.90                  | 0.097    |
| Gender               |                           |                               | 0.138    |
| • Male               | 24 (55.81)                | 41 (71.93)                    |          |
| • Female             | 19 (44.19)                | 16 (28.07)                    |          |
| Age at onset of epilepsy | 20 ± 13.59              | 18.11 ± 12.32                 | 0.470    |
| Type of seizures     |                           |                               | 0.095    |
| Focal Seizure        | 11 (25.58)                | 24 (42.11)                    |          |
| Generalized seizure  | 32 (74.42)                | 33 (57.89)                    |          |
| Drug regimen         |                           |                               | 0.044    |
| • Mono-therapy       | 22 (51.16)                | 15 (26.32)                    |          |
| • Bi-therapy         | 14 (32.56)                | 27 (47.37)                    |          |
| • Poly-therapy       | 7 (16.28)                 | 15 (26.32)                    |          |

QOLIE-31-Domains*

Seizure worry 60.53 ± 3.50 46.87 ± 9.04 0.0001
Overall quality of life 54.97 ± 5.51 39.40 ± 7.59 0.0001
Emotional wellbeing 54.74 ± 4.46 46.42 ± 7.22 0.0001
Energy/fatigue 59.16 ± 3.32 50.19 ± 7.31 0.0001
Cognitive function 60.21 ± 4.35 49.12 ± 10.23 0.0001
Medication effects 57.69 ± 3.53 46.96 ± 4.86 0.0001
Social functioning 53.25 ± 3.94 42.35 ± 10.01 0.0001
overall weighted average health-related quality of life score 57.02 ± 2.23 45.82 ± 6.28 0.0001

(*Data are represented as mean ± SD, P value = 0.001).
Table 4. Effect of individualized therapy of ASMs on quality of life in the responders group and non-responders group (n = 100).

| QOL subscales | Responders group (n = 43) | Non-responders group (n = 57) |
|---------------|-------------------------|-----------------------------|
|               | Mono-therapy | Bi-therapy | Poly-therapy | p-value       | Mono-therapy | Bi-therapy | Poly-therapy | p-value       |
| Seizure worry (mean ± SD) | 62.04 ± 3.19 | 58.43 ± 3.15 | 60.0 ± 3.05 | 0.006** | 53.26 ± 9.09 | 44.70 ± 7.81 | 44.4 ± 8.44 | 0.0044** |
| Overall quality of life (mean ± SD) | 56.09 ± 4.58 | 55.14 ± 6.70 | 51.14 ± 4.48 | 0.1156 | 42.93 ± 6.88 | 39.62 ± 6.38 | 35.46 ± 8.81 | 0.0231* |
| Emotional wellbeing (mean ± SD) | 56.31 ± 4.28 | 53.07 ± 4.37 | 53.14 ± 3.89 | 0.0569 | 48.86 ± 9.81 | 45.51 ± 6.09 | 45.6 ± 5.87 | 0.3167 |
| Energy/fatigue (mean ± SD) | 59.09 ± 3.61 | 58.71 ± 2.81 | 57.71 ± 3.09 | 0.2655 | 52.26 ± 9.33 | 50.44 ± 7.21 | 47.66 ± 4.33 | 0.2231 |
| Cognitive function (mean ± SD) | 61.40 ± 4.81 | 59.78 ± 3.19 | 57.28 ± 3.72 | 0.0813 | 53.46 ± 10.45 | 49.25 ± 8.26 | 44.53 ± 11.74 | 0.0536* |
| Medication effects (mean ± SD) | 57.54 ± 3.88 | 58.21 ± 2.99 | 57.14 ± 3.76 | 0.7825 | 47.53 ± 3.94 | 46.33 ± 4.81 | 47.53 ± 5.86 | 0.6562 |
| Social functioning (mean ± SD) | 54.00 ± 3.58 | 52.78 ± 4.54 | 51.85 ± 3.76 | 0.4030 | 47.53 ± 9.09 | 42.18 ± 9.84 | 37.46 ± 9.17 | 0.0196* |
| overall weighted average health-related quality of life score (mean ± SD) | 58.1 ± 2.03 | 56.37 ± 1.74 | 54.92 ± 1.82 | 0.0009*** | 49.71 ± 6.87 | 45.55 ± 4.86 | 42.39 ± 6.12 | 0.0042** |

Data are represented as (mean ± SD); *p < 0.05, **p < 0.005, ***p < 0.0005.

In summary, our findings suggest that the use of appropriate doses of first-generation ASMs and their combination with newer medications is critically important to managing epilepsy in tertiary care centers. We found that those PWE who were on monotherapy showed a better response in terms of the reduction in seizure frequency as compared to those who were on bi- or polytherapy in the responder groups, whereas those in the non-responders group needed the polytherapy to control seizures. When we assessed the quality of life of the selected subjects from both groups, we found similar trends. We found that those PWE who were on monotherapy showed better overall QOL than those who were on bi- or polytherapy, despite overall QOL being lower in the non-responders group as compared to the responders group.

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