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Therapeutic approach to the treatment of "Sunflower Syndrome": an international survey addressed to caregivers

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Ai miei genitori,

senza i quali nulla di tutto questo

sarebbe stato possibile

SUMMARY

ABSTRACT *1*

1. INTRODUCTION *3*

1.1 HISTORY: 3

1.2 PHYSIOPATHOLOGY 10

1.3 GENETIC BACKGROUND 11

1.4 EEG PATTERN 11

1.5 TREATMENT 14

1.5.1 Pharmacological treatment 14

1.5.2 Non-pharmacological treatments 16

1.6 DIFFERENTIAL DIAGNOSIS 16

1.6.1 Jeavons Syndrome 16

1.6.2 Janz syndrome 17

1.6.3 NEXMIF encephalopathy 17

2. AIM OF STUDY *18*

3. METHODS *19*

3.1 Patients' selection 19

3.2 Methods (The questionnaire) 19

3.3 Statistical analysis 19

4. RESULTS *20*

4.1 Benefit on seizures 20

4.2 Benefit on other areas (sleep, development, behavior) 21

4.3 Adverse events (AEs) 22

4.4 Alternative treatments 23

5. CONCLUSIONS *24*

6. GRAPHICS *26*

Bibliography *39*

ACKNOWLEDGMENT *43*

ABSTRACT

Background: Sunflower Syndrome (SS) is rare photosensitive epilepsy, characterized by an attraction to light and stereotyped seizures associated with hand waving. Seizures are often pharmacoresistant and non-pharmacological methods (e.g., blue lenses) are often used as alternative treatment strategies. We evaluated the degree of satisfaction of parents/caregivers with the treatments proposed for the management of SS.

Methods: Pediatric patients with SS were recruited through international collaboration and their parents/caregivers were provided with an *ad-hoc* questionnaire, independently completed. Perceived effectiveness was evaluated with a score ranging from -5 (highly negative) to +5 (highly positive) on 4 main areas (i.e., seizures, sleep, behavior, and development), whereas adverse events (AEs) were assigned a value from 1 to 4 based on severity (none=1; slight=2; moderate=3;severe=4)

Results: Thirteen SS patients were enrolled. Valproate (VPA) was used in 6/13 (46%) patients, followed by lamotrigine (LTG) and levetiracetam (LEV) used in 4/13 (38%) patients. Ethosuximide (ESM) was prescribed to 3/13 (23%) patients, while clobazam, topiramate, and ibuprofen were used each in 2/13 (15%) patients. Perceived effectiveness on seizures scored 1.33/5 for ESM and 1.2/5 for LTG, while the total score comprising the 4 main areas was respectively 0.17/5 and 0.4/5. VPA totalized a score of 0.83/5 on seizures and a total score of 0.19/5. As for the tolerability profile, ESM scored 2/4 and LTG 1.8/4. 2/4 and 2.75/4 were the scores assigned to VPA and LEV.

Conclusions: VPA is highly prescribed for the treatment of SS, although LTG was rated with better efficacy and tolerability profiles by parents/caregivers. New therapeutic options will be required to increase the satisfaction with the treatment of SS.

1. INTRODUCTION

1.1 HISTORY:

In 2004 Pratibha wrote, "*In reflex epilepsy, seizures are regularly elicited by some specific stimulus or event.*" The International League Against Epilepsy included reflex epilepsies as 'epilepsies characterized by specific modes of seizure precipitation' among the special syndromes and divided them into simple and complex forms. In simple forms, seizures are precipitated by simple sensory stimuli (e.g., light flashes). The intensity of the stimuli is decisive, the latency of the response short (seconds or less), and mental anticipation of stimulus without effect. In complex forms, the triggering mechanisms are elaborate (e.g., looking at one's own hands, listening to specific music, etc). The specific pattern of the stimulus, not the intensity is the decisive factor. Latency of response is longer and mental anticipation of stimulus, even in dreams may be effective. (3)

Self-induction in photosensitive patients with epilepsy has been much discussed. The compulsive aspect of the self-induction of photic epilepsy has aroused considerable interest. It has been suggested that the self-induction of seizures might be a biological pro-testing mechanism against unpleasant stimuli. (1)

In 1927 Gordon Holmes wrote: "*Some men subject to epileptiform attacks commencing with visual phenomena owing to gunshot wounds of the occipital region have told me that bright lights, cinema exhibitions, and other strong retinal stimuli tend to bring on attacks*." (2) that could be classified as the first article related to photosensitive epilepsy.

The first cases of Sunflower Syndrome (SS) were described in 1932, when Radovici, Misirliou, and Gluckman described a case of "*reflex epilepsy provoked by optic excitation from rays of the sun.*" For ten years a man of 20 years had

suffered from a tic consisting of rhythmical upward movements of the head with tremors of the eyelids when looking towards the sun on bright days. (4)

Another case was described by Catola as a"visual sensory epilepsy due to sunlight" in 1934. (5)

Afterward, a case of uncontrollable generalized masticatory movements which occurred a few seconds after the patient's face had been exposed to the sun was described by Goodkind in 1936. (4) (6)

Ten years after Goodkind's discovery Stanley Cobb described 3 cases under the title "Photic driving as a cause of clinical seizures in epileptic patients" in 1947. (7)

Another case was found in 1946 by Walter, Dovey, and Shipton who reported that intense flickering light could induce epileptic discharges in some epileptic patients. (4) (8)

Then, Gastaut in 1951 found that *grand mal, petit mal,* and bilateral myoclonus, or combinations of these, could be produced by intermittent light stimulation. He stated that it was never a question of continuous light, whatever its intensity, but always of a flickering light of rapid frequency. (4) (11)

He described two children who "*were searching for epileptogenic stimuli to provoke their absences: one of them by passing rapidly his hand with the fingers widespread before his eyes, the other by moving his hand rapidly from right to left in front of a window with colored glass*." (11)

Later Bickford, Daly, and Keith (1953) reported observations of the convulsive effects of light stimulation in 27 children, some of whom had attacks following exposure to the flickering light encountered in everyday life, as when driving along a tree-lined road when the sun was low. (4) (10)

Robertson in his case report published in 1954, divided patients into 2 groups: *Group I-Flicker Produced Manually,* the patient interrupts the sun's rays by moving

the abducted fingers or the hand across one eye. *Group II-Flickers produced by Blinking*, the flicker is produced by the action of the eyelids. (4)

In Table 1 are reported 7 patients (4 of group I and 3 of group II).

Table 1. Case series. Robertson, 1954

	Age	**Robertson's group**	**EEG pattern**	**Treatment**
PT.1	5 yr	Group I	The movement of the examiner's fingers between the sun and her eyes produced irregular outbursts of high voltage 3-4 per second waves with intervening spikes. When the eyes were exposed to the flickering light of high intensity, the occipital and parietal discharges tended to synchronize with flash rates between 4 and 9 per second. [Robertson, 1954]	Troxidone Mysoline
PT.2	12 yr	Group I	At 7 flashes per second, a marked tendency to synchronization of flash and 7 per second cerebral waves occurred. At 10 flashes per second high voltage 3-5 per second	Troxidone

			waves occurred irregularly with many intervening spikes. [Robertson, 1954]	
PT. 3	41 yr	Group I	Flicker at the rate of approximately 15 per second produced a short series of low-voltage 2-per-second waves, most clearly defined in the frontal leads, with superimposed spikes. These increase in frequency and amplitude until an outburst of high-voltage 3-per-second activity occurred in all leads, with inter- vening high-voltage spikes. [Robertson, 1954]	Troxidone Malidone Fenitoin sodium + phenobarbital Dextramfetamina
PT.4	12 yr	Group I	Six flashes per second produced high-voltage 6 cycles per second waves, with well-marked spikes in some leads, finally breaking into irregular 3-4 per second waves with high-voltage spikes. At a flash frequency of 7 there were more high voltage waves and during these outbursts the patient quickly ceased to count and	Pharmacoresistant

			did not reply to questioning. After the attack he was sometimes able to remember what had been asked, sometimes not. Flash frequencies between 7 and 10 per second were most effective, but abnormal discharges were provoked at all speeds up to 22 per second. Myoclonic twitching of neck musculature was observed to coincide with collections of high-voltage fast waves. [Robertson, 1954]	
PT. 5	18 yr	Group II	frequent appearance of 7 per second waves in rhythmical sequence during the resting period. When flicker was produced over his closed eyelids, he invariably opened them, although asserting that he was not aware of having opened them. When the flicker (at a rate of about 3-5 per second) was maintained for any length of time he had the feeling that he would lose	Troxidone Fenitoin sodium Hydantoin sodium + phenobarbital

			consciousness. [Robertson, 1954]	
PT. 6	17 yr	Group II	When in sunlight she sometimes looked directly at the sun and blinked her eyelids rapidly (about 4 blinks per second). After some four to seven seconds the blinking ceased, and after a brief period of lower voltage activity slow waves (between 3 and 6 per second) appeared, with an almost equal number of high- voltage fast waves. [Robertson, 1954]	Troxidone Paradione Phenobarbital
PT. 7	30 yr	Group II	The initial part of the record showed a remarkable tendency to synchronization of flashes between 2 and 13 per second and the response, so marked that the word " driving " seems apposite. Between 5 and 35 flashes per second outbursts of spike and 3 per second high-voltage slow waves occurred 1 to 3 seconds after the flashing started. These subsided after 2 to 4	

			seconds even when the flashing continued and recurred at intervals varying between 3 to 8 seconds. She was not aware of the dysrhythmia and was able to answer questions. [Robertson, 1954]	
Legend: PT: patient, Yr: years				

After studying these cases, Robertson stated that the easiest way to influence the electrical discharge from the cortex is by opening and shutting the eyes. The responses have been studied since the early days of electroencephalography. Later the effect of intermittent light stimulation was tried and was found to provoke clinical seizures in some subjects. (4)

In 1962 Anderman reported a case series of 34 patients, of which twenty-one elicited phenomena by themselves. (12)

Later, in 1983, heliotropism associated with seizures was described by Ames who wrote: "*the heliotropism of our patients was accompanied by stereotyped posturing of the arm on the side to which their gaze was directed. It was accompanied by repetitive movements which brought the abducted fingers back and forth across the ipsilateral eye*". (13)

In 2004 Pratibha reported a case of a 12-year-old girl who had rare self-induced photosensitive epilepsy. She used to move her right hand over the right eye while simultaneously rubbing the forehead since the age of 8. During these episodes, she was lost in herself. Lately, these episodes were followed by a brief spell of unconsciousness. The electroencephalogram (EEG) examination, in its third attempt, revealed bilateral multiple symmetric spikes on photic stimulation. She

admitted that she often induced the episode herself and derived pleasure out of it. She responded well to valproate (VPA). (3)

This constellation of symptoms, previously described, has been termed "*Sunflower Syndrome*" due to the sun-seeking behaviors of the patients and the characteristic way in which they bend their faces up toward the sun. (14)

1.2 PHYSIOPATHOLOGY

The posturing of the arm is reminiscent of the "automatic" protective gesture made by any person suddenly exposed to the noxious stimulus of strong light, but the repetitive movements do not serve any obvious physiological purpose. (12)

Similar movements have been elicited experimentally in monkeys (15) and humans (16) by direct electrical stimulation of area 24 which has an agranular cortex. (13)

Reflex epilepsy has been studied in two types of animal models: 1) creation of irritative cortical lesions and their activation by specific stimuli and 2) induction of reflex seizures in genetically susceptible animals. However, the only species in which the reflex seizures and EEG findings are similar to those of humans is the baboon Papio Papio. Although the light-induced epileptic discharges in baboons occur in the frontorolandic area, whereas in human reflex photosensitive epilepsy can be activated by the localized occipital trigger. (3)

Gastaut suggested that there was a thalamic short-circuiting of electrical responses normally carried by the optic pathways. Light impulses were assumed to pass to the pace-making thalamic mechanisms (as well as to the occipital cortex and colliculi), and there provoke irradiation of abnormal synchronized excitation to the cortex on each side. (4) (17)

The cingulum acts as a bridge between the limbic lobe and neocortex (18) and has been accepted for many years as important in the regulation of emotional and autonomic activity. (13)

In man, there is growing evidence of the subcortical origin of many epileptic discharges; direct manifestations of hypothalamic activity are seen more in epileptic variants such as narcolepsy, the akinetic attack, and the visceral and vasomotor elements of petit mal or temporal lobe epilepsies. (9)

1.3 GENETIC BACKGROUND

The highly stereotyped presentation of seizures in this patient population, as well as the positive family history for a broad range of generalized epilepsies, suggest a possible genetic component to SS. (19)

Although, up to now, no clear causative genes have been identified. Conversely, other photosensitive epilepsies variants in the gene *CHD2* have recently been described. (20) (21)

1.4 EEG PATTERN

In 1949 Bickford reported that electrical responses to flicker occurred in a considerable proportion of normal subjects. In 92 percent of 50 subjects the frequency of flashing, or a multiple or submultiple of it, was reflected in the occipital and parietal records. In 10% of patients with photosensitivity, as described by Bickford slow (delta) frequencies, unrelated to the frequency of flashing appeared. In 14 percent of paroxysmal discharges, unrelated to the flash frequency, occurred synchronously over the whole cerebral cortex. (10) (4)

Bickford, Daly, and Keith 1953 reported observations of the convulsive effects of light stimulation in 27 children (10). They found no constant pattern in the EEG. In three-quarters of the resting records, there was diffuse high voltage 3 per second spike-wave discharge. Five patients showed focal sharp wave discharges confined to the occipital regions. There were often rhythmical bursts of high voltage waves related to the closing of the eyes. Flickering light produced diffuse spike-wave discharges, in many cases with multiple spikes and a myoclonic pattern. Flash

frequencies between 10 and 20 per second were most effective. A single flash produced attacks in one patient. (4) (10)

In the same year, Denis Williams has recorded human *petit mal* discharges and has shown that the 3 per second rhythm commences in the thalamus and reaches the cortex from there, while the fast spikes originate deep in the cortex. (22) (4)

Walter and his associates (1946, 1947, 1949, and 1950) analyzed the effect of intermittent photic stimulation during electroencephalographic recording. (8) (23) (24) (25) They considered that flashes of bright light repeated at certain frequencies tended to augment similar existing frequencies and their harmonics, enlisting neighboring frequencies into the augmented waves. This augmentation of frequencies already present might facilitate explosive epileptic discharges in predisposed patients. (4)

Then, in 1950, Gastaut and Hunter showed that a single photic stimulus to the eyes of a normal animal produced a response in the lateral geniculate body and the primary and secondary visual cortices. (17) (4)

The discharges might comprise one, or all three, of the following components: 1) a rapid triphasic wave; 2) a repetitive wave of alpha frequency; 3) a slow repetitive wave of theta frequency. (4)

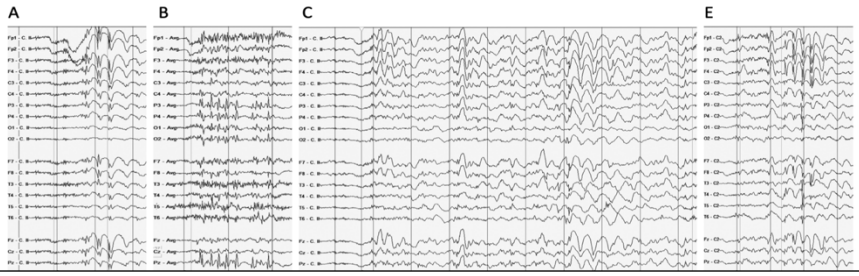
Later, Anderman in 1962 described the EEG pattern of his 32 patients and reported that the descriptions most applied to it are dysrhythmia and immaturity. Some of the seizures obtained with flicker stimulation are like those where recordings of self-induced seizures can be obtained. (12)

Afterward, Pratibha in 2004 described "*Intermittent photic stimulation (usually at 10-20 flashes/sec) to the whole of the visual field of both eyes, for short periods, provokes epileptiform discharges in EEG. These consist of bursts of bilaterally symmetrical generalized multiple spikes (poly spikes) or spike and wave complex.*

These generalized discharges usually appear after very brief stimulation and may sometimes outlast the period of stimulation. This type of response is called Paroxysmal photosensitive response (PPR) and is diagnostic of Photosensitive epilepsy". (3)

It should be noted that the ictal EEG discharge appeared only when the patient started to wave her hands in front of her eyes while looking at sunlight, and the episodes were also reproduced when we asked her to show them to us (27).

The results from analyzing vEEG recording of hand waving (HW) episodes underline the hypothesis that the HW does not induce the abnormal activity on the EEG but may be part of the ictal semiology. Supporting this, 88.89% of the HW episode-associated epileptiform activity on the EEG had a lag time below 1.00 s. (28)



Ictal Electroencephalography (EEG) traces of Patients A, B, C, and E. Patient D did not show any epileptiform activity on the ictal EEG recordings. Traces of patients A, C, and E are derived from the referential recording. Traces of patient B are derived from the average recording. The start and the end of the hand-waving (HW) episode are depicted by $ and # respectively. (28)

1.5 TREATMENT

1.5.1 Pharmacological treatment

SFS is extremely refractory to treatment, though VPA, levetiracetam (LEV), ethosuximide (ESM), benzodiazepines (BDZ), and lamotrigine (LTG) provide more effective treatment for seizures. (14) (21)

In 1962 Anderman published his case series and reported that "*A variety of anticonvulsants, mainly of the trimethadione (Tridion) sort, have been tried with equivocal success*". He also added a probable explanation about the self-induction of crises and affirmed that "*There is rarely clear evidence that it gives much pleasure, and at times it appears that attacks are elicited to get out of difficult situations, or it may be conditioned, apparently by habit*" (12).

Chao underlined that the child who takes pleasure in inducing the attacks will seldom be persuaded to wear sunglasses. However, proper encouragement of voluntary inhibition of self-provocation may be helpful. The use of trimethadione for *petit mal* and a barbiturate for *grand mal* may be beneficial. (1)

In 1985 Aicardi published a study related to the use of fenfluramine in a patient with self-induced photosensitive epilepsy. It seems likely that fenfluramine acted in his patients by reducing or suppressing a compulsive need for self-induction of seizures by its antipsychotic properties, but a direct anti-epileptic mechanism cannot be excluded. (29)

The treatment of patients with SS with add-on fenfluramine showed that most patients experienced a significant reduction in HW episodes without evidence of significant side effects. (30)

About Fenfluramine there is a study carried out by E. Thiele. The primary objective of this study was to determine the efficacy of ZX008 (Fenfluramine Hydrochloride)

on seizure frequency in children and young adults with SS. The goal of treatment was to provide a 30 percent or greater reduction of generalized tonic-clonic seizures and/or HW associated with absence seizures.

Secondary endpoints of the study included the evaluation of the effect of ZX008 (fenfluramine hydrochloride) on the EEG patterns and the quality of life (QoL). About the QoL, patients with SS often experience bullying due to the unusual motor movements associated with their seizures, school performance issues, anxiety, and depression. (31)

In the study published by Hutchinson, Troxidone (150 mg) was tried in 2 patients, but even with doubled dose, this drug was without obvious benefit. Troxidone was stopped and patients began chlorpromazine 25 mg and primidone 125 mg thrice daily, neither had any appreciable clinical effects. (32)

VPA is widely recognized as the most effective treatment for photosensitive epilepsies (33) (34) though ESM, BDZ, LTG, and more recently LEV have also proven effective in eliminating the photo-paroxysmal response on EEG and stopping seizures (35). In contrast to other photosensitive seizures, self-induced seizures are extremely refractory to treatment (36) (33) (37) (38), even when patients are compliant with medication. (14)

Fiona Baumer reported in her study that LEV was the first medication tried added to topiramate (TPM), but no patients achieved seizure freedom on LEV monotherapy. (14)

If a patient cannot use VPA, higher doses of LTG or possibly polypharmacy should be considered. (14)

A dietary therapy with a low glycemic index treatment diet (LGIT) appeared effective in a small number of patients. LGIT has proven effective for other

refractory epilepsies and could be considered a possible treatment option for SS. (19) (39)

1.5.2 Non-pharmacological treatments

Environmental measures, such as sun avoidance, use of sunglasses or specific blue-lens (Z1) glasses, or occlusion of one eye, also prevent seizures. The Z1 lenses, which have been evaluated predominantly in Europe, additionally eliminate the photo-paroxysmal response on the EEG tracing. (27)

Wearing hats and sunglasses, as well as staying indoors to avoid the sunlight, has been beneficial for some patients. (40)

Interestingly, Robertson noted in his case series that focused attention seemed to reduce the frequency of HW episodes for one patient. (40) (4)

Barnett et al. reported that approximately in 20% of patients, the focus of attention, such as while playing sports or driving, prevented HW episodes. (40) (19)

1.6 DIFFERENTIAL DIAGNOSIS

1.6.1 Jeavons Syndrome

Eyelid myoclonia with absences (EMA), or Jeavons syndrome, is a generalized epileptic condition clinically characterized by eyelid myoclonia (EM) with or without absences, eye closure-induced EEG paroxysms, and photosensitivity; in addition, rare tonic-clonic seizures may also occur. (35)

SS shares some features with Jeavons syndrome (epilepsy with eyelid myoclonia). (41) (19)

Individuals with SS often develop EM, including exhibiting symptoms of eye fluttering and eye-rolling, often years before the onset of HW episodes. (4) (13) (14) (19) (40)

There is also a similar age at onset, typically in the first decade of life, both are more common in females, both are generalized epilepsies, and both are often refractory to treatment. (4) (19) (41) (40)

SS and EMA also have similar interictal and ictal EEG features, including poly-spikes and spike-wave complexes. A photo paroxysmal response is also a common feature. (35) (19) (40)

The very stereotyped behavior of patients turning towards a light source and then waving their hand in front of their face may distinguish SS from Jeavons syndrome. (40)

1.6.2 Janz syndrome

Janz Syndrome is one of the most common genetic/idiopathic generalized epilepsies and is characterized by myoclonic and generalized tonic-clonic seizures in an otherwise normal adolescent or adult. The EEG shows generalized spike-and-wave and polyspike-and-wave. Photosensitivity is common. (42)

1.6.3 NEXMIF encephalopathy

The KIAA2022 or Neurite EXtension and Migration Factor (NEXMIF) gene encode for two protein products: a 1516 aminoacid protein called X-linked Intellectual Disability Protein Related to Neurite Extension (XPN), and an unnamed 118 amino acid protein. (43)

Nowadays, we know that NEXMIF plays an important role in early brain development (44). As a matter of fact, mutations in this gene are associated with a broad spectrum of neurodevelopmental disorders ranging from X-linked intellectual disability (XLID) up to developmental delay with autistic spectrum disorder (ASD), epilepsy, microcephaly, and facial dysmorphisms. (45)

NEXMIF associated with epilepsy is more common in females, with females more likely to have EMA. (44)

2. AIM OF STUDY

We aimed to evaluate the satisfaction of parents/caregivers of pediatric patients with SS on the currently available treatments through an *ad-hoc* online questionnaire independently completed.

3. METHODS

3.1 Patients' selection

Pediatric patients with SS were recruited through an international collaboration within the PATRE (PATient-based phenotyping and evaluation of therapy for Rare Epilepsies)

consortium.

An *ad-hoc* built, an anonymous online questionnaire was filled out by patients' parents/caregivers without the help of the clinician. Written informed consent was provided by patients or their parents/caregivers. The study was conducted following the Good Clinical Practice Guidelines and local standard operating procedures

3.2 Methods (The questionnaire)

The questionnaire was structured in two parts:

- The first one included 41 of the most used anti-seizures medications (ASMs) and an "empty space" to add possible other treatments.
- The second one evaluated the perceived efficacy and adverse events (AEs) of each therapeutic strategy used. Parents could give a score (from -100 to 100) regarding the effect of each treatment on sleep, behavior, psychomotor development, and epileptic seizures. They could also give an evaluation of the AEs (giving a score from none to severe) with a relative description.

3.3 Statistical analysis

Perceived effectiveness for each treatment was rated with a score ranging from -100 to +100, normalized with a portion to -5/+5 (highly negative= -5; highly positive= +5), on 4 main areas (i.e., seizures, sleep, behavior and development). As regards the AEs we assigned a value from 1 to 4 based on the severity

(none=1; slight=2; moderate=3; severe=4). Scores were weighted based on the number of patients rating the treatment.

4. RESULTS

A total of 13 patients were enrolled. VPA was used in 6/13 patients, (46%), followed by LEV and LTG (4/13 patients, 30%), ESM (3/13 patients, 23%), clobazam (CLB), TPM and ibuprofen (2/13 patients, 15%) and finally ketogenic diet, melatonin, carbamazepine, methylphenidate, oxcarbazepine (OXC), phenobarbital, and zonisamide each used in1/13 (7%) patients.

More accurate data are provided in **Figure 1**.

4.1 Benefit on seizures

VPA, a drug used by 6/13 patients, had a positive benefit profile with a score of 0.83/5. The benefit was not linear in all 6 patients, since 1/6 patients experienced a marked worsening of seizures attributing a score of -2.5/5. (**Figure 2**)

LTG showed an excellent benefit profile in the context of seizures. It was used in 4/13 patients totalizing a score of 1.2/5. (**Figure 3**)

ESM, like LTG, had a good profile of efficacy and scored 1,33/5 in 3/13 patients. (**Figure 4**)

CLB, a drug used in 2/13 patients, obtained a positive score of 1.025/5. (**Figure 5**)

The ketogenic diet, phenobarbital, OXC, and zonisamide scored respectively 1.1/5, 2.5/5, 1.33/5, and 2/5. All these drugs had a good profile of efficacy on seizures, but they were used in only 1 patient each.

The drugs that rated worst in the sphere of the crisis were: carbamazepine (1,55/5), LEV (-0,28/5), methylphenidate (-1/5), and TPM (-0,25/5). (**Figure 6**)

4.2 Benefit on other areas (sleep, development, behavior)

In the contest of sleep, CLB and VPA obtained a positive score. They were used in 2/13 and 6/13 patients respectively.

Their scores amounted to 0.9/5 for CLB and 0.28/5 for VPA, respectively. (**Figure 7; Figure 8**)

TPM also showed to be very effective on sleep, particularly in one of the two patients who used it. Its benefit score was equal to 1.25/5. (**Figure 9**)

OXC had an excellent efficacy profile with a score equal to 1,9/5 considering, however, its use in a single patient.

Methylphenidate and LEV, on the other hand, resulted in worsening sleep in the patients who used them (1/13 patients for methylphenidate and 4/13 patients for LEV, respectively). Scores were -1.25/5 for methylphenidate and -0.33/5 for LEV. (**Figure 10**)

On development, LTG, used in 4/13 patients showed an improvement with a score equal to 0.6/5. (**Figure 11**)

Also, methylphenidate proved effective, with a positive score of 1/5, although it has been used by only one patient.

In reverse, VPA, LEV, TPM, and OXC resulted in a worsening of the development profile.

LEV (used by 4/13 patients) and VPA (used by 6/13 patients) have obtained a score that amounts to -0.24/5 and -0.08/5, respectively. (**Figure 12; Figure 13**)

TPM had an average negative score of -1.25 / 5 in the 2 patients who took the drug (**Figure 14**); OXC (used in 1/13 patients) obtained a score equal to -0.7/5.

Finally, on behavior, VPA, LTG, CLB, OXC, and ketogenic diet obtained positive scores. VPA had a score of 0.5/5. (**Figure 15**)

LTG, used in 4/13 patients, had a positive score equal to 0.9/5; CLB in 2/13 patients obtained a score of 0.8/5. (**Figure 16**)

OXC, used by only 1 patient, had a score of 0,45/5 and, finally, the ketogenic diet got a very positive development score (1,65/5), but it was rated by a single patient.

LEV, methylphenidate, phenobarbital, and TPM resulted in a negative score. LEV had a score of -0.63/5 calculated on the 4 patients who used it (**Figure 17**). Phenobarbital totalized a score of -1/5 in the only 1 patient who used it and TPM had a score of -1.25/5 calculated on 2/13 patients who used this drug (**Figure 18**).

4.3 Adverse events (AEs)

AEs were normalized to a value of 1 to 4 based on the degree of severity (**Figure 19**).

VPA, used by 6/13 patients, obtained a score of 2/4; patients reported increased appetite, drowsiness, cognitive problems, hair loss, increased TSH, headache, nausea, bone aches, motor disturbances, weakness, confusion, hallucinations, ear disorders, and hair loss.

LTG, CLB, and the ketogenic diet demonstrated an excellent tolerability profile with little or no AEs and an average score equal to 1/4.

Methylphenidate and OXC, obtained a score of 4, considering that both were used in a single patient. The AEs experienced by the patients were, for methylphenidate, a worsening of the EEG tracings; for OXC thyroid problems, double vision, and irritability.

A score corresponding to moderate AEs, equal to 2-2.5 / 4, was obtained by drugs such as LEV, TPM, ESM, phenobarbital, and zonisamide.

ESM, in one of 2 patients who used it, caused severe nausea. LEV also caused hair loss along with behavioral disturbances. Phenobarbital and zonisamide resulted in aggressive behavior and loss of appetite, respectively.

4.4 Alternative treatments

One patient used corpus pinealis suis-Injeel, homeopathic medicine in ampoules, as an alternative treatment.

It showed overall good efficacy with a benefit score of 1.25/5 in epileptic seizures and behavior and a score of 2.5/5 for sleep and development. This treatment did not lead to any AEs.

Another patient tried to use selenium complex, it had a good profile of efficacy in all 4 spheres; in particular, totalized a score of 1.25/5 for seizures, behavior, and sleep, while had a score of 2,5/5 for development.

Acupuncture was used by a patient, who found a good improvement in seizures (score equal to 2/5) and an excellent efficacy profile about behavior, sleep, and development (score equal to 2.5/5).

Finally, ospolot (Sultiame) was used by 1 patient who referred a good profile of efficacy in seizures and development (score equal to 1/5).

The problem was the severity of the AEs which were assigned a score of 4/4.

5. CONCLUSIONS

SS is rare photosensitive epilepsy characterized by highly stereotyped seizures (40). Treatment can be pharmacological or non-pharmacological, although often there is a pharmacoresistant.

The study aimed to evaluate the effectiveness and tolerability of treatments on 4 main spheres (sleep, epilepsy, behavior, and development) perceived by patients' parents/caregivers.

Our study demonstrates that VPA, as suggested by the literature, is the most prescribed drug for this rare photosensitive epilepsy. It has a good efficacy profile on all the 4 main areas considered, but at the expense of many AEs.

Conversely, LTG is the drug with the best profile of effectiveness on all the 4 main areas and, concomitantly, with few AEs. It was the drug most appreciated by caregivers.

Other drugs such as methylphenidate and phenobarbital, used by only one patient each, show a good effectiveness profile on seizures and development, respectively, while OXC shows a good action in the sphere of sleep and ketogenic diet in the sphere of behavior.

(**Figure 20; 21; 22; 23; 24; 25)**

Regarding the non-pharmacological treatments, the most effective is acupuncture, which scored the highest total score (2.3/5) considering both efficacy and AEs. (**Figure 26**)

Our study demonstrates how, to evaluate the efficacy of a treatment, it is essential to take into consideration the opinion of parents/caregivers, that is the one who sees the client more closely

The goal for the future is to find new therapeutic options for the treatment of this rare epileptic syndrome, to ensure a positive efficacy profile that goes hand in hand with the scarcity of AEs.

6. GRAPHICS

Figure 1: most used drugs

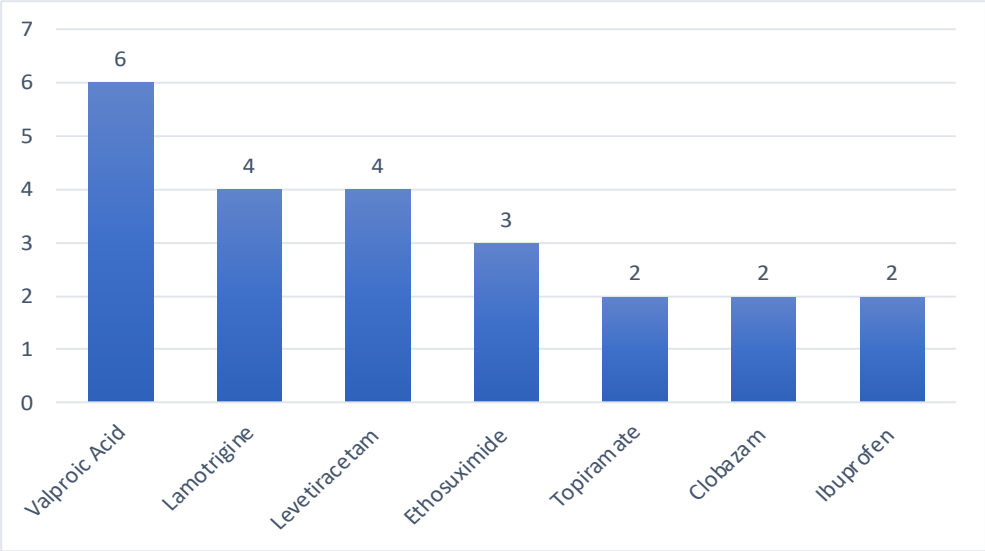


Figure 2: VPA benefit score on seizures

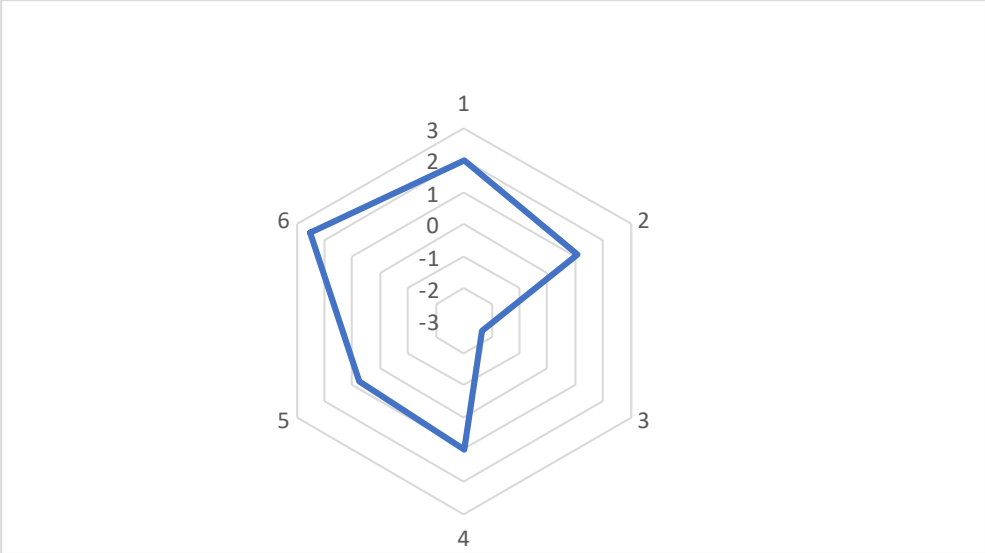


Figure 3: LTG benefit score on seizures

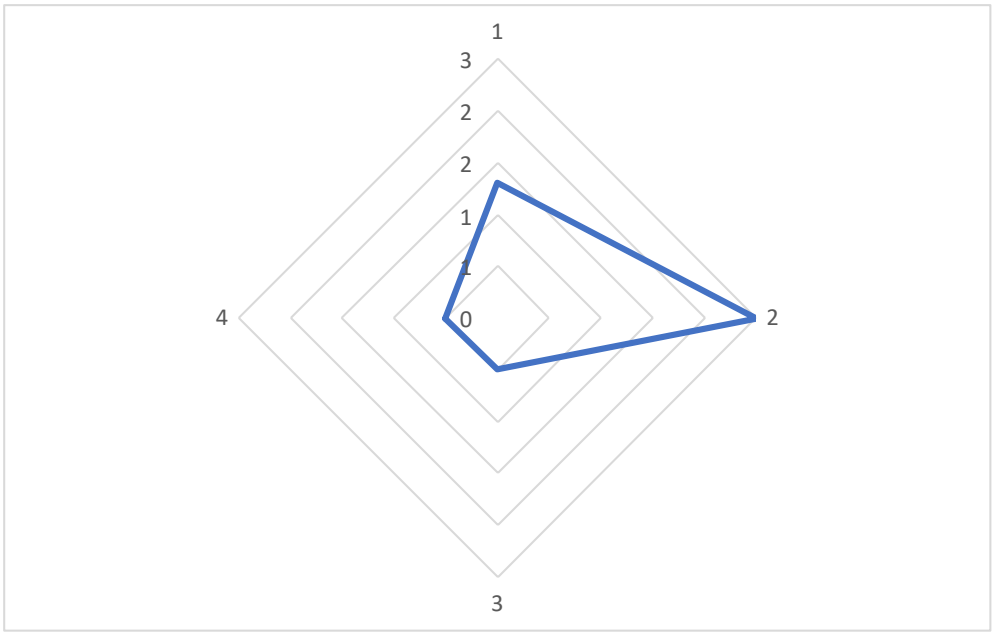


Figure 4: ESM benefit score on seizures

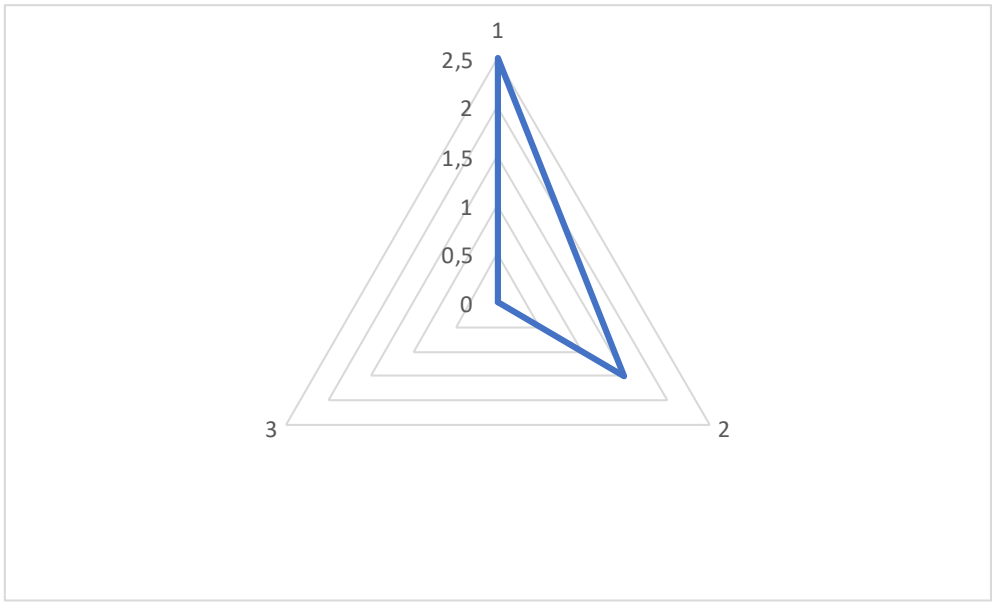


Figure 5: clobazam benefit score on seizures

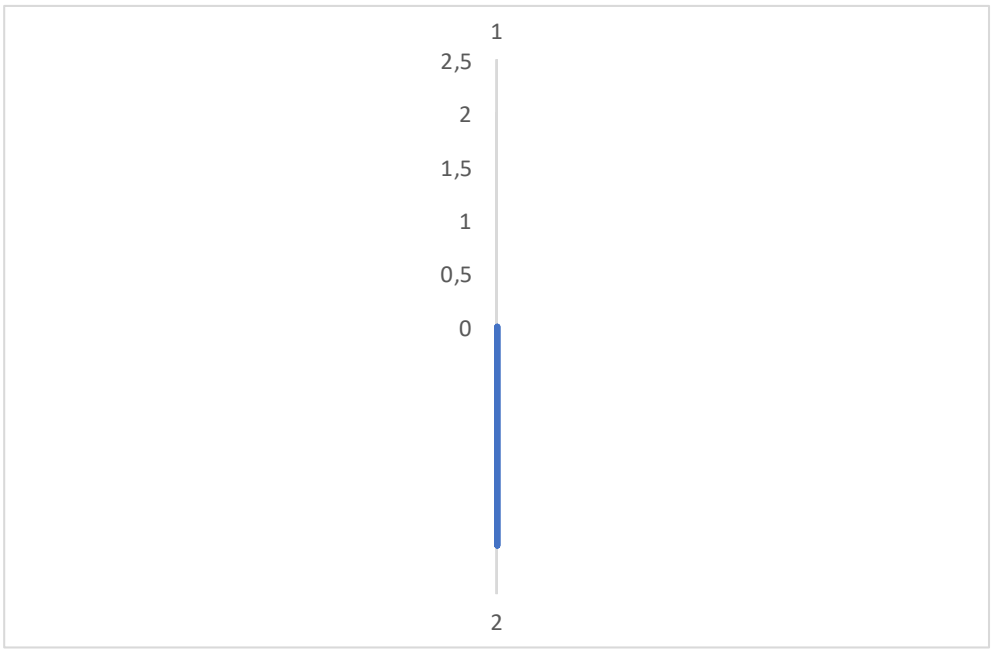


Figure 6: LEV benefit score on seizures

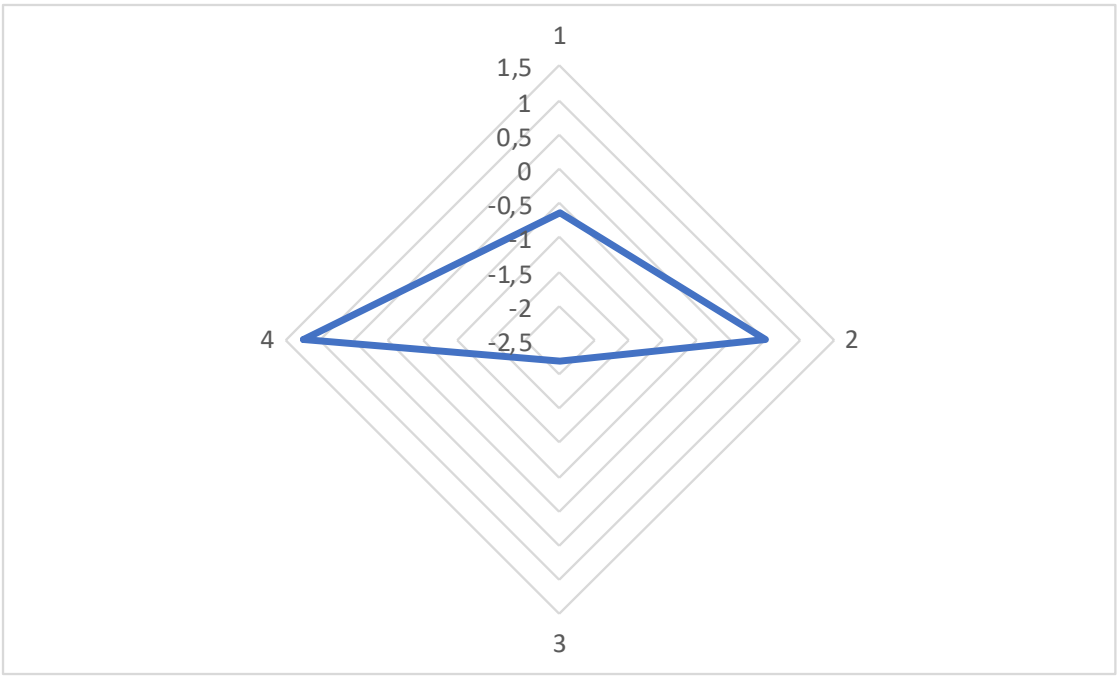


Figure 7: VPA benefit score on sleep

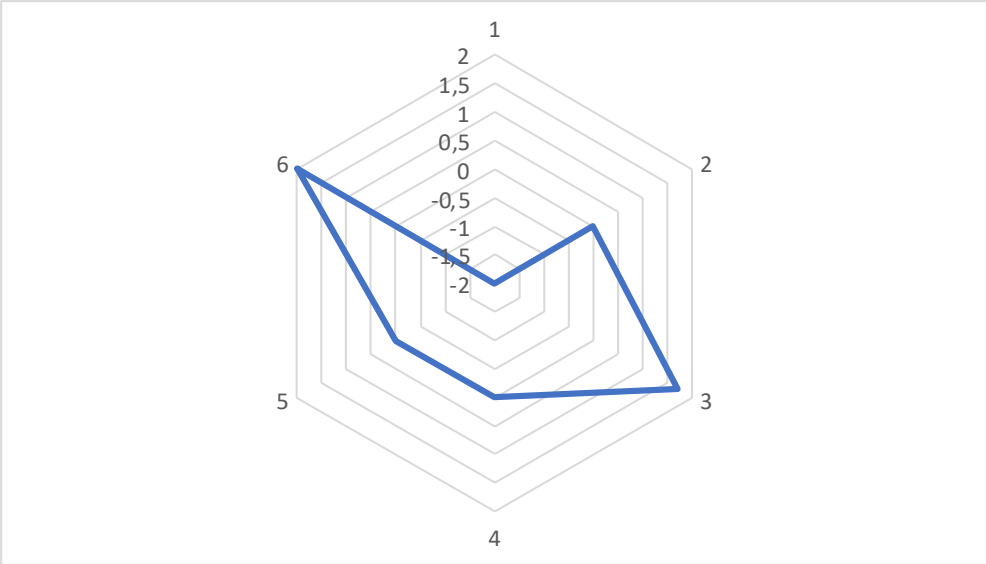


Figure 8: clobazam benefit score on sleep

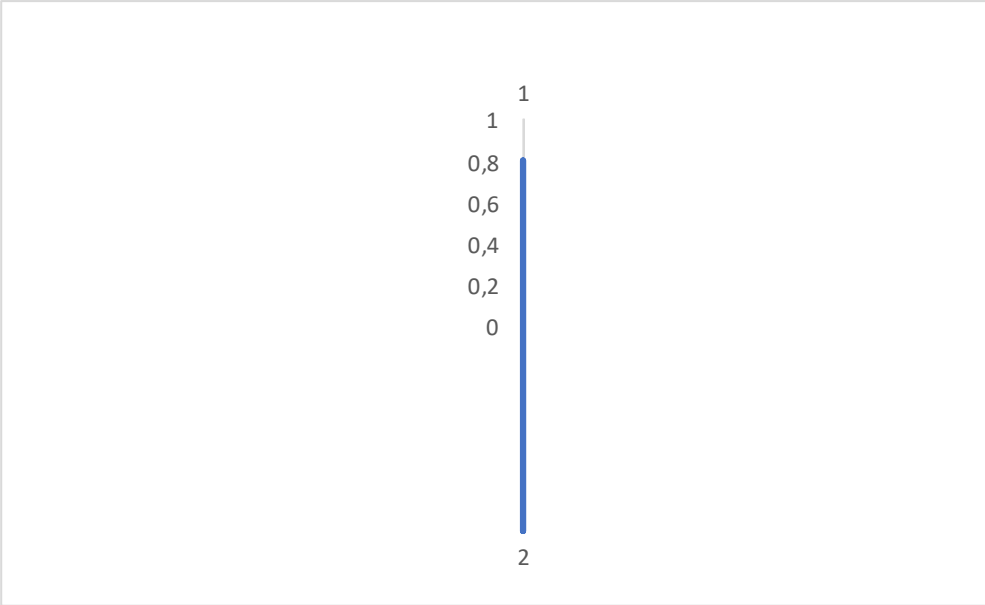


Figure 9: topiramate benefit score on sleep

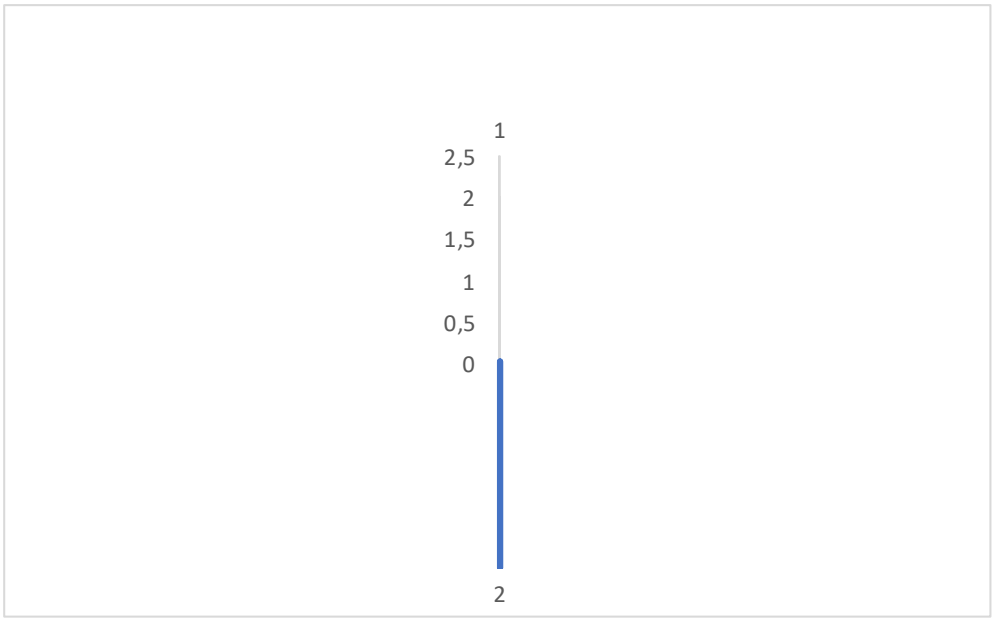


Figure 10: LEV benefit score on sleep

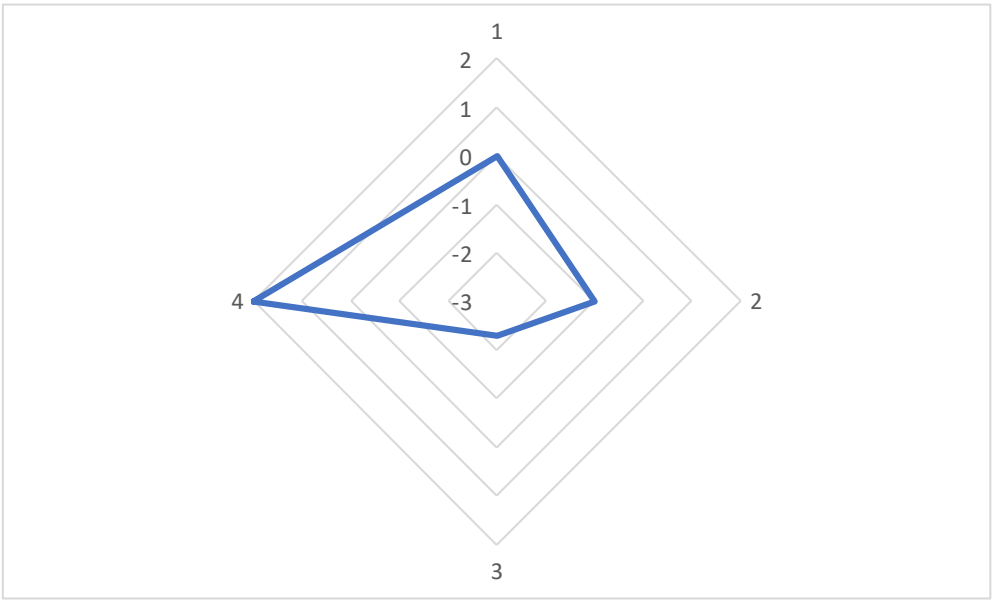


Figure 11: LTG benefit score on development

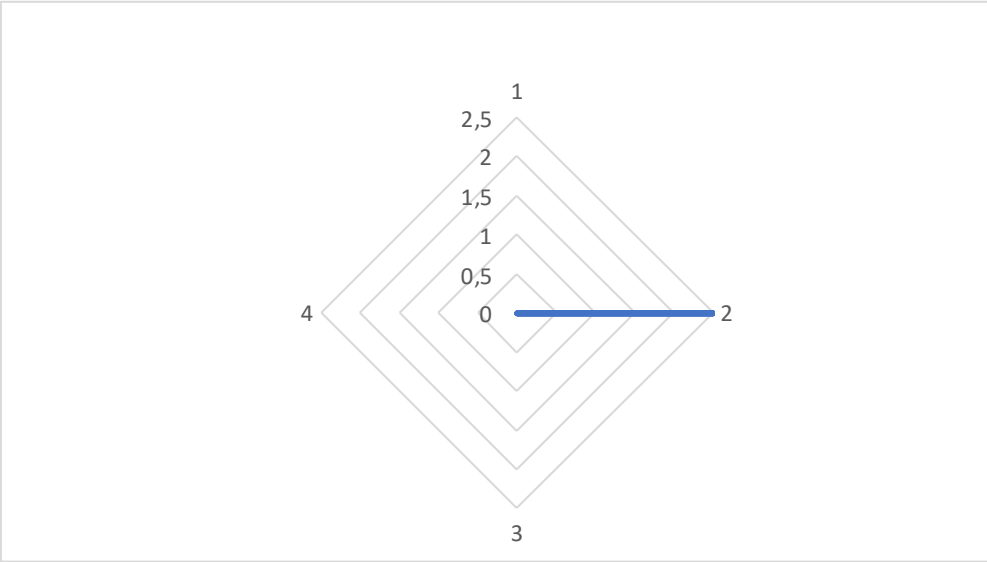


Figure 12: LEV benefit score on development

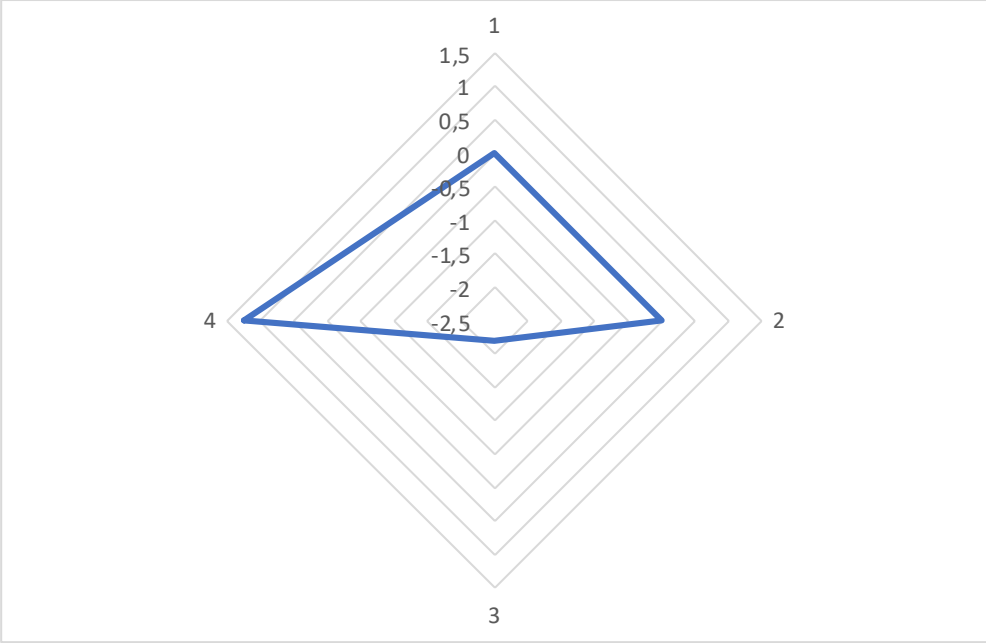


Figure 13: VPA benefit score on development

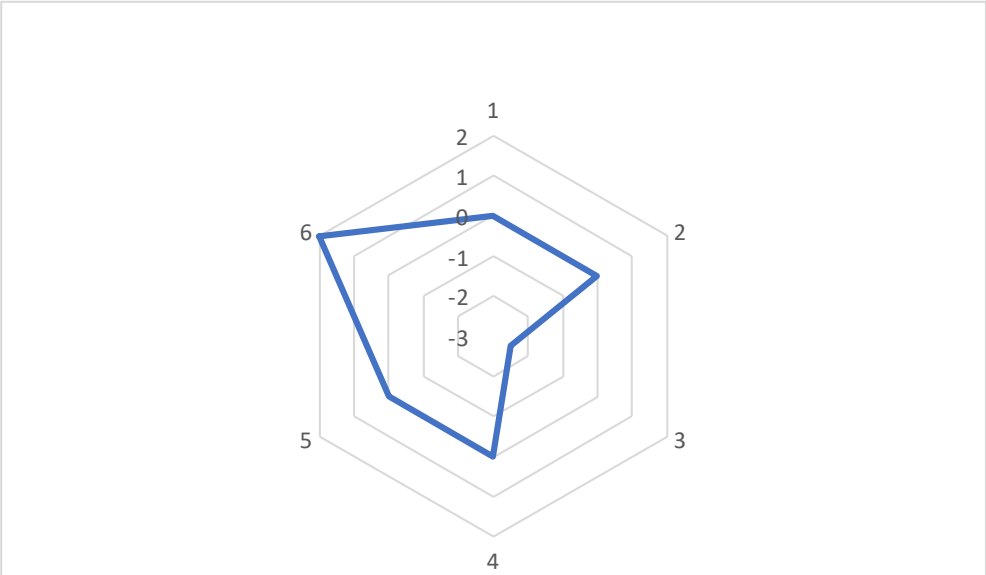


Figure 14: topiramate benefit score on development

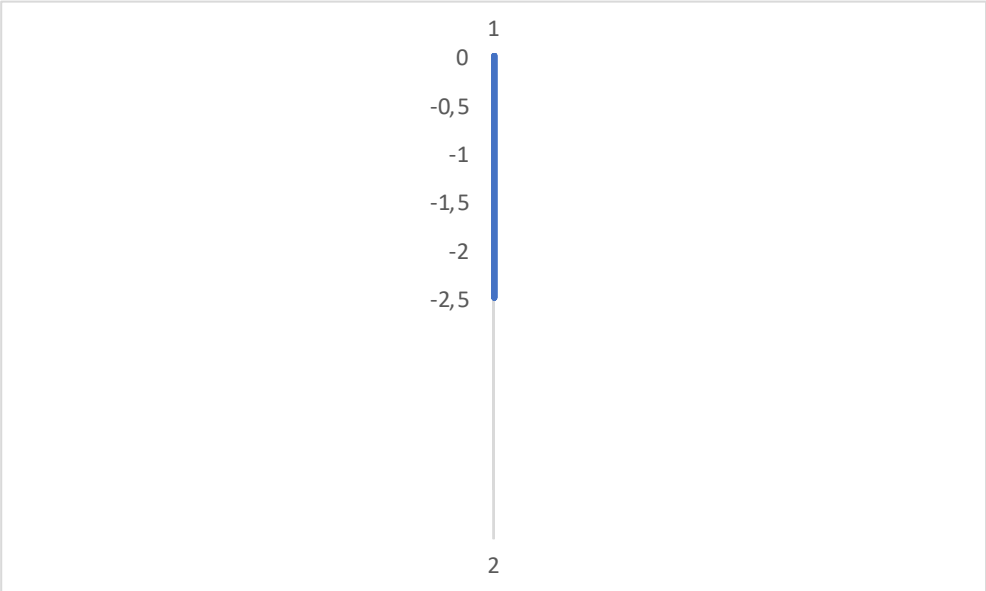


Figure 15: VPA benefit score on behavior

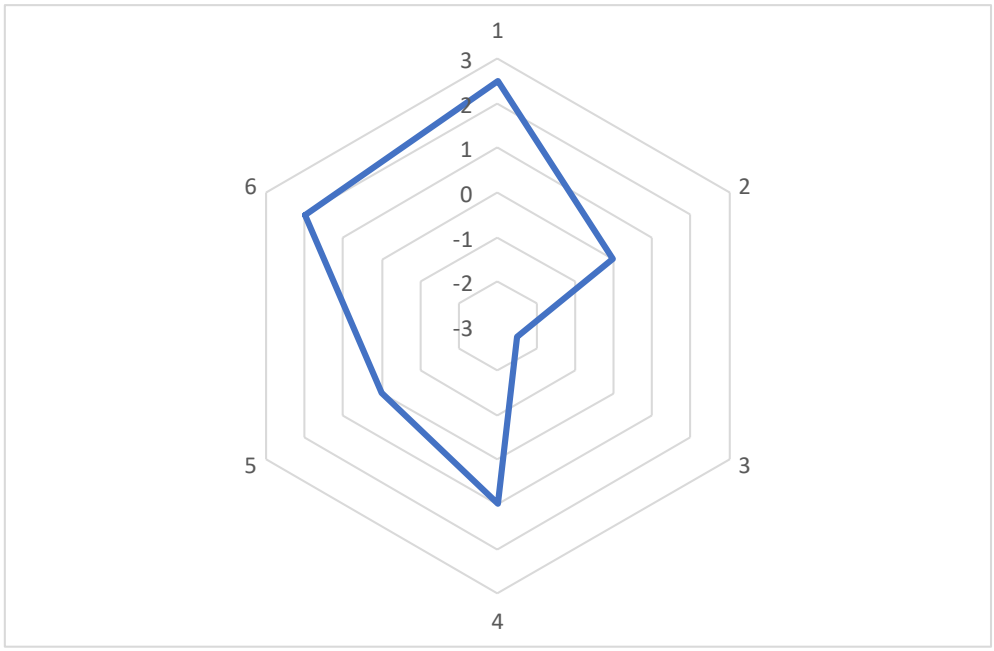


Figure 16: LTG benefit score on behavior

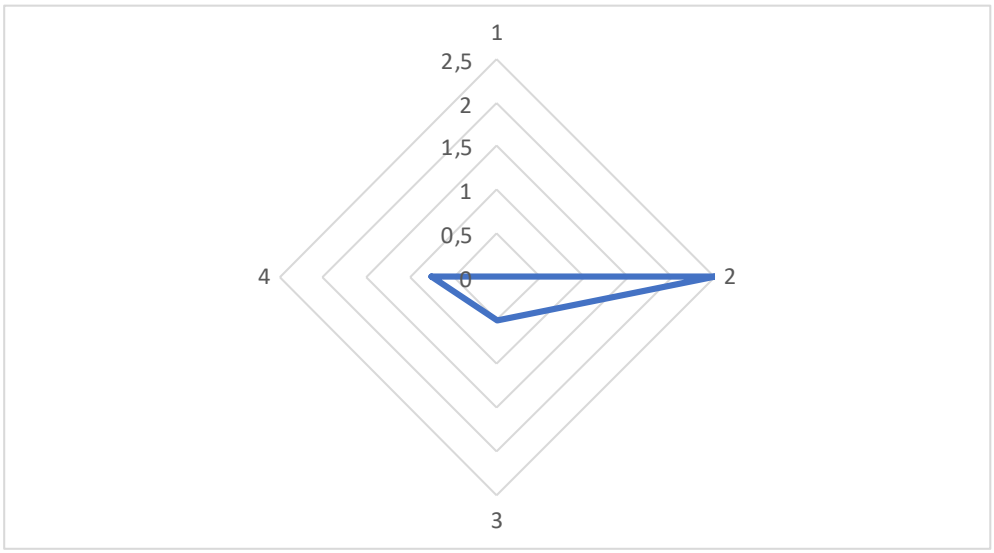


Figure 17: LEV benefit score on behavior

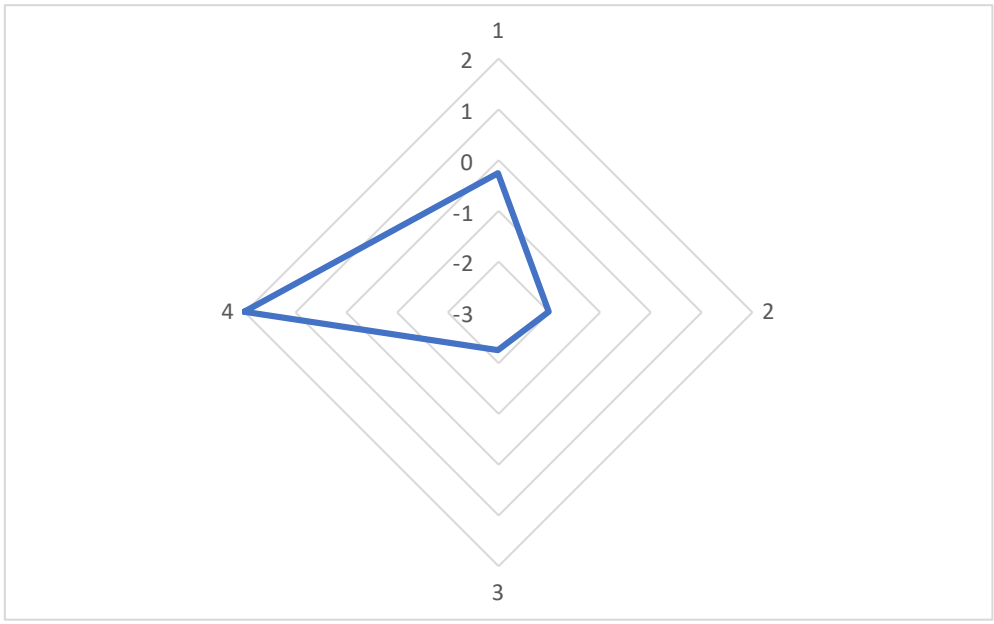


Figure 18: topiramate benefit score on behavior

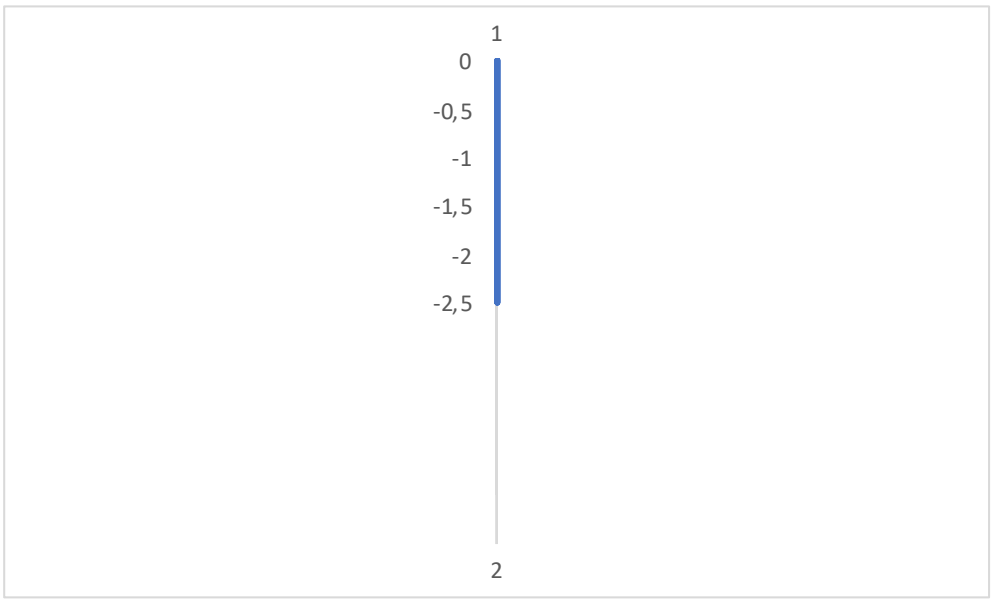


Figure 19: AEs score

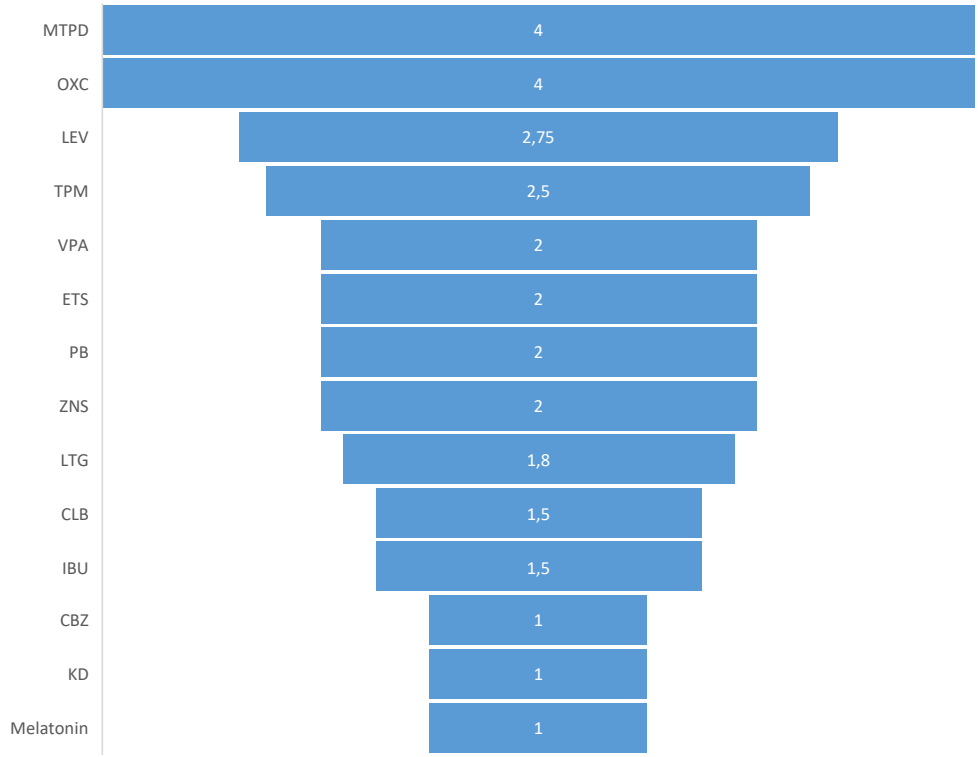


Figure 20: seizures score

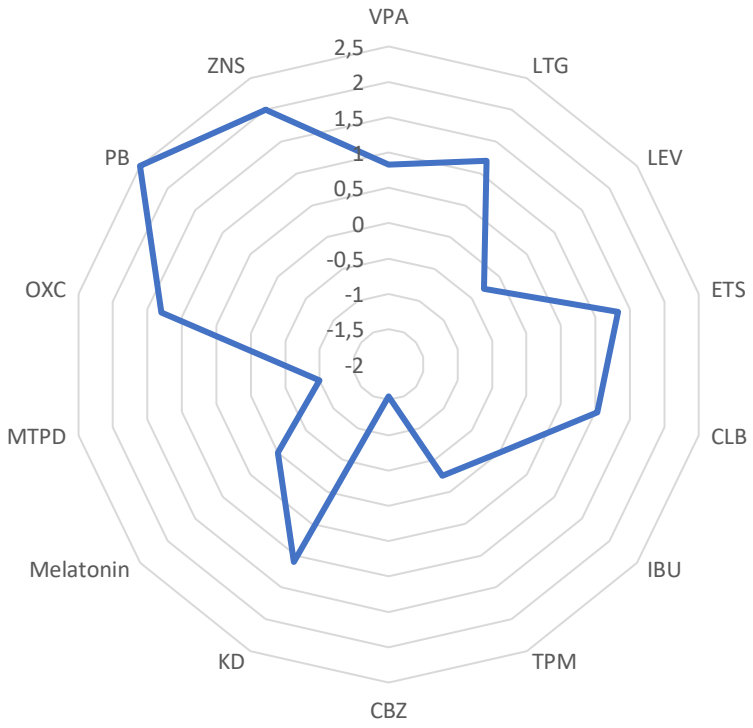


Figure 21: development score

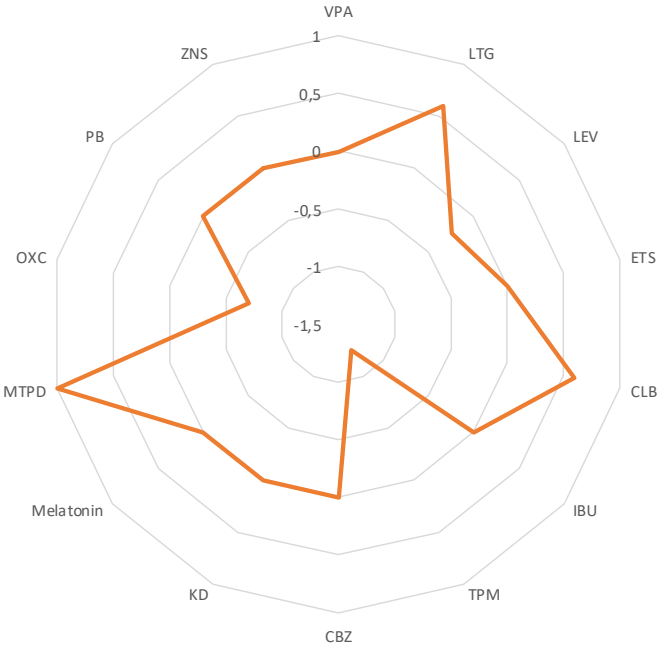


Figure 22: sleep score

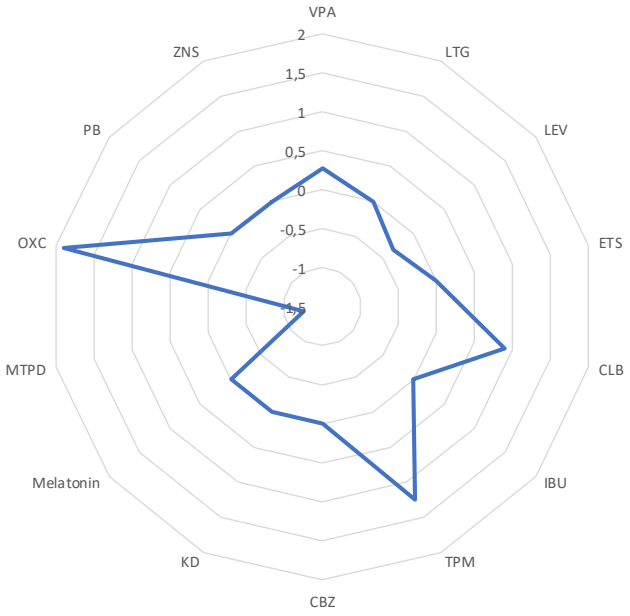


Figure 23: behavior score

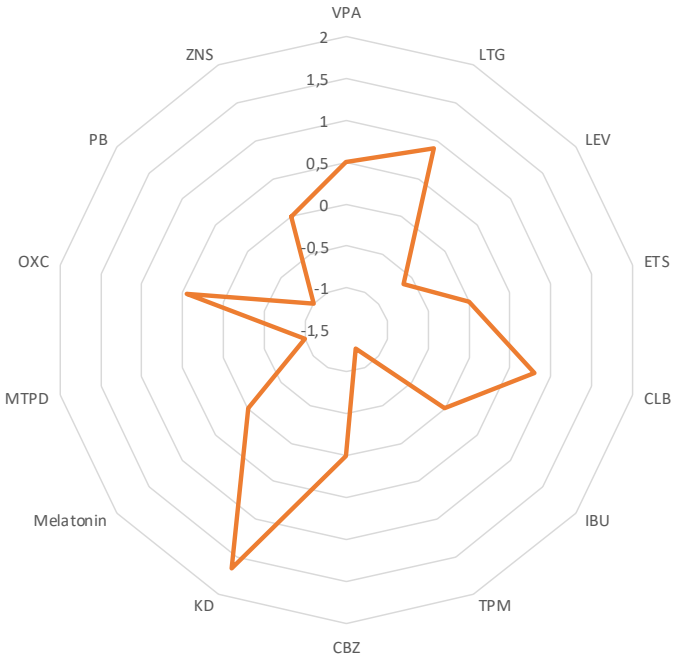


Figure 24: total efficacy score

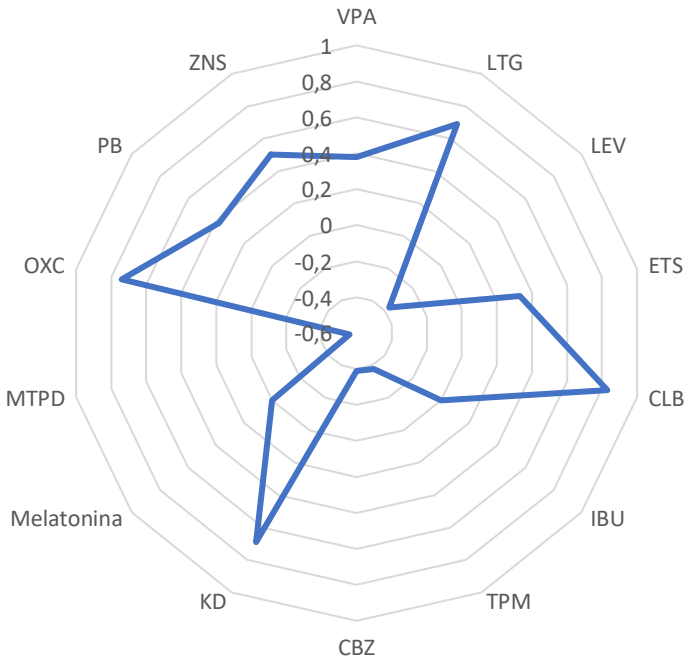


Figure 25: tolerability profile

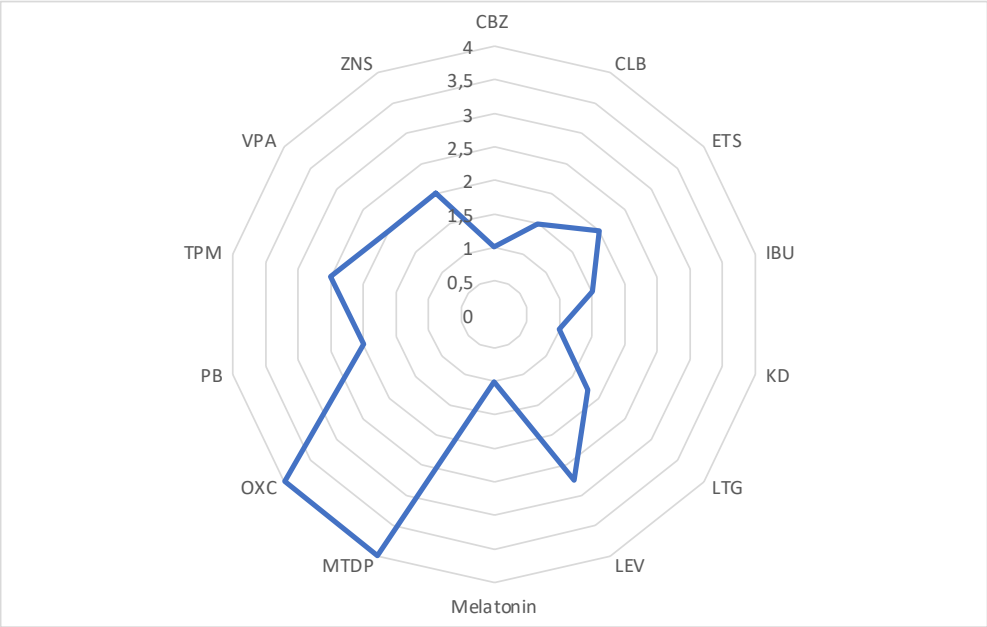
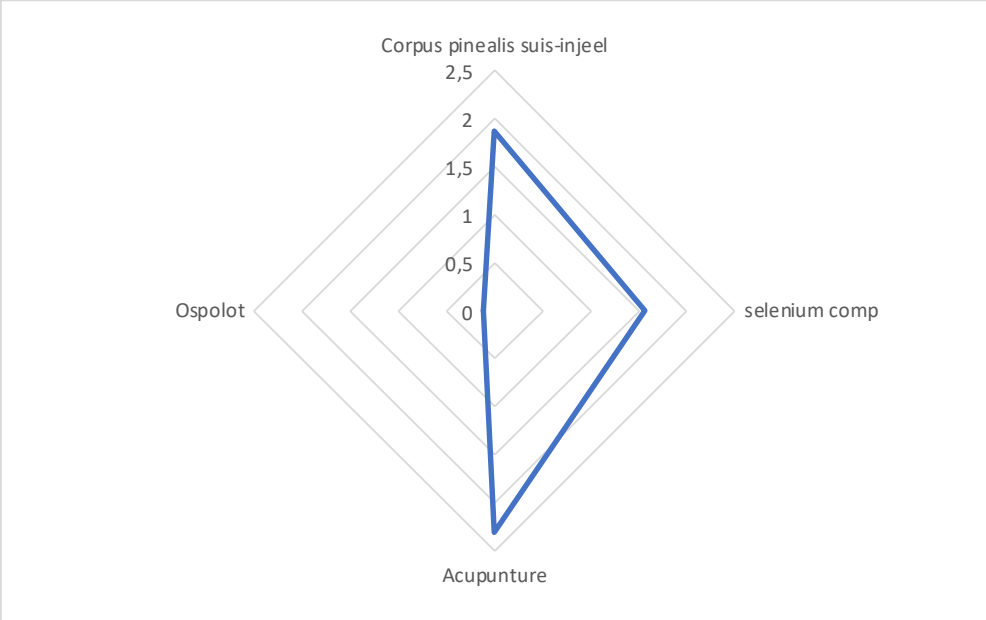


Figure 26: other treatment strategies



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