

Treatment of Photosensitivity

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Summary: Not all visually sensitive patients need antiepileptic drug treatment, and even those who do can benefit from additional preventive measures. Visually provoked seizures, in particular, can be prevented or treated by avoiding or altering the triggering stimulus. Apart from individual preventive measures (use of specific television or video screens, colored glasses, etc.), prevention and warning on a larger scale are helpful. The choice

for drug treatment will depend on the type of stimulus, the environment in which the person has to live and work, the frequency and severity of seizures, and the type of epileptic syndrome. A review is given of all treatment options with focus on the specific nonpharmacologic and pharmacologic tools used in clinical practice. **Key Words:** Prevention—TV—Colored glasses—Valproate and lamotrigine—New AEDs.

Many different clinical situations are found in the context of photosensitivity and epilepsy. Patients may have seizures that are exclusively (or predominantly) visually induced, sometimes known as “pure photosensitive epilepsy.” Alternatively the patient may have photosensitivity as an EEG response to intermittent photic stimulation (IPS) in the laboratory, and the epilepsy may be of any type with or without visually induced seizures [also see article by Guerrini and Genton (1) in this issue].

When treatment is discussed, the options range from no antiepileptic drugs (AEDs) to long-term AED prevention of seizures, apart from counseling concerning preventive measures. In most cases, nonpharmacologic approaches will be combined with AEDs. The literature on nonpharmacologic approaches is limited, and controlled comparative clinical trials are lacking. Furthermore, often “photosensitivity” is insufficiently defined, and patient selection does not discriminate patients with a photoparoxysmal EEG response (PPR) from those that have only visually induced seizures. Criteria such as the reduction or elimination of the photoparoxysmal EEG response after drug treatment influence outcome and are very dependent on the method of photic stimulation (2). Very few data separate the various epilepsy syndromes. In untreated patients, photosensitivity can persist to any age (3,4), but currently no way exists of identifying the individuals in which seizures will persist in the long term. With new insights into the genetics [also see article by

Stephani et al. (5) in this issue], it is to be expected that different therapeutic strategies will be needed in individual patients.

NONDRUG TREATMENT, PREVENTION

Background

Because the symptoms of a visually induced seizure and its likelihood both depend predominantly on the physical characteristics of the visual stimulus, avoidance is practical for many patients.

Seizures can be provoked by intermittent light and by patterns, most notably of stripes, whether flickering or steadily illuminated, static or moving. Sensitivity is usually, but not invariably, maximal at flicker rates of ~20 Hz, and the majority of patients are sensitive within a flicker frequency range of 8–50 Hz. The range of sensitivity can be greater: occasionally patients are sensitive to isolated flashes or to flicker that is so rapid as to be almost imperceptible. The patterns to which patients are most sensitive are spatially periodic: one cycle of the pattern subtending about one third of a degree at the eye (spatial frequency, 3 cycles per degree). If the pattern drifts continuously in one direction, very few patients are sensitive, but if the pattern moves with a similar retinal velocity, repeatedly alternating its direction of motion, the susceptibility can be as high as that for flicker, with similar frequency dependence as regards the temporal periodicity. Overall, sensitivity to visual stimuli increases with the total amount of retina and thus visual cortex being stimulated (6). For more details, see articles by Wilkins et al. (7) and Zifkin and Inoue (8) in this issue.

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In general

These parameters of photosensitivity provide important clues as to the best way to prevent seizures. Because it is known that the wider the range of effective IPS frequencies, the greater the likelihood of having visually induced seizures in daily life (9), avoidance of potentially provocative visual stimuli seems advisable for all patients and can be the only treatment in those who are sensitive to a relatively narrow frequency range. Discothèques should especially be avoided, because alcohol intake, emotional stress, and sleep deprivation are additional factors in lowering the seizure threshold.

Should the patient be bothered by myoclonic jerks or specific feelings whenever a provocative visual stimulus occurs, these symptoms can be avoided by looking away or by closing or covering one eye. Monocular occlusion reduces the epileptogenic effects of flicker in most patients, but not all, and the eye that is most effective varies, as can be established during the EEG examination. Covering the orbit of one eye with the palm of a hand so as to prevent light reaching the retina of one eye has therefore been recommended as a precaution if an aura is experienced, or when the patient is close to the television (TV) set, or when inadvertently exposed to flicker from other sources. The instinctive reaction of closing both eyelids may make matters worse because it may diffuse the light and increase the area of retina stimulated.

Closing one eye may also be useful in avoiding the effects of patterns. Potentially harmful patterns include the stripes on the stair tread of escalators, and venetian blinds. In some cases, it may be necessary to remove environmental sources of pattern altogether, as in the case of a major epilepsy hospital school, which used striped dresses as the school uniform and an epilepsy hospital that had a striped hall carpet.

Television

The vast majority of visually induced seizures are reported to occur when patients are close to the TV set. The seizures can be reduced by viewing a TV from a distance that is at least 3 times the width of the screen. This prevents the 25-Hz component of flicker from the line interlace being resolved by the eye sufficiently to cause seizures. TVs with a ≤ 12 -inch screen are much less a risk because the line interlace is too small to be adequately resolved even at close viewing distances. A special 100-Hz TV (120 Hz in North America) will increase the frequency of the flickering screen from 50 (60) Hz to 100 (120) Hz and make sensitivity to whole-screen flicker or the pattern of vibrating lines less likely (10). Computers with a liquid crystal display or a TFT screen are a better choice than the conventional ones. Also see article by Kasteleijn-Nolst Trenité et al. (11) in this issue for more details.

Despite these measures, it is still possible to have a TV- or computer-evoked seizure on exposure to flashing

or patterned program content. Many examples of seizures have been induced by flickering program content, the most dramatic on 17 December 1997, with a children's cartoon program, broadcast in Japan; 76% of children had no history of epilepsy (12). The UK Independent Television Commission (ITC) has initiated a set of guidelines that describe the parameters of epileptogenic material and prohibit its broadcast (13). Unfortunately these guidelines are not applied to material such as videogames, which are sold with disclaimers as the only protection. A novel method to avoid television-induced seizures is the use of temporal optical filters or video-hazard blocker (VHB) (14,15). In Japan, these new devices effectively prevent flicker- and pattern-induced seizures (15).

It has been customary to recommend the use of a lamp beside the TV (16). No field studies have tested the efficacy of this advice, and it may be questionable. Presumably the rationale was to adapt the eyes and to illuminate the screen from in front to reduce the contrast of the image displayed. Unfortunately contrast has to be reduced very considerably to eliminate the effects of epileptogenic images (6). In clinical practice, the effects of surrounding lights seem not to be a major factor; a history of seizures when viewing TV exclusively in a dark room has not been reported, and in one report, some patients were more sensitive to flicker in a light room than in a darkened room (17).

The use of spectacles with crossed-polarized lenses has been recommended for TV viewing. When combined with a sheet of polarizer over the TV, they permit normal viewing of everything except the TV, which is seen by one eye only (18). Although this is a cosmetic form of monocular occlusion, the glasses are expensive, and the money would be better spent in obtaining a television with a 100-Hz or liquid crystal display (LCD) screen.

The current habit of giving old TV screens and computers to the children (at home or in the classroom) is a source of unwanted seizure provocation; the older sets may have poorer picture stability, which may increase the risk of seizures.

Glasses

Monocular occlusion is as effective as wearing dark glasses. Polarized glasses are effective in reducing the diffusion of light, but no clear advantage is seen in use of cross-polarized lenses, unless investigated in that individual (19). Wearing colored glasses also was proven successful, but some controversy currently exists as to whether blue glasses are the most effective (20,21) or whether no common rule applies, and the beneficial color is different for each individual (22). In pathologies other than epilepsy in which the cortex may be hyperexcitable (e.g., migraine), it has been shown that to be optimally effective, a tint must be selected with precision, but differently for each patient (22). A small series using the new techniques that allow

individual precision ophthalmic tinting has shown some promise in patients with photosensitive epilepsy (23); 13 of the 23 visual-sensitive patients (57%) reported benefits of the tinted glasses in daily life. A preponderance of lenses with a rose or purple color existed, in contrast to patients with dyslexia.

Conclusion

The effectiveness of stimulus avoidance and modification (glasses, video hazard blockers, special TV screens) will depend on the individual's degree of photosensitivity, awareness of subtle warning signs and symptoms when exposed to potentially provocative stimuli, and the coping strategies of the patient. Patients with seizures exclusively triggered by visual stimuli, such as TV or flickering sunlight (also called "pure photosensitive epilepsy"), can be treated without drugs. For most patients, however, a combination with AEDs is necessary, especially because avoidance of provocative visual stimuli in modern daily life is becoming increasingly difficult.

GENERAL PROTECTIVE MEASURES

- Avoid relevant stimuli, such as discotheque lighting, striped clothing, and other striped patterns; sunlight on water; flickering sunlight; sudden changes in light and contrast; and flashing TV programs and videogames
- Use small TV, 12-inch set
- Use 100-Hz, LCD, or TFT screens
- Use remote control
- Do not adjust the controls or fast-run the video
- Avoid getting close to the screen: keep a distance of ≥ 3 times the width of the TV screen
- Cover one eye if exposed to provoking stimuli
- Wear spectacles: polarized lenses, dark glasses, or colored glasses (dark blue/green or precision tints)
- Avoid stress, extreme fatigue, sleep deprivation

DRUG TREATMENT

Often a combination of avoidance and treatment with an AED is necessary. Photosensitive epilepsies are usually diagnosed in childhood or adolescence. The prognosis for control of the seizures induced by visual stimulation is generally very good, especially in pure photosensitive epilepsy and in juvenile myoclonic epilepsy (JME). However, only ~25% of patients with these conditions will lose their IPS sensitivity, and this only in their third decade (3). Thus, most such patients will relapse if medication is discontinued and especially if this is done too early, in their teens. Serial EEG evaluation using a standardized protocol (2) with determination of the photosensitivity range can thus be helpful to assess the response to treatment and for evaluation of photosensitivity after withdrawal of medication.

In an early study of 11 children with TV-induced seizures, treated with phenobarbitone (PB) in 1962, a preventive effect was described in 10 of them with a follow-up of about a year on average (24). However, no EEG data were available. Jeavons and Harding (16) compared the effect of the various "older" drugs on the PPRs after the introduction of sodium valproate (VPA). They found poor effects with PB and phenytoin (PHT), an intermediate effect of ethosuximide (ESM), and a very strong effect of VPA. Clinical observational studies from the same group showed in 1986 a significant effect on prevention of seizure recurrence by VPA in 67 IPS-sensitive patients with seizures; 81% became seizure free. However, in the no-treatment group of 15 patients, 12 (80%) remained seizure free (25). With a follow-up period of 2–23 years (mean, 10 years), selection bias probably played a role. Because of the rapid and widespread introduction of VPA as general AED, no active controlled long-term prospective studies in visually sensitive patients have been performed.

Based on the very extensive experience of the Birmingham group and clinicians worldwide with an interest in visual sensitivity, VPA has become and remained the drug of first choice (26,27). Eighty-five percent of the visually sensitive patients will become seizure free with VPA (26). The benzodiazepines (BZDs), notably clonazepam (CZP) and clobazam (CLB), and ESM also are effective (26,28). PHT did not appear to be effective, whereas PB showed only a minor effect (28,29).

Short-term drug studies (single doses with repeated IPS and blood-level monitoring in patients) have been performed since the 1950s. Many AEDs, developed for partial and generalized seizures, have reduced or abolished PPRs in humans, suggesting that a variety of neurotransmitters and channel blockers could be involved. Trimethadione (TMO), ESM, as well as PB and the BZDs such as diazepam (DZP) and nitrazepam (NZP), were investigated in photosensitive patients after intravenous injection (24,30–32). Rowan et al. (33) investigated the influence of single oral dosages of VPA in nine photosensitive patients. Seven of them showed a clear reduction or disappearance of the photosensitivity, starting 3 h after maximal plasma concentration. This effect lasted for ≤ 5 days, although plasma VPA was not then detectable. We have used once-daily administration of VPA since 1978 and previously reported the consistent clinical and EEG response (34–36). The long-lasting effect also is seen after discontinuation of VPA; Harding and Jeavons (26) showed that the effect of VPA could persist for 3 months after discontinuation.

Other well-known AEDs also were investigated in the so-called photosensitivity model (37). Lamotrigine (LTG), progabide (PGB), DZP, ESM, and carbamazepine (CBZ) led to a reduction of the photoparoxysmal EEG response (PPR) after single oral doses (37,38). Recent studies have shown that the piracetam analog levetiracetam (LEV)

appears to be very effective (39), reducing or eliminating both the response to IPS and the myoclonic jerks. Long-term use of LEV in some visually sensitive patients has shown a remarkably good suppressive effect for >4 years; discontinuation of the drug before becoming pregnant resulted in a return of myoclonic jerks and an increase of IPS sensitivity (personal experience, D.K.). Although it is now becoming clear that drugs that prove to be effective in reducing the PPRs are good AEDs in general, this does not necessarily mean that they are specifically effective in long-term treatment of visually sensitive patients. Examples are CBZ and vigabatrin (VGB) (40). CBZ is certainly not a drug that should be given to patients with myoclonic jerks; it aggravates the jerks (41). Other drugs have abolished PPRs: the dopamine agonists apomorphine (1–2 mg, s.c.), lisuride (0.1 mg, i.v.), and levodopa (250–500 mg, p.o.) were mentioned in case reports (42–44).

Although it has not been proven scientifically that abolition of the PPR is better than reduction of range and response, treatment effects can be monitored by determining the photosensitivity range before and after drug treatment. It is even possible to titrate drug dosage in the individual patient by using the PPR. Many patients, especially children, can be adequately treated with a relatively low dosage of an AED. During adolescence, the prescribed dosage should be increased because of increased body weight and increase of the photosensitivity trait itself. Therapy should be maintained until the age of ~25 years. IPS in the laboratory will then help in predicting the relapse rate after partial or total discontinuation of the drug. This has been demonstrated in adolescent patients who have been treated successfully with VPA, but who were advised to taper and stop medication after 1 or 2 years without seizures and with complete suppression of their PPR. They have had a very high likelihood of seizure recurrence, observed in practice and also by Matricardi et al. (45). To predict the risk of seizure recurrence, we advise repeating IPS after partial discontinuation of medication. If the photosensitivity range is increased, the medication should not be diminished further.

Types of epilepsy

The specific and variable effect of VPA on different generalized epilepsies with photosensitivity did help us to understand and classify better the different epileptic syndromes. In 1982, Covanis et al. (27) reported that monotherapy with VPA was successful in 53–76% of photosensitive epilepsies (Table 1). The worst results were seen in eyelid myoclonia with absences (ELMA) and the best in pure photosensitive epilepsy (PSE). In our recent experience, the success of VPA in different types of primary PSE syndromes ranges from 74 to 86% (Table 1). Again the worst results were seen in patients with eyelid myoclonia.

TABLE 1. VPA monotherapy in different epileptic syndromes^a

Type of seizure	Patients	Mg/kg/day	Seizure free
AE-EO	2001 (1982)	2001 (1982)	2001 (1982)
CAE	19	26 ± 2.14	73%
FMA	124 (64)	28 ± 4.3 (26 ± 06)	81% (67%)
ELMA	13	24 ± 3.6	85%
EMA	50 (19)	26 ± 6 (30 ± 11)	74% (53%)
MEI/MEC	06 (06)	26 ± 2.6	85% (0%)
JME	56 (17)	28 ± 4.6 (26 ± 8.5)	84% (70%)
GTCS	45 (45)	22 ± 4.6 (21 ± 05)	85% (69%)
PSE	72 (67)	22 ± 4.2 (22 ± 04)	80% (73%)
	31 (42)	24 ± 7.5 (24 ± 6.5)	86% ^b (76%)

AE-EO, absence epilepsy early onset; CAE, childhood AE; FMA, facial myoclonia with absences; ELMA, eyelid myoclonia with absences; EMA, epilepsy with myoclonic absences; MEI/MEC, myoclonic epilepsy in infancy/childhood; JME, juvenile myoclonic epilepsy; GTCS, generalized tonic-clonic seizure; PSE, photosensitive epilepsy.

^aComparison of our recent experience with that in 1982.

^bHarding et al., 1997: 84%.

Similar results on photosensitive epilepsy with VPA monotherapy were reported by Harding, where 84% of the PSE patients became seizure free (3). Our recent experience (2001; unpublished results) showed a better overall response to VPA monotherapy. This, in our opinion, is due to the following facts: first, VPA was started early for the appropriate generalized epileptic syndromes, and second, by giving it once daily it improved compliance (34).

In JME, ~30% of patients have a PPR. VPA is considered the drug of first choice in all JME patients. A recent retrospective cohort study in 72 consecutive JME patients treated with VPA, LTG, topiramate (TPM), PHT, or CBZ revealed equal seizure control in patients on VPA and LTG monotherapy. VPA, LTG, and TPM, when compared with PHT or CBZ, demonstrated significantly better control of myoclonic seizures ($p < 0.01$ for all), but not of generalized tonic-clonic seizures (GTCSs) (46). No data were available on existence of PPRs in this group. However, our own clinical experience in patients with JME and a PPR

TABLE 2. Effect of monotherapy LTG in JME patients with a PPR

Sex/age	Seizure types (no AEDs)	AED/seizure types/ side effects	Seizure types/ side effects (with LTG)
F/18	GTCS, M, A	VPA/M, A (PPR)/ weight gain, tremor	M (PPR)/tremor
M/2	GTCS, M	VPA/GTCS, - (PPR)/ sedation	-
F/22	GTCS, M	VPA/- tremor	M (PPR)
F/19	M, A	VPA/- weight gain	-
F/24	GTCS, M, A	CBZ/M, A (PPR)/ sedation	-

LTG, lamotrigine; JME, juvenile myoclonic epilepsy; PPR, photoparoxysmal EEG response; AED, antiepileptic drug; GTCS, generalized tonic-clonic seizures; VPA, valproate; M, myoclonus; A, absence seizure; CBZ, carbamazepine; -, seizure free.

suggests a good clinical response on LTG monotherapy in patients with VPA side effects (see Table 2).

Self-induction

Fewer than 10% of photosensitive patients are therapy resistant, but most of these, engaged in self-induction, may be noncompliant (3,47). Patients who deliberately use visual stimulation to induce either overt seizures or "sub-clinical" epileptiform EEG discharges are very resistant to VPA and to any combination of AEDs, even if they are compliant (46). Waving the outstretched fingers in front of the eyes in a source of bright light or slow eye closures with rapid eyelid blinking is the usual way of self-inducing seizures (1).

Monotherapy with VPA was successful in only 40% of our self-inducing photosensitive patients. Dopamine-receptor antagonists, such as pimozide, seem to reduce this behaviour, apparently by making self-induced discharges or seizures nonrewarding, even if the drug itself is slightly aggravating the sensitivity to IPS (47). Fenfluramine, a serotonergic agonist used in dosages ≤ 1 mg/kg/day, stops seizures (48) but has no effect on EEG discharges (49). Fenfluramine has, however, serious cardiopulmonary side effects. Treating self-induced epilepsy early and successfully with relative high dosages of an AED (VPA) or possibly strong new AEDs like TPM, LEV, and pregabalin is likely to prevent the habitual pleasurable behavior to develop and sustain itself. Conditioning methods have been less effective and less popular (3).

Side effects such as behavioral abnormalities and irregular menstruation with weight increase could be a reason for discontinuing VPA (50). Newer AEDs with a broad clinical profile such as LTG, TPM, zonisamide (ZNS), and LEV seem to suppress generalized spike-and-wave discharges and may become an alternative, as supported by preliminary data and clinical experience. We have used LTG monotherapy in eight patients with photosensitive epilepsy. Five had GTCSs on awakening, two eyelid myoclonia with absences, and one pure PSE. LTG controlled the seizures completely in 62.5% of them, and the EEG became normal in only 25%. We have used LEV in 50 patients between the ages of 2 and 25 years as add-on therapy, and in 10 of them, who also are photosensitive, as monotherapy. LEV abolished the spike-and-wave discharges with a daily dose as low as 15 mg/kg. Our results are preliminary, and we are still in the process of finding the optimal daily dose. Large studies with the new AEDs are needed to be able to assess their advantages and disadvantages in treating visual-sensitive patients.

Preferred drugs

- First choice: Valproate
- Second choice: Lamotrigine
- If not successful: Topiramate, Levetiracetam, Ethosuximide, or Clobazam

CONCLUSION

Changes in luminance, contrast, pattern, and color can provoke seizures in photosensitive individuals. Preventive measures are nearly always possible and should be discussed with the patients and parents. Make them aware of provoking factors. Unnecessary constraints on people's lifestyle must be avoided, so the advice must be individual. Above all, restrictions should never be placed on people with epilepsy on the assumption that they are photosensitive.

The choice for drug treatment will depend on the type of stimulus, the environment in which the person has to live and work, the frequency and severity of seizures, and the type of epileptic syndrome. In the vast majority of persons with epilepsy and photosensitivity, the use of AEDs is necessary. The drug of first choice is VPA in monotherapy. Experience suggests that CLB could be a helpful adjunct. LTG, LEV, ESM, and possibly TPM also have been recommended as possible second choices, but no conclusive studies have been performed of prolonged use of these drugs in human photosensitivity.

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