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Focusing on an EEG Biomarker, the Photoparoxysmal Response (PPR), to Identify Promising Investigational Anti-Seizure Medications (ASMs) and Differentiate the Efficacy of Existing ASMs

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1 | Introduction

When many health care professionals hear that a patient has "photosensitivity" they immediately think about skin reactions to a chemical or drug, which is a considerable concern. However, in the world of neurology/epilepsy, there is a subset (0.6%–30%) [1] of patients with epilepsy that have sensitivity to flashing lights, also termed "photosensitivity." This type of photosensitivity results in either changes that appear on the electroencephalogram (EEG) as electrographic seizures only or clinically manifest seizures for some patients. The waveforms that appear on an EEG induced by flashing or flickering lights in the patient's environment can be reproduced mechanically by intermittent photic stimulation equipment ("IPS," i.e., strobelight). The induced abnormal brain waveform, characterized by spikes, sharp waves, or other abnormal discharges on EEG, is termed a photoparoxysmal response (PPR); its waveform EEG characteristics are nearly identical to that found in patients with epilepsy having spontaneous seizures [2]. This commentary emphasizes how IPS use during EEG recording in patients with epilepsy plus photosensitivity, who act as patient-volunteers for Phase 2a studies for new experimental ASM development, can utilize the PPR to help predict an ASM's activity on neuronal function. We have posed ten logical questions an audience may have about this topic, then crafted our best answers to these ten prompts to deliver a best understanding of this either overlooked or underappreciated subject to interested readers.

2 | How Does the EEG PPR Assist the Clinician in Epilepsy Diagnosis and Treatment, in General?

Since Bickford's sentinel characterization of the relationship of EEG discharges to epilepsy [2], plus early pertinent IPS EEG work from trained clinical neurophysiologists (reviewed by others [1, 3, 4]), IPS, with PPR generation on EEG, has been routinely used in the EEG identification and diagnosis of certain generalized and focal epilepsies [1, 3, 4]. Patients with epilepsy plus photosensitivity can then be treated clinically by avoiding flashing or flickering lights, wearing specific sunglasses or hats, and by treatment with anti-seizure medicines (ASMs), or the combination of these strategies [1]. The non-profit Epilepsy Foundation has compiled a broad array of questions they have received from clinicians and patients over many years concerning the diagnosis, prevention, non-pharmacologic or ASM treatments available, and life-style choices relevant to visually sensitive seizures. These questions have been answered via a comprehensive, evidence-based, scientific and well-defined clinical expert

opinion resource [5], in a very simple, readable "Questions and Answers" format for both clinicians and patients.

3 | How Does the EEG PPR Function as a Clinical Biomarker for New Investigational ASM Development in Epilepsy? What Is the History of the Use of the Human Photosensitivity Model of Epilepsy ("PMoE") With Examples of Its' Use?

The presence of an EEG PPR Hz range, from the entire range of 2–60 Hz, or a portion of that range, or even the presence of a *singular* PPR at any Hz in the range, is highly predictive of the likelihood of future seizure events; the greater the range the more likely the patient with epilepsy plus photosensitivity will continue to have seizures [6–9]. As an example, this concept of the relationship of the presence of a PPR to clinical seizures is well illustrated in a review of the "PMoE," [9] for a female patient undergoing valproate withdrawal where the measured PPR Hz range expands over time, ultimately resulting in a generalized tonic–clonic seizure (GTCS).

The Human Photosensitivity Model of Epilepsy ("PMoE") incorporates the EEG PPR as the primary biomarker of ASM activity historically. Some decades ago, it was determined that the EEG PPR could serve as a surrogate marker or biomarker for determining the activity of potential new investigational ASMs in Phase 2a, proof-of-principle (PoP) trials to help serve patients with epilepsy not optimally responding to currently available ASMs [6, 10, 11]. These Phase 2a ASM development studies ask patients with epilepsy plus confirmed, robust photosensitivity to act as paid volunteers to participate in institutional review board/human ethics-approved ASM trials after signing the approved informed consent form. Historically, there have been many older ASMs, notably levetiracetam [12], lamotrigine [13], brivaracetam [14], newer ASMs, such as cenobamate [15] and inhaled alprazolam—(under FDA review) [16], that have used the PPR biomarker construct to then launch pivotal Phase 2b and Phase 3 trials for efficacy versus placebo, and ultimately gain FDA approval. Many other investigational ASMs have been studied using the PPR biomarker, but development was stopped for adverse events/toxicity or marketing reasons [17–22]. In fact, this "PMoE" accurately identified the full NMDA antagonist, Org-6370, to paradoxically increase the PPR frequency, that is, it was seizure provactive [22]. Its' further development was immediately stopped based on this critical PPR biomarker information. It is very important to note that the Phase 2a PoP trials mentioned above included patients with epilepsy plus photosensitivity in the protocols, resulting in new ASMs achieving FDA approval for *all* patients with epilepsy, both focal and generalized, not just in those with photosensitivity. Recent published reviews [9, 23] comprehensively detailing the utility of the PPR for early ASM development and an entire new book [24] devoted to the understanding of epilepsy plus photosensitivity, in general, and specifically, the EEG PPR in photosensitive clinical epilepsy are available.

While the PMoE using the PPR biomarker clearly shows how a novel investigational ASM can diminish or eliminate PPRs *qualitatively*, Yuen [25] has shown that the PMoE *quantitatively* predicts the efficacy in epilepsy; in PoP trials reviewed, the investigational ASM mg doses that corresponded to 50%–100% PPR response were within 2-fold of the minimally effective dose used in both focal and generalized epilepsy. Plus, he found the difference in the ratio minimum effective ASM FDA-approved dose to the effective dose (ED50–100) used in PoP PPR biomarker studies for focal epilepsy (0.82) was not significantly different from that of generalized epilepsy (1.08) ($p = 0.51$) [25]. These earlier findings have been confirmed and expanded by Loscher: [23] utilizing the EEG PPR for thirty-five investigational ASMs tested in the "PMoE," a highly significant correlation exists between effective doses to suppress PPRs and effective doses in the treatment of patients with both generalized and focal epilepsy.

4 | How Is the "PMoE" Performed and How Is the EEG PPR Metric Measured Technically for Meaningful Clinical Effect?

The EEG-IPS procedure to generate PPRs is performed in a very standardized, safe manner, accounting for such factors as the distance of the patient's eyes to the strobe-light, type of strobe-light, Hz flash frequencies (typically 2 Hz-60 Hz) to be tested, contrast used, etc.; the IPS EEG technical guidelines have been recently updated [26]. A PPR may be generated over a number of flash frequencies, typically testing occurs from 2 Hz, the lowest threshold tested, up to 60 Hz, the highest Hz tested on an EEG (using either a 14-point [27] or in some cases, a 15-point [9] scale), yielding a range of Hz values (flashes/s) across lower and upper Hz-thresholds to which the patient is sensitive. While it is best to test the patient when ASM-naïve, many patient-volunteers with epilepsy plus photosensitivity have already been placed on ASMs, but frequently can still display photosensitivity via a PPR, even while being medicated with two FDA-approved ASMs.

After IRB approval and written informed consent have been obtained from each patient-volunteer, clinician-investigators have the patient-volunteer undergo three consecutive IPS testing days: On Day 1, a placebo dose is administered in the morning and a full day of hourly IPS testing under placebo conditions, noting the PPR Hz range. On Day 2, a single a.m. dose of investigational ASM is administered and the IPS procedure is repeated again at corresponding hours, together with blood sampling for plasma [ASM] concentration determination, allowing for pharmacokinetic:pharmacodynamic correlation, that is, PK:PD analysis. Importantly, patient-volunteers are thus their own control. On Day 3, a placebo dose is repeated, allowing for data acquisition of the duration of ASM effect and presence of adverse effects experienced by the patient. This Phase 2a PoP protocol can be designed with either a single fixed ASM dose or as a dose-ranging ASM trial, where several cohorts of four patients take a range of singular oral ASM doses.

All PPR-EEG data is read by the same blinded EEG board-certified investigator. Qualitatively, the PPR reaction on EEG to the new ASM either shows no response whatsoever, or a partial response (a decrease in upper to lower Hz range) or full response—total PPR elimination. A clear example of the latter upon gross inspection of an EEG is given for an actual patient-volunteer involved in the investigational ASM (coded LO59) study (see our Figure 1, Panels "A" and "B," with highly detailed Figure legend), where a single 1000 mg oral dose of LO59

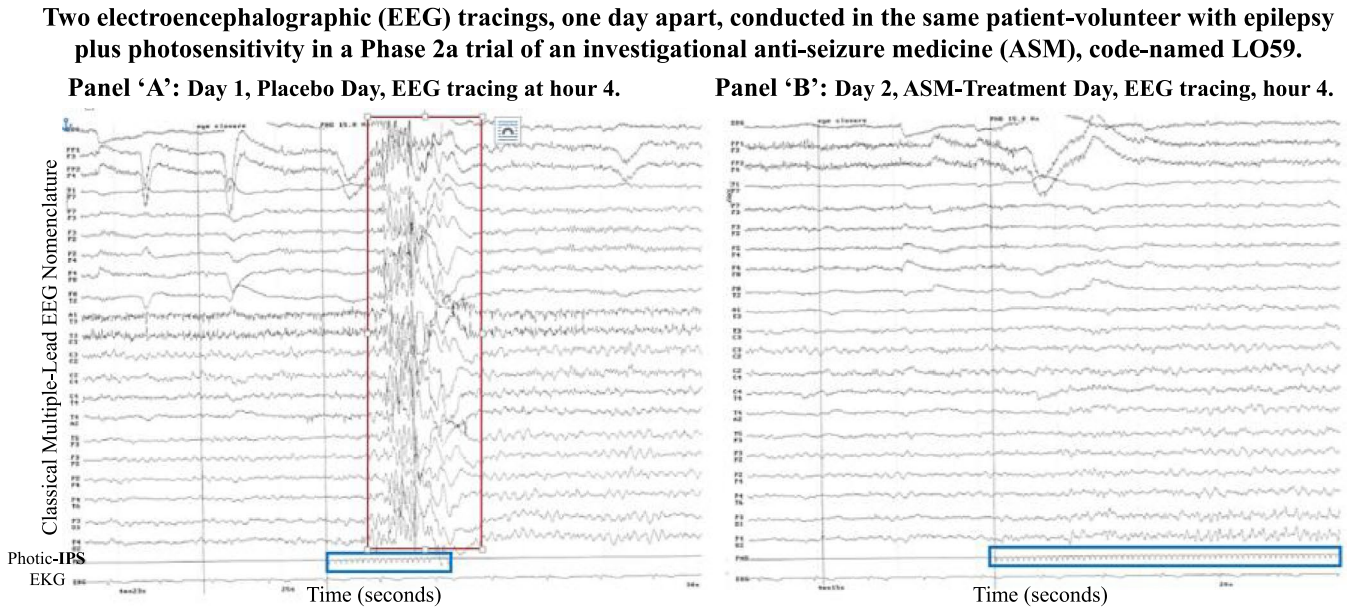

FIGURE 1 | Two actual typical, multiple-lead (across brain cortex) electroencephalographic (EEG) tracings in the same patient with epilepsy plus photosensitivity are shown (neither tracing was included as part of the publication cited) [12]. This patient had volunteered to participate in, and had given written, informed consent for an Institutional Human Ethics Committee-approved Phase 2a dose-ranging study of a new, investigational ASM, code-named LO59, which was developed by UCB Pharma in the mid-1990's. Panel "A": Day #1, a Placebo Day, depicts just one segment, at hour no. 4, of the patient's serial EEG tracings over 7.5 h, starting at 8:00 am, during the "eye closure" condition at 15 Hz (Hz: Flash frequency per second) on EEG. The first several seconds of the EEG tracing on the left-hand side is judged to be within normal limits by a *blinded* reader (author D.K.N.T., who had read all EEG tracings for all patients in this cited study) [12]. Then, about one-half second after the start of intermittent photic stimulation (IPS; each photic-stimulus is shown as downward spike-symbols in the 2nd-last line of the EEG [blue box, bottom]), a classical generalized (all EEG leads) photoparoxysmal response (PPR) is observed mid-tracing (shown within the red box). Frequently, these EEG waveform changes outlast the photic stimulation before returning to normal. This actual EEG tracing depicts just one Hz test of many different Hz tests on a 14-Hz point scale from a range of 2–60 Hz in the eye closure condition conducted. Panel "B": Day #2-ASM Treatment Day. This EEG tracing, performed in the same patient under the same "eye closure" condition at 15 Hz, at 4 h post-oral administration of a single dose of 1000 mg of LO59, shows no generalized nor focal PPR response throughout the EEG tracing even after several seconds of IPS (blue box). LO59, at the plasma [LO59] concentration achieved at hour no. 4, had totally suppressed the PPR. Earlier half-hourly tracings for this same patient (not shown here), revealed that PPR suppression had started at 1.5 h, attaining PPR elimination at 2.0 h. An EEG tracing for the entire 7.5 h of Day #3, repeating Placebo administration, (not shown here) is typically done to assess duration of experimental ASM effect and adverse effects within the patient. Importantly, serial blood samples are obtained in patients concurrent with IPS-conducted times on ASM Treatment Day 2, thus establishing a pharmacokinetic/pharmacodynamic (PK/PD) relationship for the investigational ASM. Patients exhibiting elimination of PPR on EEG with orally administered LO59 were found to have peak plasma [LO59] concentrations of 16.5–29.0 mg/L at 1.5–2.0 h and a duration of EEG effect from 6 to 24 h [12]. The promising results of this pivotal Phase-2a proof-of-principle LO59 biomarker study showing the efficacy of LO59 at a 1000 mg single oral dose in reducing and/or eliminating the EEG PPR [12] led to further conventional Phase 2b and Phase 3 testing. Two separate Phase 3 trials (one in the USA [28], one in Europe [29]), performed in parallel, randomized, double-blind, placebo-controlled fashion, showed LO59 to be statistically superior ($p < 0.001$) to placebo as an add-on ASM to each patient's ASM regimen for reducing focal (or partial)-onset seizure frequency. Thus, the utilization of this EEG PPR biomarker, reducing and/or eliminating the IPS-generation of a PPR, accurately predicted clinical seizure outcome in two large-scale, chronically dosed LO59 clinical trials. LO59 was ultimately FDA-approved in November 1999 and was re-named levetiracetam. Subsequently, this EEG PPR biomarker model has helped to successfully identify many new ASMs and quantitatively (based upon ASM dose) predicts seizure outcomes, including focal seizures [9, 23].

eradicates the PPR. For a clear visual of a PPR study worksheet for a participant's partial EEG response, the reader is referred to another published Table [30] illustrating a hypothetical patient-volunteer with epilepsy plus photosensitivity, showing the diminution in, and calculation for, the upper to lower Hz range for the ASM treatment Day 2 compared to placebo Day 1. Some investigators choose not to display the actual EEG for each patient-volunteer, but instead, typically show the diminution in Hz range of PPR via vertical lines calculated from their worksheets for EEGs conducted on placebo Day 1, then ASM treatment-test Day 2. The reader is referred to several other key figures, noting the suppression in EEG PPR for investigational ASM (ICA105665), then the diminution in Hz range, denoted by the use of decreasing length of vertical lines, from placebo-to-test ASM (brivaracetam {BRV} and seletracetam {SEL}), and the consequences of valproate withdrawal in a patient with epilepsy plus photosensitivity, with an increase in Hz ranges tested, depicted by vertical lines, all published elsewhere [9]. Moreover, the timeline of the study design for the standard three Phase 2a study days and events, including frequency of IPS testing, for the classical photosensitivity model has been detailed in a table elsewhere [9].

Finally, to measure PPR change quantitatively and statistically for placebo- versus ASM-test Days, using a 14-point scale, one of two methods can be used: (i) The PPR Hz range is transformed

into a standardized photosensitive response (SPR), with unit-less "steps" (see published example [27]), then the *change* in number of steps within-patient for pre-to-post-ASM treatment is calculated. A non-response is a value of zero (a pre–post-ASM therapy indicates no change/no response in photosensitivity range at all), while a SPR pre-to-post change value of −1 or −2 denotes an inadequate, clinically non-meaningful response; a change in SPR value of at least −3 up to −13 is a clinically meaningful, yet less than optimal SPR change value (recall that a "negative" value is desirable, occurring when the photosensitivity range is reduced after an ASM single dose or after chronic therapy). An optimal response is PPR elimination (a SPR change of −14). (ii) Alternatively, the mean for within-patients, placebo-to-ASM treatment change in "area-under-the-effect-curve (AUEC)" computed from time zero to the last time-point measured in the EEG PPR, using the arithmetic trapezoidal rule method, can be calculated for the cohort of patients tested (see published example [14]). Note that mean changes in Hz range (preferably a decrease), pre-to-post within-patient ASM treatment, are nice for visual display, but, to date, have not been used in statistical evaluation of the ASM effect in the EEG PPR model.

5 | What Are the Potential Advantages of Using PPR as a Biomarker Compared to Alternative Options?

If the new ASM definitively shows PPR substantial reduction and/or elimination of PPRs on EEG, the typical next step is to conduct a conventional parallel, randomized, double-blind, placebo-controlled Phase 2b trial to document ASM efficacy with chronic ASM dosing, using quantitative measures of seizure *outcomes* (i.e., mean decrease in seizure counts over time for the ASM patient group versus placebo group and/or number of patients with a 50% reduction in seizures between groups). Using the PPR biomarker in Phase 2a ASM development, especially when it incorporates a dose-ranging element, provides a relatively quick (8–15 months to complete) and less expensive way (requires less patients and resources) to determine potential ASM efficacy, compared to merely launching the typical, larger, longer, multicenter Phase 2b parallel study designed to evaluate seizure outcomes. The Phase 2a PPR biomarker is accurate, validated, and sensitive, providing valuable dose information for the next phase of ASM development (Phase 2b); in that sense, the PPR biomarker study is very complementary to the conventional Phase 2b study. The promising efficacy results of this pivotal Phase-2a PoP LO59 biomarker study [12] led to its' further conventional, successful Phase 2b and Phase 3 testing [28, 29] and ultimate FDA approval (see Figure 1 legend for details). The alternative to not conducting a Phase 2a PPR biomarker ASM study is simply to execute the usual parallel Phase 2 ASM study immediately post-Phase 1 PK studies.

6 | Can the EEG PPR Be Used as a Biomarker to Ascertain Differences in the Clinical Pharmacology or Efficacy ASMs in Epilepsy?

The EEG PPR biomarker has been successfully used to answer clinical pharmacologic questions concerning ASMs in an efficient and safe way. It is fascinating that the biomarker PPR can be used creatively to differentiate pharmacological activity of ASMs [27, 30, 31]. The PPR biomarker has been employed to identify statistically significant between-sex differences in chronic valproate therapy for seizures: [27] Males had a greater mean decrease in SPR, baseline to post-VPA IPS EEG testing, of -7.0 ± 2.6 versus -3.9 ± 3.3 for females ($p = 0.0018$) and a 3.2-fold greater percent of patients with complete PPR elimination, or a SPR value = 0 post-VPA treatment, ($p = 0.0237$). The percentage of males with a VPA clinically meaningful to optimal response was 1.93-fold greater than females, at 100%: 51.8%, respectively ($p < 0.0001$), despite twice-higher, yet non-significant, plasma [VPA] concentrations in females.

The ASM brivaracetam, an n-propyl chemical derivative of levetiracetam, has much greater lipid solubility, 10- to 15-fold greater potency plus greater SV2A-ligand binding affinity, all suggesting faster CNS action clinically—but does this really matter? [31] A heavily adapted procedure of the PMoE has been successfully performed to assess the rate of CNS entry for equi-potent mg doses of intravenous brivaracetam versus i.v. levetiracetam in a double-blind, randomized, crossover, Phase 4 EEG PPR study at two different infusion rates, at 5 and 15 min [31] The combined infusion rate data from this clinical pharmacology study demonstrated that time to elimination of the PPR was 61% faster with i.v. brivaracetam ($p < 0.039$), and as a whole, entered the brain 5.5 min faster than levetiracetam. This study answered a clinical pharmacology question but was not an outcome study of convulsive events; that needs to be done. Based upon our study results [31], and the fact that the latest, exceedingly well performed multicenter, blinded, randomized study on benzodiazepine-refractory status epilepticus in adults showed equivalency (only ~45%–47% patients with seizure cessation) for high-dose intravenous levetiracetam, valproate, and phenytoin [32], we have proposed to clinician-investigators that brivaracetam deserves to be considered in the next large-scale status epilepticus study [33].

In another example of the creative use of the PPR biomarker, a Phase 4 investigator-initiated study was designed to determine if very small increases in plasma valproate [VPA] concentrations influenced a patient's PPR [34]. The larger concern was testing the concept of whether or not substitution of a generic divalproex-extend-release-(ER) oral tablet for the brand-ER tablet formulation would result in perturbation in [VPA] concentrations, potentially increasing the likelihood of seizures. A patient study testing the brand-to-generic formulations head-to-head would have been desirable, but would have taken too long and been too costly. As such, another study was planned, using i.v-infused NaVPA instead along with the PPR biomarker. Post-informed consent, 13 patient-volunteers were given an initial NaVPA i.v. loading dose sufficient to achieve 30 mg/L, quickly followed by an ascending dose-infusion to achieve a serum [VPA] 100 mg/L over 12 h. Clinician-investigators sought to determine the impact of very small increases in plasma [VPA] concentration, by 6.5 mg/L/h, over 12 h via IPS and the PPR biomarker. VPA modestly attenuated the PPR within the time frame of 12 h. The authors concluded that: (i) the suppressive effect of VPA on PPRs occurred in a concentration-dependent manner, starting at plasma [VPA] levels ~43 μg/mL, which correlated with the lower threshold of the therapeutic range (50–100 μg/mL) typically used in clinical care; (ii) only large [VPA] changes

impacted the PPR ranges—a statistically significant decrease in PPR was seen over the 30–100+ mg/L range of VPA; (iii) our change in EEG PPR effect requiring a large increase in [VPA] concentration was in line with the results of a chronic outpatient seizure outcome study with oral VPA therapy which established that large increments, not small, in serum [VPA] concentrations of 123 μg/mL were statistically superior to 56 μg/mL for reducing focal seizures and GTCS [35]; iv. our EEG PPR study [34] with a single VPA i.v. dose also hinted that achieving optimal VPA effect may be both concentration and time dependent.

7 | Does the EEG PPR Biomarker Have Utility in Other CNS Diseases?

No other clinical investigator has specifically researched the mere prevalence of the PPR on EEG in other CNS diseases, such as schizophrenia, migraine, Alzheimer's dementia, or other neurodegenerative disorders, much less its' utility in CNS drug development beyond epilepsy. Migraine with aura/photophobia and epilepsy surely co-exist, but migraine photophobia may not be the same as electroencephalographic photosensitivity via IPS. There is an interest in disease-induced and/or drug-induced neurotoxic EEG changes, but infrequently utilizing IPS, while mentioning EEG PPRs is exceedingly rare; a few examples mentioning IPS or PPR are provided here. Portnova [36], studying EEG while employing IPS on a 4-point scale, found alterations in time perception accompanied by corresponding EEG changes in healthy volunteers, but curiously, it was absent in patients with schizophrenia. In a series of ten clozapine-treated patients [37], five had myoclonus and one had a generalized tonic–clonic seizure, with seven exhibiting clozapine-induced EEG abnormalities (bilateral spike, polyspike and slow wave discharges, with only one having a PPR on EEG). Wada [38] performed quantitative EEG analysis during a single-point IPS (10 Hz) in drug-naïve patients with paranoid schizophrenia, finding significantly lower alpha-2 band amplitude compared to age- and sex-matched controls, suggesting a dysfunction in EEG alpha band generation in those patients. Wada's group [39] also investigated sequential changes in EEGs during IPS (again 10 Hz) via quantitative EEG analysis for the alpha band in 18 drug-naïve schizophrenic patients and 18 sex- and age-matched control subjects. During IPS, the absolute 9–11 Hz band power of the patient group was higher at the posterior than that at the anterior sites, but during the non-stimulus period, posterior dominance of 9–11 Hz band power was prominent in the patient group throughout, but with minor differences in the controls. Schizophrenic patients show fewer changes in posterior alpha activity during both stimulus and non-stimulus, and this continuity of posterior dominance reflects hyperarousal, counteracting any decrease in vigilance throughout the IPS.

8 | Does the EEG PPR Biomarker Have Limitations in the Study of Patients With Epilepsy Plus Photosensitivity?

The PMoE/EEG PPR biomarker certainly has limitations. First, patients with epilepsy plus photosensitivity may be limited in a clinician-investigators' database due to lack of routine thorough IPS testing as part of the diagnostic EEG procedure in patients with epilepsy; finding good patient-volunteers requires systematic screening of patients. Second, the current pool of patient-volunteers may not display a sufficient Hz range of PPRs on EEG, due to their currently prescribed ASMs—finding the efficacy of an investigational ASM is more difficult if the patient's baseline PPR Hz range is small to begin with. Young adults are most sensitive and are either ASM free or on one ASM [24]. Third, there is some historical controversy as to whether or not this PMoE is effective at identifying new ASMs for patients with *focal* seizures [40], given that the majority of patients with photosensitivity display generalized PPRs on EEG. However, this concern has been dispelled—all the investigational ASMs launched by the use of the PPR biomarker, then subsequently achieving FDA approval, are useful in treating focal seizures [9, 23, 41]. Plus, Yuen clearly showed that the difference in the ratio minimum effective ASM FDA-approved dose to the effective dose (ED50–100) used in PoP PPR biomarker studies for focal epilepsy (0.82) was not significantly different from that of generalized epilepsy (1.08) ($p = 0.51$) [25]. The authors have identified that, in essence, all photosensitive patients (those with focal or generalized PPRs) can be included in studies dependent on the pharmacological question that needs to be answered.

9 | Do Other EEG Parameters or Metrics, Beyond the EEG PPR for Epilepsy, Function as Biomarkers for CNS Diseases?

While it is well recognized that the EEG has been and still is a very useful, widely available tool for assisting the clinical diagnosis of many different types of epilepsy (not reviewed here) beyond photosensitive epilepsy, a few investigators have astutely recognized its' potential for evaluation of a variety of central nervous system (CNS) drug treatment effects, in general, using a variety of EEG metrics [42–48]. For instance, PK:PD modeling of the EEG effects, namely, the *amplitudes* in the 11.5 to 30 Hz frequency range (beta range) of benzodiazepine agonists—flunitrazepam, midazolam, oxazepam, and clobazam—were quantified and correlated with receptor affinity and anticonvulsant effect [42]; a follow-up study by Mandema again used the *amplitudes* in the 11.5–30 Hz frequency range on EEG to study the concentration-effect relationships of midazolam, partial agonist bretazenil, and antagonist flumazenil [43]. The concentration-EEG effect relationships of the intravenous anesthetic, alfentanil, along with the sedative/hypnotic effect of benzodiazepines, have been studied via recording the changes in the amplitudes in the beta frequency band of EEG signals, reflecting their affinity/intrinsic efficacy at the central gamma-amino-butyric acid (GABA)-benzodiazepine receptor complex [44]. Tuk [45] utilized quantitative EEG and saccadic eye movements in predicting temazepam's improvement in primary insomnia. Interestingly, Saletu [46] took raw EEG data, transformed it into a visual map that shows the distribution of electrical activity across the scalp by using color-coded maps, where different colors represent different levels of brain activity (EEG topography), producing pharmaco-EEG maps of neuroleptics, antidepressants, tranquilizers, hypnotics, psychostimulants, and nootropics/cognition-enhancing drugs. Saran [47], studying the neurotoxicity of a haloperidol-lithium combination, found 5 of 11 (45.4%) patients (mix of primary affective disorder-manic phase or schizophrenia) displaying abnormal responses on

EEG: 3 showed abnormal photic responses, and two showed slowing in posterior alpha activity. Varma [48] found a strong positive correlation between increasing dose of the antipsychotic clozapine and the occurrence of EEG abnormalities (most commonly non-specific generalized slowing), with each 100 mg increase accounting for an 8% increase in abnormal EEG findings ($p = 0.022$); yet, IPS and PPR measures were not mentioned. These two review articles concerning EEG-based PD measures and quantitative EEG to assess CNS drug therapeutic response may be helpful to our readers [49, 50].

10 | What Are the Potential Future Applications for the EEG PPR as a Biomarker for Epilepsy, or for Other CNS Diseases?

The EEG PPR biomarker is now well established for ASM development and will continue to be used [9, 23]. Yet, only a handful of epilepsy centers or clinical practice sites in the USA participate in such Phase 2a studies since clinicians claim "they do not have patients"—but, have they really searched for them properly? Obtaining an EEG is routine as part of the diagnosis of epilepsy in clinical practice, and a few steps could be taken to determine whether or not the patient is also electrographically photosensitive. If any patient with epilepsy claims to have symptoms related to photosensitivity (overt seizures or myoclonic jerks occurring in temporal relationship with seeing flickering lights—from riding in a car on a road among trees on a sunny day, staring at shimmering lights from small waves on a lake on a sunny day, a discotheque, etc.), then the patient will automatically have a full EEG investigation with IPS. Frequently, however, patients do not share such episodes with clinicians, nor do clinicians routinely ask their patients about this within their busy clinical practice. More clinical sites are needed to be involved in ASM development trials in epilepsy.

No systematic research has yet been conducted on the mere prevalence of photosensitivity in patients with other CNS diseases; conducting EEG-IPS work, identifying either a PPR or other EEG anomalies in such patients would be a great research project for those clinicians interested in the subject.

11 | Summary: What Are the Key Takeaway Messages Concerning the EEG PPR and Other EEG Parameters for the Study of CNS Therapeutics?

The EEG PPR biomarker has profound utility for the investigation of new investigational ASMs via Phase 2a trials and for Phase 4, investigator-initiated study (IIS) projects attempting to differentiate currently available ASMs. The EEG PPR is objective, sensitive, and reproducible and has aided in ASM development immensely. Furthermore, all other EEG parameters, beyond the EEG PPR, mentioned herein represent many of the characteristics of ideal, objective pharmacodynamic measures, which, when meticulously studied, will advance our understanding of CNS pharmacotherapeutics. Nevertheless, utilization of EEG as a pharmacodynamic measure alone or in PK/PD relationships seems to be either unnoticed or undervalued in the clinical pharmacy and pharmacology community, considering the paucity of publications in the area by those with an interest and/or expertise in clinical pharmacotherapeutics. We heartily encourage those interested readers to familiarize themselves with EEG parameters/metric tools, in general, and the EEG PPR specifically, to advance our understanding of currently available or investigational and marketed CNS Drugs and new experimental ASMs, respectively. The EEG PPR biomarker and other EEG parameters present a great opportunity for some potentially fruitful clinical pharmacotherapeutics research.

Author Contributions

Ronald C. Reed: conceptualization (lead); data curation (equal); formal analysis (lead); funding acquisition (not applicable); investigation (equal); methodology (lead); project administration (lead); resources (supporting); software/EEG analysis (supporting); supervision (lead); validation (equal); visualization (lead); writing – original draft preparation (lead); writing – review and editing (lead). **Dorothee G. A. Kasteleijn-Nolst Trenite:** conceptualization (supporting); data curation (equal); formal analysis (supporting); funding acquisition (not applicable); investigation (equal); methodology (supporting); project administration (supporting); resources (lead); software/EEG analysis (lead); supervision (supporting); validation (equal); visualization (supporting); writing – original draft preparation (supporting); writing – review and editing (supporting).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this manuscript are available from the corresponding author upon reasonable request.

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