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Title:
"Anti-Epileptic Drugs (AEDs) Reduce the *Upper* Photosensitivity Threshold-Limit More Than the Lower Threshold in the 'Photosensitivity Model of Epilepsy'."

The Methodological Question Being Addressed
Can the procedure for testing AED efficacy via the '*Photosensitivity Model* for AED Effect in Epilepsy' be truncated without jeopardizing data integrity by only testing the *upper* photosensitivity EEG threshold in each epilepsy patient-volunteer?

Introduction (Aims)
The electro-encephalographic (EEG) 'Photosensitivity Model' (Kasteleijn-Nolst-Trenité...Reed, *Epilepsy Research* 2017) has been successfully employed as a proof-of-principle, Phase-2a paradigm for detecting potential new AED efficacy. This 'Photosensitivity Model' traditionally tests *intra*-patient diminution in a patient's photosensitivity-Photo-Paroxysmal Response (PPR, a *biomarker of epileptic activity*) range on EEG. This range is measured (from high point=60 Hertz [Hz], to low=2 Hz) on placebo day=no AED being administered and subsequently, another day post-AED intake. Three separate eye conditions (eyes open, during closure, eyes closed) at each designated time-epoch are studied, 2-60Hz. AED efficacy means substantially diminished/abolished photosensitive range. The standard EEG 'Model' utilized requires specialized neurologist expertise, is labor-intensive and places the patient at convulsive risk. We sought to determine if a difference exists for the upper vs. lower photosensitivity response when testing AEDs overall.

Methods
PPRs of n=236 regular photosensitive patients (unpublished data, 163F; 69%), mean age= 20±10yr (7-60yrs) were analyzed. In all patients, standardized photic stimulation, 2-60 Hz, using a Grass PS-33plus had been performed with determination of upper/lower sensitivity ranges in 3 eye conditions. Our visual inspection of all individual photosensitivity cases treated with any AED (n=236 patients on AEDs, [unpublished data, DKNT]) revealed that:

i. The 'eye closure condition' seemed to have the greastest sensitivity and change in PPR;
ii. AED treatment (n=152 patients on AEDs vs. placebo) produced a lowering of the *upper* photosensitivity limit, whereas the lower limit moved upwards marginally.

The PPRs for patients with vs. without AEDs were compared (t-test; Mann-Whitney; ANOVA regression analysis).

Results
Of 236 patients with a PPR, 233 had a PPR on eye-closure, 206 with eyes-closed, 149 with eyes-open. Most patients were on stable AEDs (n=152,64%) and monotherapy (n=104,44%; mostly with VPA). Some patients (n=48,20%) took 2-4 AEDs (polytherapy). The upper sensitivity limit decreased with AED(s) treatment versus each individual's baseline (for eye closure, p = 0.002; eyes closed, p = 0.008 and eyes open, p = 0.04). The lower threhold

changed minimally with AED treatment *(p=NS)*. Similar decreases in the upper threshold were seen for all AEDs.

Advantages to determination of the upper threshold or limit alone (during eye closure) in this adapted 'Model' procedure include:

i. total IPS number is reduced by half, potentially reducing costs;
ii. potentially increased patient safety from limiting provocative photic stimuli;
iii. the procedure becomes more "nimble", allowing frequent serial measurements in a short period of time.

Conclusions

In the '*Photosensitivity Model* for AED Effect in Epilepsy', AED treatment (mono- or polytherapy) of photosensitive epilepsy patients statistically and substantially lowered the upper sensitivity/threshold Hz limit compared to each patient's pre-treatment baseline. Reductions in EEG upper Hz threshold were seen in all eye conditions (eyes open, during eye closure and with eyes closed). The 'Photosensitivity Model' procedure can be truncated, if needed.

Disclosures:

The authors have nothing to disclose; no funding was received for this data mining project.