
Ronak
Pharmaceutical Co.

ROPAKIN® Chrono
Sodium Valproate 500 mg

Advantages of controlled release systems

Dr Kazem Hashemin
R&D Manager

Ronak Pharmaceutical Co.

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Advantages of controlled release systems

- ❑ Sustained release
- ❑ Controlled release
- ❑ Chrono

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1. Simplification of dosing regimens
2. Reduction in pill burden
3. Reduction in the peak-to-trough fluctuations in serum drug concentration that may be associated with a decreased risk of adverse effects and of seizures.

Potential to

1. Increase adherence to antiepileptic therapy
2. Improve the quality of life of patients
3. Reduce health care costs

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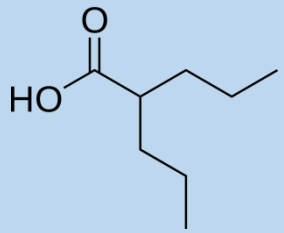
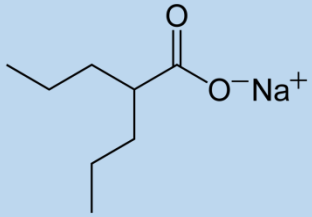
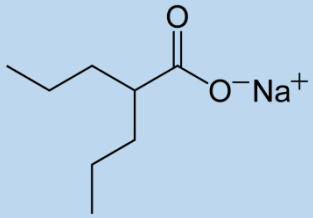


Valproic Acid
145 mg

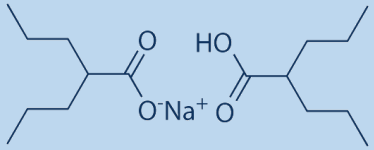
+



Valproate Sodium
333 mg



Valproate Sodium 500 mg



diValproex Sodium 467 mg

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Valproic Acid Dosageforms (US)

1- Valproate Sodium Syrup
2- Valproic Acid Capsule
3- Divalproex sodium sprinkle capsule
4- Divalproex sodium enteric-coated delayed-release tablet
5- Divalproex sodium extended-release tablet

Valproic Acid Dosageforms (Europe)

1- Valproate Sodium Syrup
2- Valproic Acid Capsule
3- Sodium valproate, valproic acid modified release granules
4- Sodium Valproate enteric-coated delayed-release tablet
5- Sodium valproate, valproic acid controlled release tablet

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An assessment of the clinical equivalence of valproate chrono and extended release divalproex formulations

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Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India

Abstract

Objective: No guideline currently exists to choose the clinically equivalent dose of divalproex extended release (ER) formulation while switching over from valproate chrono formulation. To address this issue, we evaluated the serum valproate concentration following switch over from valproate chrono to divalproex ER in persons with epilepsy. **Materials and Methods:** An open label study was conducted in two parts, each for a period of two months. During Part I, patients on regular twice-daily dose of valproate chrono were switched over to once daily divalproex ER (DESVAL ER®) based on the dose escalation recommended when switching over from divalproex DR to ER formulation as the guideline. During Part II, we switched from valproate chrono to divalproex ER with same dosage. Serum valproate concentration, seizure frequency and side effects were assessed serially for two months after changeover and compared with the preswitch data. **Results:** During Part I, compared to the baseline level, there was a significant increase in mean serum valproate level at two months (67.0 ± 28.4 μg/ml versus 91.9 ± 3.5 μg/ml, *P* 0.004). With the same dose conversion during Part II, the mean valproate level did not significantly differ before and after the switch (81.5 μg/dl versus 85.7 μg/dl, *P* 0.08). The mean monthly seizure frequencies and serum ammonia levels did not change during either part. No significant adverse effects occurred. **Conclusion:** The results of this open label study with small number of patients need to be replicated among larger patient sample through a randomized control design before recommending same dose conversion from valproate chrono to divalproex ER without change in efficacy and tolerability.

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Divalproex to Divalproex Extended Release Conversion

Sandeep Dutta and *Ronald C. Reed*

Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, Illinois, USA

Abstract

Objective: Divalproex extended release (ER) tablets have lower bioavailability than conventional divalproex tablets. Objectives were to provide dose-increment justification for conversion of a patient from conventional enteric-coated divalproex to a once-daily divalproex ER regimen and to discuss the pharmacokinetic factors affecting these unequal total daily dose conversions.

Methods: Three bioavailability studies (two in healthy volunteers and one in epilepsy patients; total n = 69) compared equal total daily doses, and two studies (one each in healthy volunteers and epilepsy patients; total n = 99) compared 8–20% higher divalproex ER daily doses with corresponding divalproex total daily doses. In all five studies, multiple doses were administered over 6–14 days in each regimen.

Results: For equal total daily dose comparisons, the divalproex ER/divalproex bioavailability (area under the concentration-time curve [AUC] ratio) was ~0.89 and when the divalproex ER dose was higher, the two regimens were equivalent (AUC ratio ~1.0). Divalproex ER administered once daily had less fluctuation in valproic acid concentrations, i.e. divalproex ER achieved equal or significantly higher minimum concentrations and significantly lower maximum concentrations compared with divalproex administered multiple times daily. Divalproex ER predose trough concentration consistently represented the lowest concentration during a dosing interval, whereas for divalproex this was not true because of absorption lag time (from enteric coating), diurnal variation and multiple doses during a 24-hour interval.

Conclusions: An 8–20% higher divalproex ER daily dose should be used when converting from a total daily dose of divalproex. The lower fluctuation of valproic acid concentrations, consistent time to trough concentration, and lower dosing frequency of divalproex ER should offer benefit to the patient by providing convenient once-daily administration, and to the clinician by facilitating easier and reliable therapeutic drug monitoring and improving patient adherence.

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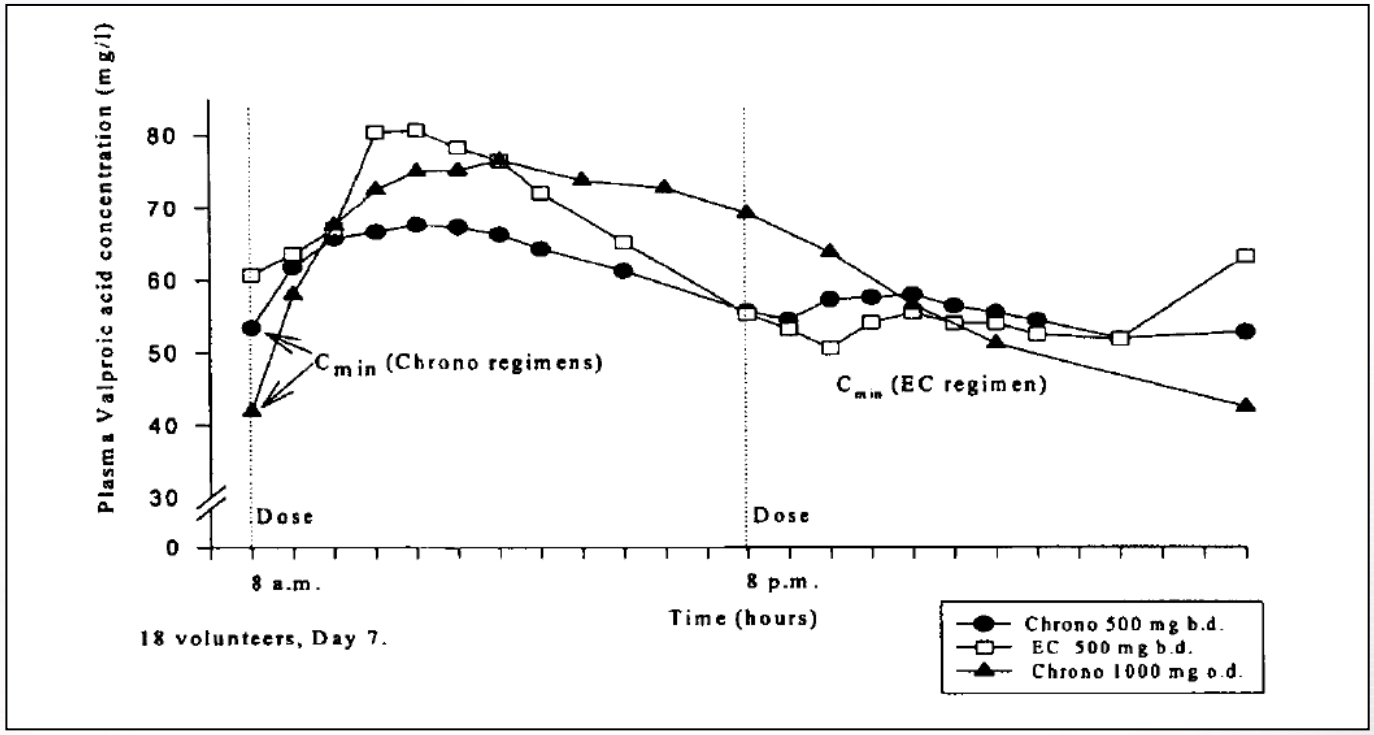
SVEC VS SVSR

Roberts D, Easter D, O'Bryan-Tear G. Epilim chrono: a multidose, crossover comparison of two formulations of valproate in healthy volunteers. Biopharm Drug Dispos. 1996 Mar;17(2):175-82. doi: 10.1002/(SICI)1099-081X(199603)17:2<175::AID-BDD946>3.0.CO;2-J.



- **T_{max}:** No major Difference
  C_{max}: EC 500 bd> Chrono 1000 mg od> Chrono 500mg bd
  C_{min}: Chrono 500mg bd > EC 500 bd> Chrono 1000 mg od
- **Peak-trough** variation is the least with Chrono 500 BD.
- Once-daily Chrono matches the twice daily EC more closely than the twice-daily Chrono.

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Comparison of the pharmacokinetic profile of a multiparticulate formulation with an enteric coated tablet formulation

Both formulations showed comparable extent of absorption at steady state, BUT

The plasma fluctuations on dosage of the multiparticulate formulation were only one-third of those seen on dosage of the enteric-coated tablet formulation.

1. Wangemann M, Retzow A, Vens-Cappell B. Pharmacokinetic characteristics of a new multiple unit sustained release formulation of sodium valproate. Int J Clin Pharmacol Ther. 1999 Feb;37(2):100-8. PMID: 10082174.
2. Levy RH, Shen D, Abbott F, et al. Valproate. Chemistry, biotransformation, and pharmacokinetics. In: Levy RH, Mattson RH, Meldrum BS, et al., eds. Antiepileptic Drugs. 5th ed. Philadelphia: Lippincott-Williams & Wilkins; 2002:780-800.

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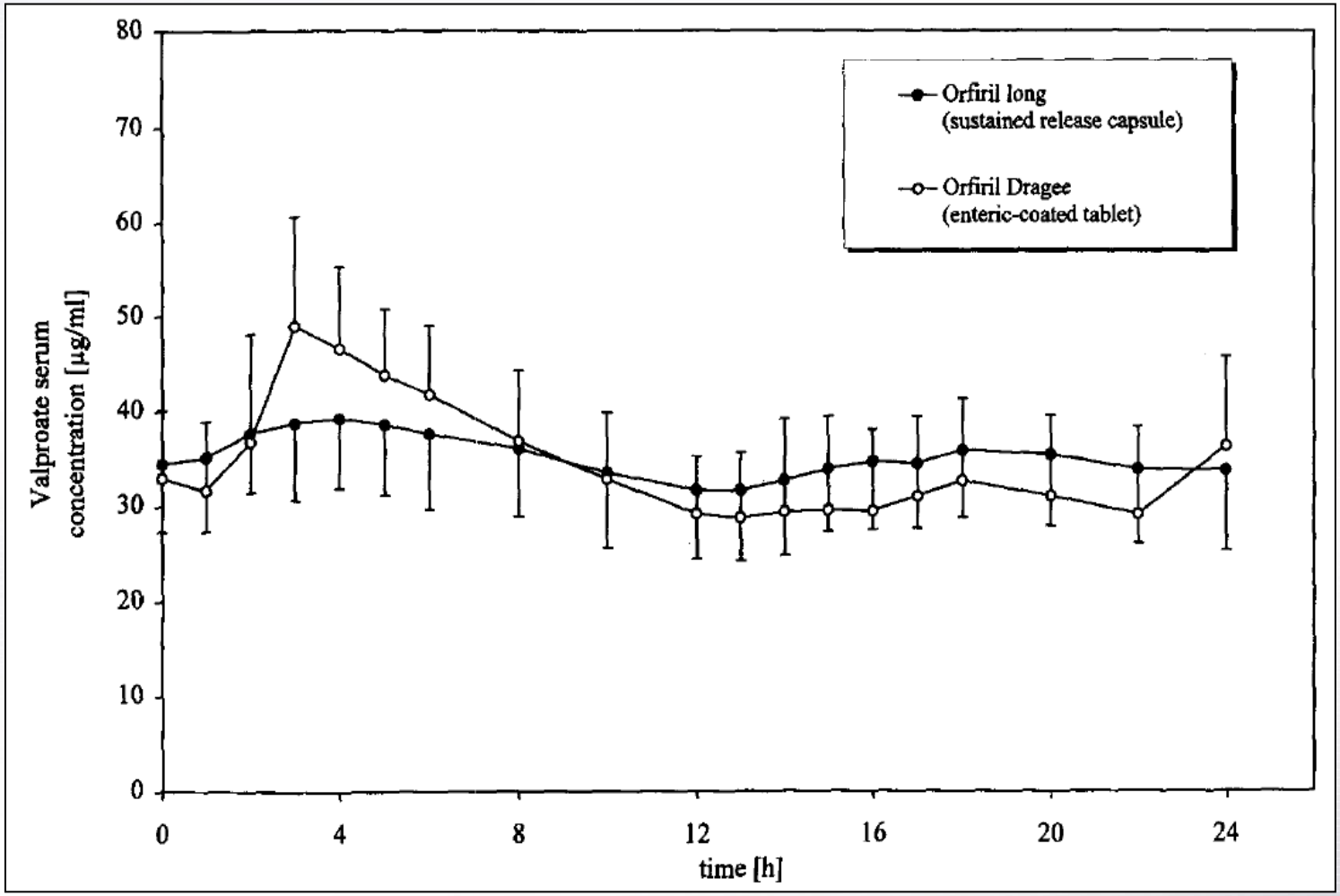

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With or without FOOD

INFLUENCE OF FOOD INTAKE ON THE PHARMACOKINETICS OF A SUSTAINED RELEASE FORMULATION OF SODIUM VALPROATE

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ABSTRACT

The effect of food intake on the pharmacokinetics of DEPAKINE® CHRONO 500 mg (Sanofi, France), a sustained release formulation containing 333 mg sodium valproate and 145 mg valproic acid, was studied in 12 young healthy female volunteers. Relative to fasting conditions (F), when the tablet was given at the midpoint of the breakfast (NF), the maximum concentration (F: $34 \cdot 6 \pm 8 \cdot 9$ μg ml^{-1} and NF: $40 \cdot 9 \pm 7 \cdot 3$ μg ml^{-1}; $p = 0 \cdot 014$) and the mean cumulative amount absorbed up to time 6 h (F: $76 \cdot 3 \pm 11 \cdot 8$% and NF: $90 \pm 10 \cdot 4$%; $p = 0 \cdot 0099$) were significantly increased. Nevertheless, the extent of absorption (F: $46 \cdot 7 \pm 9 \cdot 9$ mg l^{-1}; NF: $48 \cdot 7 \pm 7$ mg l^{-1}) was not significantly affected. There was no change in the area under the curve (1129 μg.h ml^{-1}), in the mean residence time (28 h), or in the elimination half-life (16 h). On the basis of this study, the question as to whether DEPAKINE® CHRONO should be administered to subjects in the fasting or non-fasting state would not appear to be a major consideration when deciding on the regimen.

KEY WORDS Valproic acid Sustained release formulation Food Kinetics

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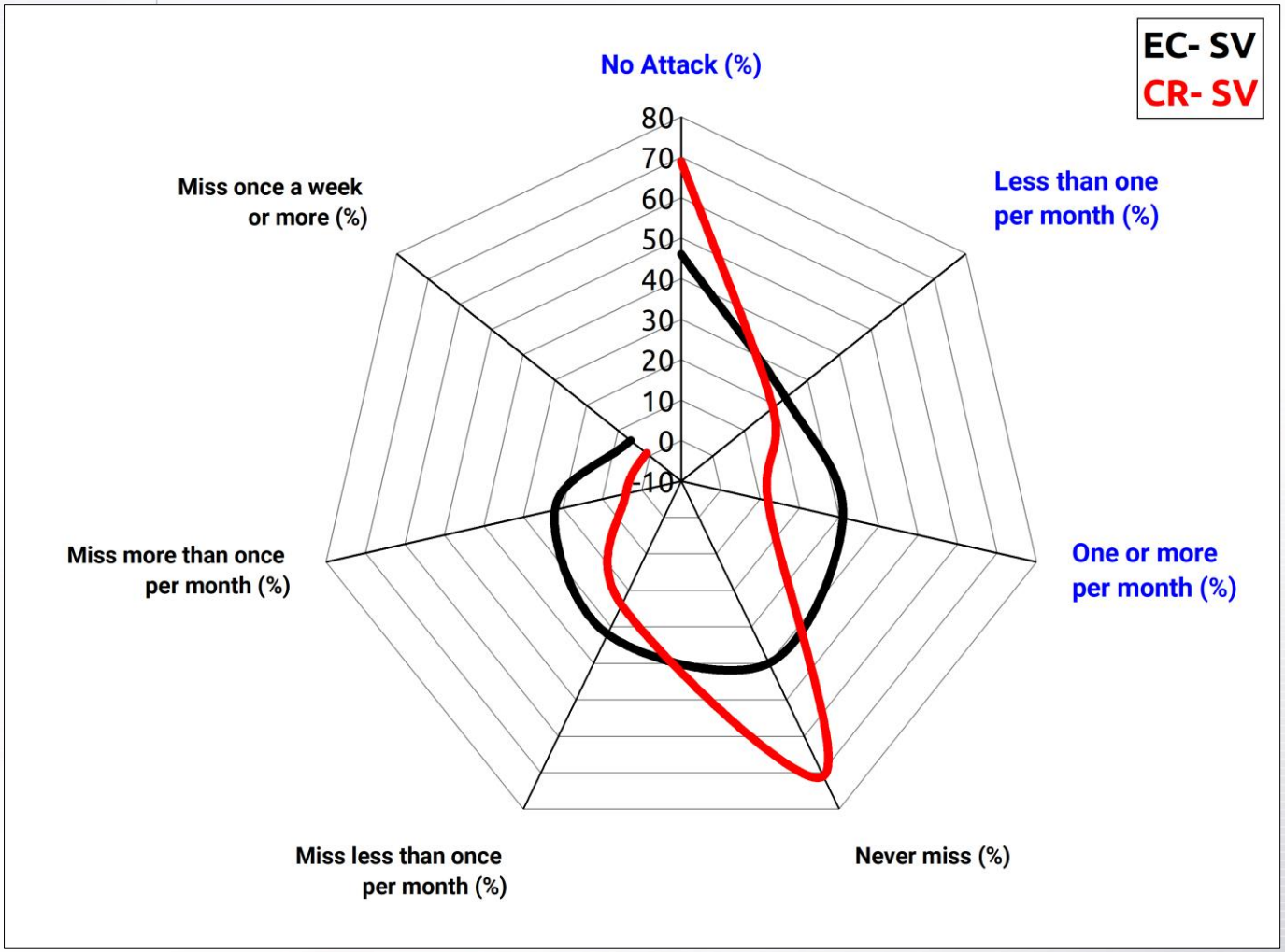
Doughty J, Baker GA, Jacoby A, Lavaud V. Compliance and satisfaction with switching from an immediate-release to sustained-release formulation of valproate in people with epilepsy. Epilepsy Behav. 2003 Dec;4(6):710-6. doi: 10.1016/j.yebeh.2003.08.013. PMID: 14698705.



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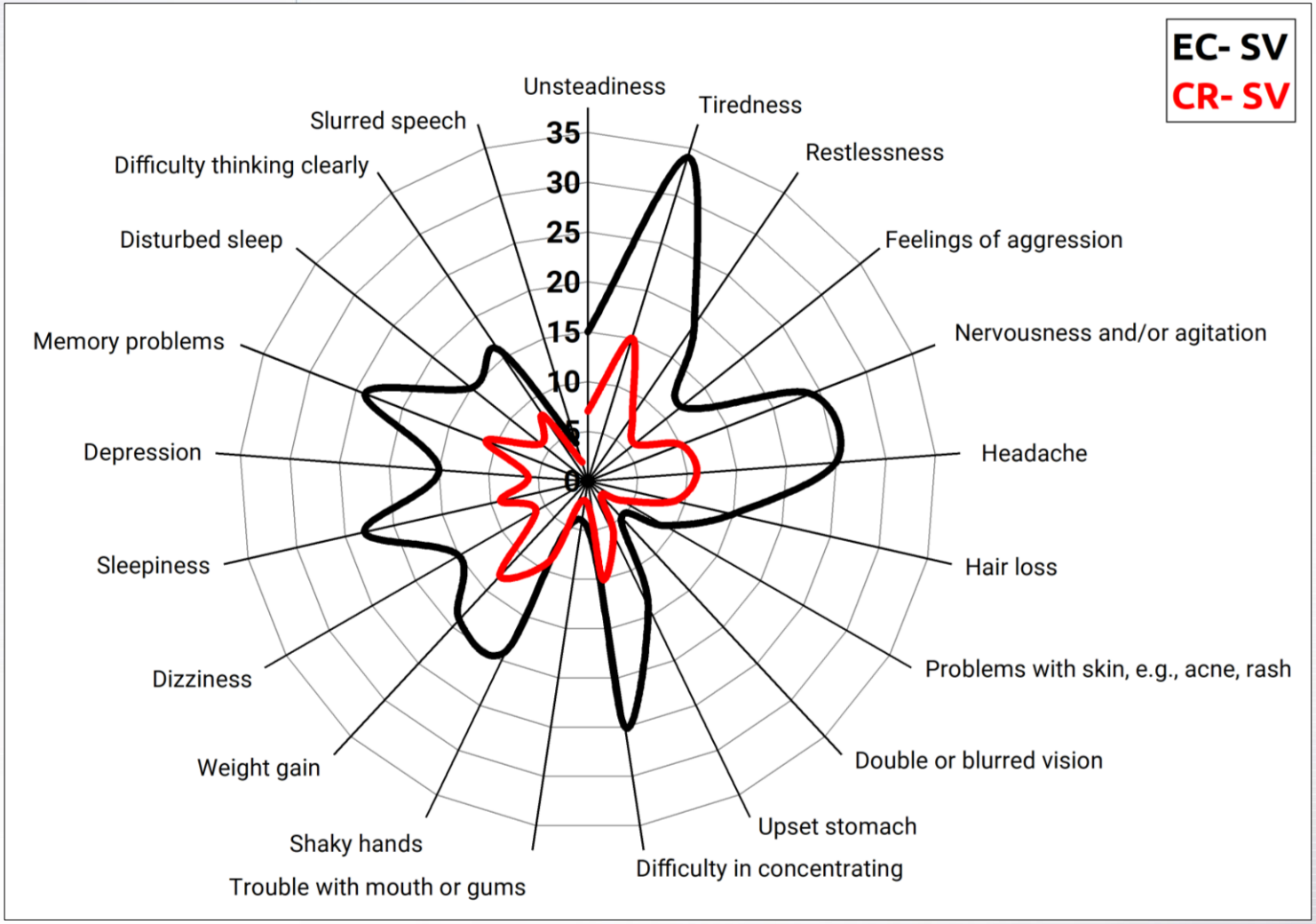

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Thank you for your attention