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Improving Clinical Trials in Epilepsy: Addressing the Hurdles and Filling the Gaps

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Why Are High-Quality Trials Essential to Improve Outcomes for People with Epilepsy?

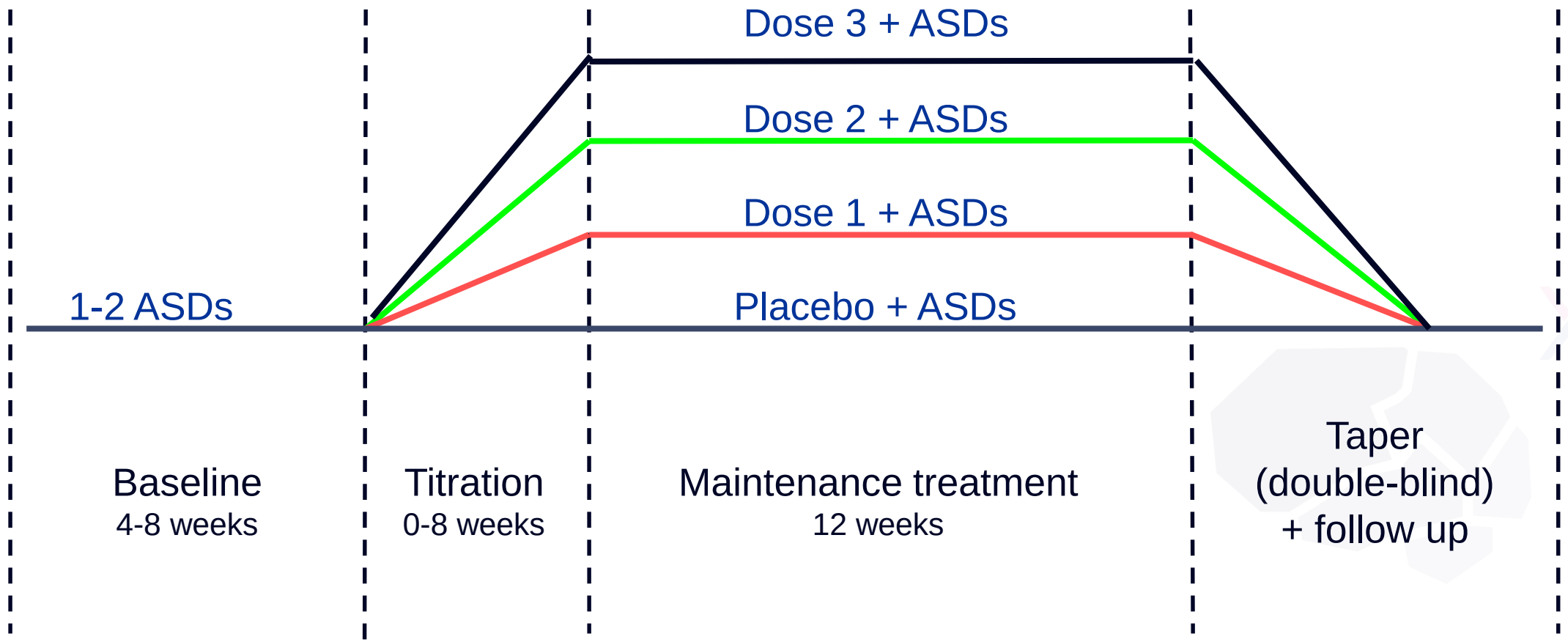
- Clinical trials are needed to demonstrate the efficacy and safety of innovative treatments, and to obtain regulatory approval

- Well designed trials are required to provide an evidence base for rational prescribing

Clinical Trials in Epilepsy: Do We have a Problem?

- Traditional trial designs used to demonstrate efficacy and safety of anti-seizure medications are failing
- We lack validated trial designs to test anti-epileptogenic and disease-modifying treatments
- There are major shortcomings in trials conducted to date with available antiseizure drugs (ASDs)

The Traditional Trial Design Used to Test New Antiseizure Drugs (ASDs)



Why is the Traditional Trial Design Failing?

- Ethical concerns – patients randomized to placebo in these trials have been found to have a 6-fold increase in SUDEP risk
- Feasibility of enrolment into these trials is increasingly challenging
- Steady increase in placebo-response over time → increasing difficulty to differentiate active treatments from placebo
- Concerns with assay sensitivity - particularly for non-inferiority monotherapy trials complying with EMA guidelines
- Transatlantic regulatory divide discourages industrial investment

Perucca, CNS Drugs 2008;22: 917-38; Ryvlin et al, Ryvlin et al, Lancet Neurol 2011;10:961-8; Rheims et al, Epilepsia 2011;52:219-33; Perucca, Epilepsia Open 2018 (in press)

Some ASDs Not Differentiated from Placebo in Recent Well Powered Add-on Trials in Focal Epilepsy

- Brivaracetam
- Pregabalin
- Lamotrigine
- Levetiracetam

Xiao et al, Eur Neurol. 2009;61:233-9; Baulac et al, Epilepsy Res 2010;91:10-9; Haltford et al, Epilepsia 2011;52:816-25; Van Paesschen et al, Epilepsia 2013;54:89-97

Did Clinical Trials with Available ASDs Provide the Information Needed for Rational Prescribing?

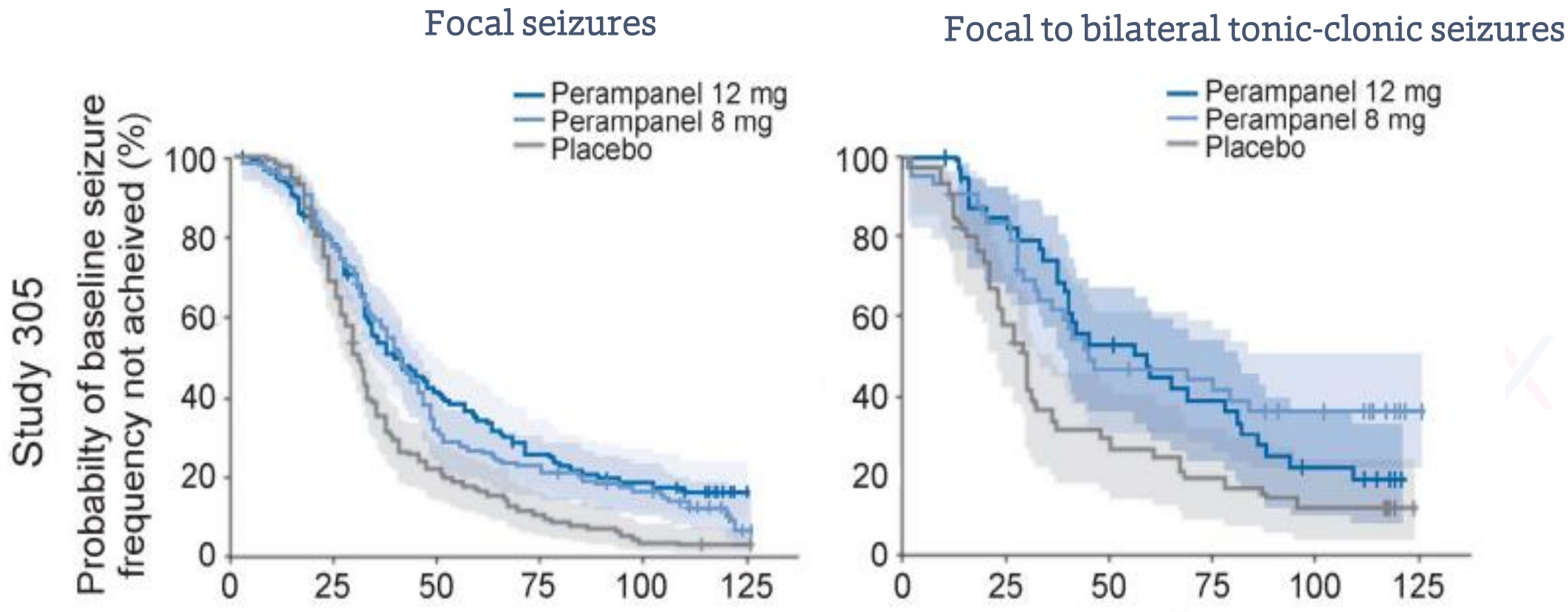
- *'…many RCTs and especially those involving new antiepileptic drugs, are methodologically flawed and cannot answer important clinical questions'*
- *'…there continues to be an alarming lack of well designed, properly conducted epilepsy RCTs for patients with generalized seizures/epilepsies and in children in general.'*

Glauser T. et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epilepsy seizures and syndromes. Epilepsia 2013:54:551-63

Can We do Better? Some Potential Solutions (1)

- Improve trial designs, e.g. by using time-to-event designs that minimize placebo exposure
- Improve patient selection, through diagnostic validation and prioritization of highly qualified enrolling centers
- Step-up efforts to identify individuals most likely to respond (e.g., biomarker-, or etiology-guided drug development)
- Promote dialogue among stakeholders, and consider the benefits of harmonizing regulatory requirements across the world

Time-to-Event Analysis Demonstrating Rapid Differentiation between Active Treatments and Placebo



French JA et al. Neurology 2015; 84:2014-20

Can We do Better? Some Potential Solutions (2)

- Promote the conduction of unbiased comparative effectiveness trials, including pragmatic randomized trials – public funding essential!
- Stimulate creation of collaborative networks – and utilization of those already existing (most notably, EpiCARE)
- Exploit opportunities offered by electronic health records, and address issues that hamper communication among existing systems
- Streamline bureaucratic hurdles to the implementation of high-quality academic trials

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