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Try, Try Again: Success Rates After Continued Treatment Attempts in Refractory Status Epilepticus

Staged Treatment Response in Status Epilepticus: Lessons From the SENSE Registry

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Objectives: Although in epilepsy patients the likelihood of becoming seizure-free decreases substantially with each unsuccessful treatment, to our knowledge this has been poorly investigated in status epilepticus (SE). We aimed to evaluate the proportion of SE cessation and functional outcome after successive treatment steps. Methods: We conducted a post-hoc analysis of a prospective, observational, multicenter cohort (SENSE), in which 1049 incident adult SE episodes were prospectively recorded at 9 European centers. We analyzed 996 SE episodes without coma-induction before the third treatment step. Rates of SE cessation, mortality (in ongoing SE or after SE control), and favorable functional outcome (assessed with modified Rankin Scale) were evaluated after each step. Results: SE was successfully treated in 838 (84.1%) patients, 147 (14.8%) had a fatal outcome (36% of them died while still in SE), and 11 patients were transferred to palliative care while still in SE. Patients were treated with a median of three treatment steps (range 1-13) with 540 (54.2%) receiving more than two steps (refractory SE, RSE) and 95 (9.5%) more than five. SE was controlled after the first two steps in 45%, with additional 21% treated after the third, and 14% after the fourth step. Likelihood of SE cessation ($p < 0.001$), survival ($p = 0.003$), and reaching good functional outcome ($p < 0.001$) significantly decreased between the first two treatment lines and the third, especially in patients not experiencing convulsive generalized SE, but remained relatively stable afterwards. Significance: The significant worsening of SE prognosis after the second step clinically supports the concept of RSE. However, and differing from findings in human epilepsy, RSE remains treatable in around one third of patients even after several failed treatment steps. Clinical judgement remains essential to determine the aggressiveness and duration of SE treatment and avoid premature treatment cessation in SE patients.

Commentary

"Look before you leap." Clinicians want to understand the chance of success before embarking upon new treatments. We are most familiar with Glasgow data[1]—What is the chance of becoming seizure-free after trying an increasing number of ASMs? Among 1795 attempting a first anti-seizure medication (ASM), 820 (46%) attained a period of seizure-freedom, whereas among those trying a second ASM, 28% achieved seizure-freedom (only 12% of the total cohort), and among those trying a third ASM, 24% achieved seizure-freedom (4% of the total) with diminishing returns from there.

While newly diagnosed incident epilepsy is an important context, there are many others in which the probability of treatment response with successive attempts is not well clarified. This particularly applies to status epilepticus (SE), in which the consequences of under- or over-treatment are potentially serious. Seizures continue despite benzodiazepines in up to a third of patients, convulsive SE still does not abate in almost half of benzodiazepine-refractory patients,[2] and many treatments are available for refractory SE oftentimes with limited comparative effectiveness data.[3,4] Current guidelines recommend a staged approach, with benzodiazepines followed by intravenous (IV) ASMs as first- and second-line treatments, followed by sedatives if refractory.[5] However, real-world data are lacking documenting the probability of becoming seizure-free and functional outcomes after successive treatment steps to inform how far to go.

Beuchat et al[6] responded to this call. They analyzed 996 patients in the Sustained Effort Network for treatment of Status Epilepticus (SENSE) cohort, a European multicenter prospective observational registry of adults presenting in SE 2011-2015 with clinical seizures $\geq$5 minutes or repetitive seizures without return to baseline.

They reported outcomes according to the number of "steps" (a.k.a. unique treatments) received by each patient. The percent achieving SE cessation was 450/996 (46%) after steps 1 to 2. There was a statistically significant decrease in seizure

cessation rates after the first 2 steps, but still 206/540 (38%) achieved seizure cessation after step 3, 131/318 (32%) after step 4, 67/176 (38%) after step 5, with small sample sizes in subsequent steps but percentages typically remaining around at least 30%. Mortality unsurprisingly also increased with subsequent steps (8% after steps 1-2, 16% after step 3, 20% after step 4), and good functional outcome decreased (modified Rankin Scale 1-2 or unchanged from prehospitalization; 75% after steps 1-2, 63% after step 3, 54% after step 4). Eight patients underwent more than 10 steps (max 13) with very small sample sizes, but still a nonnegligible number persisted with good outcomes even with extensive drug trials.

The authors use these data to make the case for not giving up too soon. This makes sense, as the stakes are high, and each patient deserves care as intensively as appears consistent with their wishes. There was a statistically significant drop-off in response after the first 2 steps, but this should likely not be enough to dissuade the clinician from moving onto further attempts while correcting any identifiable underlies etiologies, and one wouldn't want to deny a patient the possibility of another chance at seizure cessation given such a large array of options exist with distinct mechanisms of action.[3,4] For example, animal data suggests that GABAergic internalization and glutamatergic receptor upregulation may render certain treatments less effective with time.

Note an important caveat, though. These numbers describe prognosis, but not the effect of treatment, without untreated comparisons. Therefore, the contribution of treatment initiation or maintenance to seizure cessation, functional outcome, or mortality remains unknown from these data. Though, admittedly, such an observational comparison would be extremely challenging. Patients would systematically differ between those that ended up being treated versus untreated. The data do contain many relevant baseline variables (e.g., etiology categories and age which are major prognostic factors, plus convulsive or not and baseline Rankin Scale), yet other key factors remained unmeasured such as withdrawal of care tendencies (which in my opinion is a considerably undermeasured variable when studying critical care EEG outcomes), specific electrographic patterns, or even what drugs or interventions were used at what step or at what dosages or targeted depth of sedation when applicable or what attempted duration. In other words, those patients who made it to step 10+ still seizing yet still tried new drugs are assuredly markedly different in severity and goals of care than others who did not, making it difficult to directly compare earlier versus later steps. Interpretability is also limited by not knowing exactly what occurred at each step. Ketamine, resection, ketogenic diet, and barbiturates are all dramatically different "steps," and even the same "step" may look quite different if targeting different depths of sedation or attempted duration and whether previous steps have been continued (not specified in these data). Still, these data provide important high-level insights into the chances of treatment success at each step.

Also note—this population was somewhat exceptional. The median age was 70, the median duration of SE was 8 hours, and many super-refractory patients were not intubated (presumably due to this older population mostly in nonconvulsive SE, which implies avoiding IV anesthetics when possible). Thus, perhaps this was a particularly at-risk population that was less aggressively treated.

What high-quality data guides us regarding how far to go? Not much. The 2016 guidelines' relevant section[5] points to the 1998 Veterans Affairs study,[5] which randomized 518 adults with generalized convulsive SE to 4 initial treatments (lorazepam, phenobarbital, diazepam/phenytoin, or phenytoin; no placebo). They also assigned everyone backup second- or third-line drugs, different from their initial drug (e.g., if failing lorazepam, phenytoin then phenobarbital). In "overt" SE, the overall success rate of the first drug was 56%. If the first drug failed, the second drug succeeded in an additional 7% (presumably, 7%/[100%-56%] = 16% second-line success among those who failed first-line) and the third drug succeeded in another 2% (presumably, 2%/(100%-56%-7%) = 5% third-line success among those who failed second-line). While the Veterans Affairs study thus laid out each "step" more precisely than the SENSE cohort, still, the Veterans Affairs study informs only prognosis after next-line treatments rather than truly the effect of treatment, in absence of a placebo comparator. Of course, a placebo comparator would pose clear ethical problems, but nonetheless its absence does limit conclusions.

So, what chance is enough? How far to go? There will inevitably never be any single answer. Rather, this remains an individualized decision based upon goals and circumstances. What we can say from these data is that, unsurprisingly, seizure suppression with favorable discharge functional status decreases but remains possible even for patients whose seizures continue despite initial treatments. Much work remains to be done studying the effects of different particular treatments, combinations, and intensities.

Samuel W. Terman, MD, MS
Department of Neurology,
University of Michigan

ORCID iD

Samuel W. Terman http://orcid.org/0000-0001-6179-9467

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