When treatment of status epileptics (SE) is delayed, seizures become self-sustaining and refractory to benzodiazepine therapy. Chemical warfare nerve agents (CWNAs), such as soman (GD), increase acetylcholine through inhibition of acetylcholinesterase and can lead to SE if seizures are not treated quickly and controlled. Prolonged seizures may lead to extensive neuropathology, spontaneous recurrent seizures and long-term performance deficits. During SE, synaptic GABAA receptors (GABAAR) become internalized, while spare NMDA receptors (NMDAR) assemble, move to the membrane and become synaptically active. As the number of synaptic GABAARs is reduced benzodiazepine therapy cannot fully restore inhibition. To treat pharmacoresistant seizures, drug combinations aimed to reverse the effects of SE-induced receptor trafficking were used. Rats were implanted with telemetry transmitters for continuous monitoring of electroencephalogram (EEG) activity. One week after surgical recovery, rats exposed to 1.2 LD50 GD were treated with atropine sulfate and HI-6 after exposure and then 40 min after seizure onset with drug combination aimed to terminate SE. The delayed treatments included midazolam (to stimulate the remaining GABAARs), ketamine (to counter the effect of the NMDAR increase) and valproate (to enhance inhibition at a non-benzodiazepine site), all at low doses. This drug combination effectively stopped SE, reduced toxic signs, prevented epileptogenesis, reduced performance deficits and prevented loss of neurons in the piriform cortex and other brain regions. Similarly, combination of phenobarbital, ketamine and midazolam reduced total time in seizure, reduced the number of animals that developed SRS, prevented hyperactivity that develops in the weeks after GD exposure and reduced loss of neurons in the piriform cortex and thalamus compared to GD/MDZ monotherapy. Combination triple therapy was more effective than mono- or dual therapies in GD-exposed rats and may be a highly effective approach against pharmacoresistant seizures, such as those caused by GD exposure. In addition, combination therapy may allow for administration of lower doses, resulting in fewer side effects than are often seen with large doses of individual drug therapies.