Comment on: “Perispinal Etanercept for Post-Stroke Neurological and Cognitive Dysfunction: Scientific Rationale and Current Evidence”

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I read with interest the paper titled “Perispinal Etanercept for Post-Stroke Neurological and Cognitive Dysfunction: Scientific Rationale and Current Evidence” [1]. However, it misuses the Bradford Hill Criteria. The Bradford Hill Criteria are for disease causation, not evaluation of treatments for disease. Misuse of the Bradford Hill Criteria is not rare; multiple authors warn against it, including Bradford Hill [2]. Phillips and Goodman reiterate his extremely important point that “systematic error is often greater than random error” [3].

Systematic error cannot be eliminated after data have been collected. Systematic error can only be eliminated by using proper data-collection techniques. To evaluate disease treatments, the proper technique is the double-blind placebo-controlled trial. Double-blind placebo-controlled trials have not been reported for perispinal etanercept.

By applying the Bradford Hill Criteria, are the authors naively suggesting that post-stroke neurological and cognitive dysfunction is caused by the lack of an endogenous tumor necrosis factor (TNF) blocker? The observation that a TNF blocker acutely resolves neurological and cognitive dysfunction is no more proof that the underlying pathology is caused by an absence of an endogenous TNF blocker, than the observation that opiates acutely resolve chronic pain proves that chronic pain is caused by a lack of endogenous opiates.

When opiates are used to treat pain, habituation can occur, requiring escalating doses. Does habituation occur when TNF blockers are used to treat chronic post-stroke neurological and cognitive dysfunction? Does continued

resolution require escalating doses? If escalating doses are not provided, does inflammation get worse, as pain can get worse when habituation to opiates occurs? Do escalating doses cause other problems? Do they accelerate progression? Unfortunately, because there are no reported blinded clinical trials measuring such effects, no one has the data to know one way or the other.

It is not an inability to embrace new ideas that makes the medical community wary of new treatments untested in clinical trials. It is concern for patients who may be harmed by untested treatments; by clinicians who mean well but have fooled themselves into thinking a treatment is safe and effective without proper clinical trials. Heroin was once sold as a cure for morphine addiction. Later experience showed the cure was worse than the disease. Clinicians would love new treatments that achieve better results for their patients. However, clinical judgment requires data, not testimonials.

There is now a report that acetaminophen is equivalent to placebo for lower back pain in a blinded clinical trial [4]. Is a placebo a leading cause of acute liver failure? [5]. This is reminiscent of the use of mercury in teething powder (a useless treatment for an imagined need), which killed over a thousand children with pink disease [6].

Placebo effects can be surprisingly robust in neurological disorders. In Parkinson’s disease, sham treatments can produce clinically significant improvements in symptoms, which improvements are tracked by clinically significant changes in brain imaging [7]. We know these clinically significant effects are mediated through the placebo effect, because they were observed with sham treatments in a blinded clinical trial.

It is extremely frustrating to lack sufficient data. Good data for differentiating two treatments unavoidably requires some patients receive the inferior treatment so the

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other treatment can be shown to be superior. Good clinical trial design requires periodic assessment so that patients receiving the inferior treatment do so for the minimum time necessary to determine it is inferior so they can be switched to the superior treatment at the earliest possible moment. That some patients must receive inferior treatments to determine relative effectiveness of treatments is immutable. Ideally, patients receive inferior treatments early in the life cycle of a treatment, so the total number of patients receiving inferior treatments (or inadequate if the new treatment is superior) is minimized.

Are the numerous, clinically significant case reports of perispinal etanercept due to placebo effects? [8]. We cannot know because the trials were not blinded and there were no placebo controls. It would be wonderful if such treatments could be demonstrated to be safe and effective in blinded clinical trials and then become standard-of-care treatments, because then insurance reimbursement would open up treatment opportunities to many more patients.

COI statement Potential conflict: DRW is employed by and owns stock in AOBiome LLC, a company commercializing ammonia oxidizing bacteria for the human microbiome. The opinions expressed here are the personal opinions of DRW and do not reflect the opinions or policies of AOBiome LLC. No sources of funding were used to prepare this letter.

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