

Nocebo phenomena refer to unfavorable outcomes after application of an inert treatment and mostly reflect the patients' negative expectation that treatment most likely will harm instead of help, among other reasons. Like placebo, the nocebo phenomenon is a cognitive and idiosyncratic brain function with specific biological bases, controlled by distinctive neurotransmitters within mapped brain areas located within the network of the limbic system. In clinical trials nocebo responses can be easily evaluated by addressing the adverse events (AE) reported by the patients treated with placebo. Several nocebo outcomes have been proposed including the proportion of placebo treated patients reporting any AE, any severe AE and dropouts due to AE. In an extensive project, these parameters have been calculated after meta-analyses of pooled data from trials targeting several brain disorders. Pooled AE rates in the placebo groups vary from 25% in the symptomatic treatment for multiple sclerosis RCTs to almost 80% in motor neuron disease RCTs. Pooled dropout rates because of AEs in the placebo groups (i.e., nocebo dropout rates) vary from 2% in multiple sclerosis RCTs to almost 10% in RCTs for Parkinson's Disease. Across all brain disorders, the nature of AEs reported in the placebo-treated subjects mirrors those reported by active drug-treated subjects, suggesting that awareness of drug side-effect profiles might have influenced patient expectations and, thus, nocebo responses. Not only in RCTs, but in clinical practice nocebo phenomena limit treatment efficacy and adherence. Physicians should be aware of nocebo and its consequences and educate patient to border it.