DOUBLE BLIND PLACEBO CONTROLLED TRIALS FOR SURGERY IN PD– YES

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Double blind parallel-group, placebo-controlled randomized studies are the gold standard for performing clinical trials. This approach controls for placebo effect, and physician bias. Open label uncontrolled, non-randomized trials are prone to overestimate benefit and to underestimate adverse effects. Open label studies are particularly compromised by the possibility (real or subconscious) that physicians might obtain benefit related to monetary reward, fame, and academic advancement. Double blind trials are routinely required for regulatory approval of a new pharmaceutical agent. And yet, there has been resistance to employing double bind trials in surgical trials even though they frequently expose patients to greater risk and are more expensive than medical therapies. Arguments that have been put forward justifying the use of open label trials in surgery include the idea that one surgeon is more talented than another and results from two surgeons cannot be properly compared, it is unethical to expose patients to any surgical procedure without the possibility of obtaining some benefit, and double blind studies aren't required because it is clear that the procedure is logical and works. This line of thinking has proven to be fallacious, particularly for surgical trials in PD, where inany positive open label studies have not been replicated in prospective, randomized placebo-controlled, double-blind trials. Some examples include fetal nigral transplantation (2), spheramine transplantation, fetal porcine nigral cell transplantation, intraventricular delivery of GDNF, cather delivery of GDNF into the putamen, and gene delivery of neruturin into the putamen +/- the substantia nigra (2). Adverse effects are also subject to being overlooked as was the case with graft induced dyskinesias which were not identified in open label studies but were recognized to affect as many as 50% of subjects in double blind sham-controlled trials. The failure of open label surgical trials to be confirmed in double blind trials which control for placebo effect and bias raises the issue of whether open label studies have any value at all in evaluating experimental therapies. For PD. Indeed, false positive estimates of safety and efficacy in underpowered open label trials have caused many patients to be exposed to unnecessary risk, and wasted time and resources. These might be avoided if early studies had either been proper double blind controlled trials, or when that is not feasible, at least to utilize studies that include randomization, a control group,, blinded observers, and are adequately powered.. It is obvious that it is no longer reasonable to continue to perform open label studies of experimental surgical therapies for PD patients.