

Clinical Cases

## **Heads or Tails: Randomized Placebo-Controlled Trials**

**Physicians are obligated to inform patients involved in a clinical trial that there is a chance of receiving a placebo, which can result in a deterioration of a medical condition.**

Commentary by Charles Weijer, MD, PhD, and Karen Kreiner, MS

Upon inspecting his schedule for the day, psychiatrist David Kimball was surprised to learn that his first patient of the morning was Geoffrey Allen. Geoff had been in for an appointment less than 2 weeks ago to discuss his response to a monoamine oxidase inhibitor (MAOI) as treatment for chronic depression. At the time, it seemed as though the medication was working, a relief for both Geoff and Dr. Kimball after several years of searching for the right way to manage Geoff's illness.

Geoff had been referred to Dr. Kimball's practice by Student Health during his freshman year. After discussing Geoff's symptoms of insomnia, lethargy, and weight loss as well as learning of a family history of depressive disorders, Dr. Kimball prescribed the first of what would be a long list of medications. Through the course of his *magna cum laude* degree in political science and now into his doctoral dissertation, Geoff had tried several tricyclic antidepressants, selective serotonin reuptake inhibitors, and second generation antidepressants. While he would have periods of stability ranging from a few weeks to a few months as in the case of fluoxetine, eventually either the medication stopped working or the side effects became too bothersome.

At his last appointment, Dr. Kimball had been pleased with Geoff's clinical response to the MAOI, even though a brief physical exam revealed the presence of mild orthostatic hypotension. When queried, Geoff himself said he felt better than he had in months with the exception of the fact that he and his girlfriend were less than thrilled about the side effects. In response, Dr. Kimball adjusted the prescription and reminded Geoff not to hesitate to schedule another appointment if things changed.

"Well, you're always reminding me to come see you if something comes up," Geoff said, when Dr. Kimball asked about the purpose of Geoff's visit, "and there's something I need to talk about. I'm starting to feel tired again, like I have no energy, and my motivation to do things is slipping." Geoff went on to describe an elevation in his depressive symptoms as well as a growing dissatisfaction with the MAOI side effects. Then, he mentioned a recent conversation with one of his cousins—also with a history of depression—and her enthusiastic description of her participation in a clinical trial for Licol, a new lithium-based antidepressant. Dr. Kimball was familiar with Licol and thus far it showed great promise for the treatment of atypical depression, especially in younger adults. However, ongoing clinical trials for the medication utilized double-blind placebo controls. In addition, data was not yet available concerning the follow-up treatment of patients who withdrew from the trials. "So I'm thinking I might like to try something like that," Geoff continued. "Something new maybe, since I've tried so many older drugs. And I might be able to help make a difference. I mean, what, have I got to lose? I'd really like to participate in the trial—how do I sign up?"

### **Commentary 1**

by Charles Weijer, MD

The question facing Dr. David Kimball is this: Ought he to recommend that his patient, Geoffrey Allan, enter a randomized trial in which he has a 50 percent chance of getting a new and potentially beneficial drug, Licol, and a 50 percent chance of getting placebo? Is doing so consistent with his duties to the patient? The general permissibility of physicians enrolling patients in clinical trials received a great deal of scrutiny in the literature in the 1980s and 1990s. Some argued that the physician has a duty to provide the patient with the best possible care. Accordingly, offering enrolment in a clinical trial in which treatment would be determined by the flip of a coin seems problematic. The concern is well expressed as follows:

Consider first the initial formulation of a trial...A new agent that promises more effectiveness is the subject of study. The control group must be given either an unsatisfactory treatment or a placebo. Even though the therapeutic value of the new agent is unproved, if physicians think it has promise, are they acting in the best interests of their patients in allowing them to be randomly assigned to the control group? [1].

But do physicians owe patients the best possible care? And, is offering enrolment in a randomized controlled trial inconsistent with important legal and moral duties physicians have towards their patients?

Philosopher Benjamin Freedman offers an authoritative answer to both questions with his concept of clinical equipoise [2]. Clinical equipoise starts from the recognition that physicians owe patients competent care, that is, treatment endorsed by at least a respectable minority of expert clinicians. For any one condition, there may be a range of treatments that may be competently prescribed. Thus, a patient seeking treatment for a condition might see physician X and receive a recommendation for treatment A, or she might have seen his colleague across the hall, physician Y, and received a recommendation for treatment B. Under these circumstances, it would be unproblematic for either physician X or Y to offer the patient enrolment in a clinical trial that would randomize her to treatment A or B. Treatments A and B are consistent with competent medical care, and whatever the idiosyncratic choices of physicians X and Y, they must respect the preferences of equally competent colleagues.

Formally, clinical equipoise states that at the start of a randomized clinical trial there must exist a state of honest, professional disagreement as to the preferred treatment in the community of expert clinicians. To put it bluntly, doctors must disagree as to the preferred treatment. In the case of treatments A and B above, the disagreement is actual. Clinical equipoise also covers cases of potential disagreement. In these cases, a particular treatment, perhaps Licol, the new and experimental treatment, is supported by sufficient evidence, perhaps from Phase I and Phase II clinical trials, such that, were it widely known, physicians would disagree about the preferred treatment. Thus, clinical equipoise allows trials to proceed in instances of actual and potential disagreement as to the preferred medical treatment.

The use of the placebo control poses special challenges for clinical trials [3]. Generally speaking, when there exists a standard treatment for a medical condition, a novel treatment ought to be compared to *it* rather than to a placebo. The use of a placebo control is legitimate in a number of circumstances: (1) where there is no known treatment for a medical condition; (2) where the subject population of the trial has failed to respond to first and second line standard treatments for the condition and there exists no effective third line treatment; (3) where a new treatment is being tested as an add-on to a regimen of standard treatments, and all subjects will receive the regimen of standard treatments; (4) when research is conducted in an undeveloped country in which no treatment is broadly available due to cost or short supply; and (5) for minor conditions for which receiving no treatment is consistent with competent medical care (eg, seasonal allergies).

As the story is told to us, Geoffrey Allan has suffered chronic depression for years and has tried most available drugs at one point or another. After initial relief with the latest drug, an MAO-I, he feels the effect is declining and the side effects are increasing. It seems therefore that he may well fit into the second exemption for the use of placebo controls. He has tried first and second line drugs and they have failed him, and now there exists no standard third line drug for him. At this stage, entering a placebo controlled clinical trial testing the effectiveness of Licol seems appropriate.

Dr. Kimball will, of course, want to make careful inquiries regarding the trial before suggesting it for Geoffrey Allan. What is the evidence to date supporting the safety and efficacy of Licol? Has the study been approached by a duly constituted (and not for profit) Institutional Research Board (IRB)? What safety features are built into the trial should

Mr. Allan begin to deteriorate on study? Will he be withdrawn promptly and treated? Finally, what if Mr. Allan does very well on Licol? Will he be assured of access to the drug until the drug becomes licensed? This last fact is of great importance to patients who have searched for years for a treatment that will alleviate their symptoms.

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## Commentary 2

by Karen Kreiner, MD

This case presents a common clinical dilemma physicians face when treating patients who have depression that is difficult to manage or refractory to available treatments. This high-functioning patient has tried numerous antidepressants in a clinically sound way, yet, while he has a temporary response to treatment, he has been unable to achieve either effective long-term maintenance or a tolerable degree of treatment side effects. In clinical psychiatry, both of these problems are common. In an effort to control his symptoms and address his challenging medical history, the patient now wants to try an investigational drug which has shown some promise in a controlled clinical setting.

The most desirable way for the psychiatrist to handle this situation is to enter into a dialogue with the patient to carefully go over each of the potential treatment options and ensure that the patient understands the risks and benefits of each one. First, if Geoff is willing to consider it, the psychiatrist could entertain the possibility of increasing the current dose of monoamine oxidase inhibitor (MAOI). MAOIs work by inhibiting the monoamine oxidase enzymes that metabolize serotonin, a neurotransmitter linked to mood disorders. By slowing the breakdown of serotonin, MAOIs can be effective pharmaceutical agents for the treatment of depression. Increasing the MAOI dose could lead to more severe side effects—but MAIOs also have a strong history of clinical utility—and for Geoff to make a truly informed decision, greater dialogue would need to take place between him and Dr. Kimball.

If Geoff is unwilling to consider increasing his current MAOI dose, another MAOI should be offered since he responded so well initially to the first one. Several different MAOIs have been approved for use in the treatment of depression, and it is important to consider all of the possibilities. Furthermore, the psychiatrist should also make sure that Geoff has tried all appropriate antidepressants as well as considered the use of mood stabilizers like lithium or lamotrigine. Lamotrigine was originally used as an anticonvulsant medication but was recently approved by the FDA for use in the treatment of depression; it is particularly effective in patients like Geoff who have failed to respond to more traditional antidepressants or mood stabilizers. Finally, additional atypical antipsychotics like olanzapine may be useful.

If Geoff still wants to enroll in the research trial after adequately considering all of his nonexperimental options, he

should be informed that he has a 50 percent chance of getting the placebo pill, in which case his condition could truly deteriorate. However, if he does get the investigational drug and responds, he will most likely be unable to continue the drug when the study ends. In the event of a successful clinical outcome, some drug companies will continue to supply the drug on a compassionate basis, but this is highly variable and cannot be guaranteed. More likely, Geoff will experience an ensuing drop in function due to the lack of medication, and that can be traumatic for many patients. According to the *AMA Code of Medical Ethics*, the physician should assist in trying to secure an ongoing supply of the drug until it is approved and reaches the open market, if there is a clear medical benefit [1]. Geoff should be aware of the hardship he may have to endure: to feel well during the trial therapy and then become depressed again because he loses access to an effective yet still-investigational medication.

Patients who have the capability to make decisions about their care always have the right to choose; we, as doctors, support the autonomy of the patient. If Geoff does decide to enter the study, it is the psychiatrist's responsibility to ensure that he is fully informed prior to making that decision. Unfortunately, for many treatment-resistant patients, research studies are their only hope of getting some relief from their disease. In terms of human suffering, depression exacts a high toll.

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