The Validity of "Identical Matching Placebos"

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This study was a laboratory simulation of the double-blind clinical study in which inactive control drugs are described as "identical matching placebos." For five of six drug categories, subjects simulating experimenters or patients significantly ($P \leq .001$) differentiated active drug from placebo based on physical characteristics of the medications. Thus, many of the identical matching placebos were not in fact identical but were different from the active drug in physical properties such as texture, color, and thickness.

The results suggest that the assumption that "identical matching placebos" as used in a study should be tested by preliminary comparison of the placebo with the active drug. Major recommendations are that active drug and control be administered as capsules, that research assistants be minimally aware of the experimental design of the study, that the Federal Drug Administration or National Institutes of Health formulate standard capsules for use in controlled clinical evaluation studies, and that the placebo contain active ingredients to mimic the side effects of the active drug.

In double-blind clinical drug studies, neither patients, investigators, nor clinicians should know which patients are assigned to treatment with the active drug to be evaluated or the placebo control.[1-3] An essential principle of the double-blind procedure is that the active and inactive medication be matched to each other as closely as possible in such properties as vehicle, size, color, etching, texture, taste, dissolvability, and possibly even the pattern of side effects.[1-12] These considerations underlie the customary statement in double-blind studies that "an identical matching placebo" was used as a control. In our experience doing six double-blind studies, research assistants noticed that the active drugs could be distinguished from the placebos by small differences in physical properties. The purpose of this study is to demonstrate that drugs and placebos differed significantly in their physical appearances so that they could be differentiated by participants in a double-blind study.

Methods

The subjects in this study were 52 first-year medical students, spouses, laboratory assistants, nurses, and secretaries in the Cornell University Medical College community. Thirty-two of these subjects were designated the patient-simulated group, and were given the following instructions: This is a study of the drug categories that will be used in a controlled evaluation of psychochemotherapeutic drugs. There are six tablets in the plastic container before you. Examine the tablets and decide whether they are all of one type or of two types. If you decide that the tablets are all of one type, place them in one of the empty plastic medicine cups. If you decide that the tablets are of two types, place tablets of each type in separate medicine cups. If you have decided that the tablets were of two types, describe the reason(s) for your decision.

The first four drug categories contained three active and three placebos in each of the categories: (1) minor tranquilizer, (2) minor tranquilizer, (3) major tranquilizer, and (4) antidepressant. Category 5 contained six pink antidepressant capsules consisting of two antidepressants of one type, two antidepressants of another type, and two placebos. The instructions were modified slightly for category 5 to indicate that there might be one, two, or three types of capsules. The six bottles of liquid medication in category 6 contained three bottles of a red liquid cherry-flavored antidepressant and three bottles of a matching liquid placebo. The instructions were similar except that subjects were instructed to pour the liquid medication into six plastic cups and to discriminate between samples as instructed for the tablets.

Twenty additional subjects comprised the experimenter-simulated group. In many double-blind studies research assistants, unlike patients, are aware that both active and inactive medication are included in the design of the study. The experimenter-simulated group were given the previously described instructions, but were also told that there were definitely two (or three) drug types in each of the six drug categories.

We noticed the following differences between active and inactive drugs in each of the six drug categories used in the study.

1. Minor Tranquilizer (Pressed White Tablet).—The differences were subtle and included texture (placebo was more granular), etching (placebo had sharper edges), and color (active drug was whiter).

2. Minor Tranquilizer (Pressed Yellow Tablet).—In addition to the subtle differences described above for the minor tranquilizer, the color of the active tablet was a brighter yellow.

3. Major Tranquilizer (Pressed White Tablet).—In addition to subtle differences in the texture and color, the active medication was at least 50% thicker than the placebo.

4. Antidepressant (Coated Yellow Tablet).—Subtle differences included brighter yellow color for the active drug, and the placebo had sharper edges.

5. Antidepressant A, Antidepressant B (Powder in Pink Capsules).—Differences were not detectable except that the placebo capsule floated in water.

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Percent Correct Differentiation of Active Drug From "Identical Matching Placebo"			
Drug	**No.**	**%**	χ^2
Patient-Simulated Group			
1. Minor tranquilizer	6	19	25.8*
2. Minor tranquilizer	12	36	125.0*
3. Major tranquilizer	26	82	646.0*
4. Antidepressant	6	19	25.8*
5. Antidepressant A & B	0	0	. . .
6. Antidepressant	32	100	992.0*
Experimenter-Simulated Group			
1. Minor tranquilizer	18	90	477.0*
2. Minor tranquilizer	17	85	424.0*
3. Major tranquilizer	17	85	424.0*
4. Antidepressant	18	90	477.0*
5. Antidepressant A & B	0	0	. . .
6. Antidepressant	20	100	594.0*

* $P \leq .001$

6. Antidepressant (Red Liquid).—The placebo was clearly a deep maroon color, while the active drug was a light red.

The differences noted by us and their degrees of subtlety were supported by the results.

Analysis of Data

Correct or incorrect separation of drugs by subjects was determined by objective methods such as measurement of pH, protein content, and so on. A correct response consisted of separating all active medications from all inactive medications. Any other response was incorrect. In almost every case, if a subject did not detect a difference, no further attempt was made to separate the tablets and all subjects who perceived differences correctly separated the medication.

Chi square analyses were used to determine statistical significance. A subject in the patient-simulated group, behaving in a random manner, could form groups of three plus three, four plus two, five plus one, or not separate the medications at all. Summing the random ways to form groups yields (10 + 15 + 6 + 1) possibilities. Random groups for subjects in the experimenter-simulated group could yield the same previously described possibilities except for not separating the drugs at all, thus yielding 31 possibilities.

Results

Our expectations were confirmed (Table). The patient-simulated group was able to differentiate between active drug and placebo significantly better then chance for all drug categories except for the pink antidepressant capsules. Even better differentiation was achieved by the experimenter-simulated group, although this group also failed to differentiate among the pink capsules. The difference in success rate between the two groups is accounted for by the additional information the experimenter-simulated group received that different types of medication were definitely present.

The percent correct differentiation for the six groups of medications paralleled the degrees of subtlety or obviousness noted by us. A few subjects also tasted the medications as a means of discrimination. The active medications, in contrast to the placebos, definitely numbed the tongue.

Our results indicate that placebo and active medication used in double-blind clinical trials have to be carefully formulated and matched so that research assistants and patients will be unable to detect physical differences. Though patients in a study given only active drug or placebo could not make such a distinction, those in crossover studies would be able to do so. Such differentiation by patient and treating and research staff could nullify the basic premise of the double-blind procedure, rendering it nonblind, and, in effect, an uncontrolled study.[4,8]

Comment

The results of this study suggest that capsules can be made more easily identical and matching than pressed or coated tablets or liquid medication, and should be used as the vehicle for drug and placebo administration in double-blind studies.

Personnel associated with a double-blind study should have no contact with the medication except for possible dispensing in closed containers. Only personnel without patient contact should be engaged in counts of returned medication, if this is a part of the research design, or personnel in the pharmacy separate from the study should dispense medication.

Differentiation between drugs and placebos used in double-blind studies can be minimized if personnel associated with the treatment of patients are unaware of the experimental design.

The Federal Drug Administration or National Institutes of Health should formulate standard capsules for use in controlled clinical studies. These capsules should be matched in all physical characteristics and should contain active ingredients to mimic the side effects of the active drug.

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References

1. Modell W, Houde RW: Factors influencing clinical evaluation of drugs. *JAMA* 167:2190-2198, 1958.
2. Chassan JB: *Research Design in Clinical Psychology.* New York, Appleton-Century Croft Inc, 1967.
3. Shapiro AK: The placebo response, in *Tice's Practice of Medicine.* New York, Harper & Row Publishers Inc, 1970.
4. Baker AA, Thorpe JG: Placebo response. *Arch Neurol Psychiatry* 78:57-60, 1957.
5. Greiner J: Problems of methodology in research with drugs. *Am J Ment Defic* 64:346-352, 1958.
6. Kast EC: Alpha ethyl tryptamine acetate in the treatment of depression, a study of methodology in drug evaluation. *J Neuropsychiatry* 1(suppl):114-118, 1961.
7. Nash H: The double blind procedure: Rational and empirical evaluation. *J Nerv Ment Dis* 134:34-47, 1962.
8. Nash H: The design and conduct of experiments on the psychological effects of drugs. *J Nerv Ment Dis* 128:129-147, 1959.
9. Feldman PE: Reflections on browsing research in psychopharmacology, in Cole JD, Gerard RW (eds): *Psychopharmacology: Problems in Evaluation.* Washington, DC, National Academy of Sciences, 1959.
10. Dubois EF: Cornell conference on therapy. *NY State J Med* 46:1718, 1946.
11. Kurland A: Placebo effect, in Uhr L, Miller JG (eds): *Drug and Behavior.* New York, John Wiley & Sons Inc, 1960.
12. Rivers WHR: *The Influence of Alcohol and Other Drugs on Fatigue.* London, Arnold, 1908.