Classical Conditioning in the Treatment of Psoriasis

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It has been argued that the placebo effect represents a learned response. Research is suggested to address the utility of applying principles derived from classical (Pavlovian) conditioning to the design of drug treatment protocols. In the present instance, it is hypothesized that, by capitalizing on conditioned pharmacotherapeutic responses, it may be possible to reduce the cumulative amount of corticosteroid medication used in the treatment of psoriasis.

As in many other clinical situations, a concern for the deleterious effects of prolonged drug treatment warrants consideration of rational variations in the treatment protocol that might reduce the amount of corticosteroids (or other pharmacologic or nonpharmacologic interventions) required to treat psoriasis patients—or eventually enable their symptoms to be controlled using relatively small amounts of medication. One such variation of the standard pharmacotherapeutic regimen involves the application of principles and operations derived from classical (Pavlovian) conditioning, which is an inherent component of the treatment protocol.

In classical conditioning, an unconditioned stimulus (UCS), such as food in the mouth, elicits a response, such as salivation, which is referred to as an unconditioned response. When a neutral conditioned stimulus (CS), such as a tone, is repeatedly paired with the food (the UCS), the CS alone will eventually elicit salivation, a conditioned response. Similarly, when environmental stimuli are coincidentally or purposely associated with the physiologic effects of many drugs, these environmental or conditioned stimuli (CSs) will eventually elicit the physiologic effects induced by the active drug (the UCS). That is, the physiologic effects of drug administration can be conditioned, and several investigators have likened the response to an inactive drug (the placebo effect) to a conditioned response.[1] Unfortunately, the possibility that the placebo effect is a conditioned response has remained at a descriptive level: the response to a placebo *looks like* the response to a CS. If the placebo effect does result from conditioning, what are the implications for pharmacologic treatment protocols and for psychopharmacologic research?

Presently, the evaluation of drug effects involves only 2 groups. Irrespective of dose, route of administration, frequency, or duration of treatment, experimental subjects or patients receive active drug and control patients do not. From a behavioral perspective, the experimental group is being treated under a continuous (100%) schedule of reinforcement (ie, stimuli associated with drug administration are consistently followed [reinforced] by the unconditioned effects of the drug). Patients in the control group engage in the same behaviors and experience the same environmental cues, but taking the "medication" is never followed (reinforced) by the unconditioned effects of the drug (a 0% reinforcement schedule). Thus, conditioning is an inherent component of many active drug treatment protocols and prompts one to ask about the efficacy of reinforcement schedules that are between 0% and 100%. That is, instead of evaluating drug effects by administering drug *or* placebo, one could administer drug *and* placebo. Varying the schedule of pharmacologic reinforcement would then become an alternative means of titrating cumulative drug dose and, by taking advantage of conditioned pharmacotherapeutic responses, it might be possible to maintain some physiologic state within homeostatic limits using lower cumulative amounts of drug.[1]

The heuristic value of viewing a course of drug treatment as a series of conditioning trials originated from a study that capitalized on conditioned immunosuppressive responses in the treatment of autoimmune disease in mice genetically prone to the development of a lupuslike disorder.[2] One group of animals received weekly pairings of a saccharin-flavored drinking

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solution (the CS) and the immunosuppressive drug, cyclophosphamide (the UCS). Another group of (conditioned) mice was treated on a 50% reinforcement schedule. These animals were exposed to saccharin weekly but received cyclophosphamide on only half of the trials; on the remaining trials they received only the CS. The development of proteinuria and mortality was delayed in these conditioned mice relative to untreated animals and nonconditioned animals that were treated with the same (reduced) amount of drug administered on a continuous schedule of reinforcement. These latter 2 groups did not differ. Thus, reexposure to a CS previously paired with active drug delayed the onset of disease and mortality using a cumulative amount of immunosuppressive drug that was not, by itself, sufficient to alter the course of the autoimmune disease. When active drug treatment was discontinued, conditioned animals that continued to be exposed to the CS survived significantly longer than a conditioned group that was given neither the drug nor the CS.[3] There is a single case report describing an apparently successful application of these conditioning principles to the treatment of a child with systemic lupus erythematosus.[4]

A good deal of placebo research has concentrated on the variables that influence the initial response to an inert agent. Although relevant, these variables (eg, the size, color, and shape of the pill; the sex and age of the patient; placebo "reactors," the physician-patient relationship) may not be sufficient for a full understanding of the long-term therapeutic potential of the placebo effect. There is, however, already literature that is directly relevant to a conditioning interpretation of the placebo effect. Greenberg and Roth[5] successfully reduced the amount of tranquilizing drug given to schizophrenics by substituting a placebo for active drug on a gradually increasing number of days per week. Other studies have implicated learning processes in the therapeutic response to drugs by showing that placebo effects are greater when placebo treatment follows rather than precedes effective drug treatment.[6-8] Also, patients that receive placebo following active drug treatment frequently display effects that persist for a period that exceeds the known residual effects of the drug.[9] Such effects could reflect indirect residual drug effects, but they could also reflect conditioning because the patients are being reexposed to a CS repeatedly associated with effective drug treatment in the immediate past.[10] The results of a recent crossover study of antihypertensive medication[11] conform precisely to results predicted from a conditioning analysis of the placebo effect.[10] In patients treated with a placebo following effective pharmacotherapy, the effects of the active drug therapy were prolonged beyond the point at which there were any direct or indirect residual drug effects as defined by the addition of a "no treatment" group following active drug treatment.

Conceptualizing pharmacotherapeutic regimens as a series of conditioning trials suggests new strategies for assessing drug and placebo effects and testable hypotheses that derive from a learning perspective. For example, cumulative drug dose might be titrated, not by a gradual reduction or increase in the concentration of drug administered on each of the hourly, daily, or weekly drug "trials," but by a change in reinforcement schedule (ie, by keeping drug concentration constant and varying the percentage of trials on which active drug is actually administered). Although one could not expect conditioned responses in situations in which drugs are prescribed to replace what a target organ is unable to provide, such a strategy has several possible advantages in a number of other clinical situations. A case in point may be the application of conditioning principles in the design of a protocol for the treatment of patients with psoriasis.

It could and, perhaps, should be determined whether, capitalizing on conditioned pharmacotherapeutic effects, psoriasis patients can be effectively treated with smaller cumulative amounts of corticosteroids. For illustrating purposes, one such study would involve 3 basic treatment conditions: 1) a group that continues on a standard regimen of pharmacotherapy at the preexperimental dose of drug that has been effective in the maintenance of these patients (Group S); 2) an experimental group of psoriasis patients who would be treated on a partial, rather than a continuous, schedule of pharmacologic reinforcement (Group E); and 3) a dosage control group (Group C) that is treated under the standard continuous schedule of reinforcement, but the concentration of drug is reduced so that the cumulative amount of medication received is the same as that received by experimental patients in Group E being treated under a partial schedule of reinforcement. Such an experiment might proceed as follows.

During an initial (baseline) period, all patients who have been selected on the basis of some criteria regarding the severity and extent of psoriatic lesions and who have responded positively to steroid medication are treated (maintained) with the effective dose of corticosteroid administered twice per day in an emollient that has a distinctive color and odor. After a period of weeks, patients would be divided into Groups S, E, and C, as defined above. For perhaps 3 to 6 weeks, Group S would continue to be treated with the maintenance dose of medication. Group E would be treated under a partial (eg, 50%) reinforcement schedule such that only a selected percentage of the strip of individual packets containing

emollient also contained the full concentration of active drug. (In the absence of any empirical data, the choice of a reinforcement schedule is arbitrary and a semirandom schedule could be used to assure patients received no more than 2 consecutive placebo treatments.) Group C would also be provided with a strip of packets, each of which contained a dose of medication that, over time, was equivalent to the cumulative amount of medication being received by patients in Group E. If, for example, patients in Group E were on a 50% reinforcement schedule (full dose medication 50% of the time), patients in Group C would receive 50% of the effective dose 100% of the time. Weekly clinical assessments carried out by "blinded" observers would be used to define any exacerbation of symptoms or relapse.

It is possible that a given noncontinuous schedule of pharmacologic reinforcement (and the concomitant reduced amount of active drug) will exert effects that are indistinguishable from a continuous regimen of pharmacotherapy (a higher cumulative amount of drug). That outcome or comparison, however, is not critical for evaluating the role of conditioning in the pharmacotherapy of psoriasis. Specifically, it is hypothesized that *patients treated under a noncontinuous schedule of steroid medication (Group E) will show a greater amelioration of symptoms than that achieved by patients treated with that same (reduced) amount of drug administered under a continuous schedule of reinforcement (Group C).*

If there are no indications of relapse in Group E or C under the conditions selected, the investigator has 2 further options: the partial reinforcement schedule can be lowered for Group E and the dosage reduced correspondingly for Group C, or a period of extinction can be introduced. *Experimental extinction* is operationally defined as unreinforced exposure to the CS that will eventually eliminate the conditioned response and constitutes a particularly sensitive measure for evaluating the strength of learned responses. If one proceeds to an extinction period, Groups S, E, and C would be subdivided into those who are taken off all medication (to define the residual effects of the active drug) and those who no longer receive active drug but do continue to be exposed to CSs. Under these circumstances, it is hypothesized that: 1) *relapse will occur more quickly following withdrawal of active medication in patients who do not continue to receive CSs than in patients who continue to receive CSs (placebo medication);* and 2) *when active drug is withdrawn and replaced by CSs alone, resistance to extinction will be greater (ie, rate of relapse will be less) among patients treated under a partial schedule of reinforcement than patients treated with the same cumulative amount of drug administered under a continuous schedule of reinforcement.*

It is reasonable to assume that many of the effects of corticosteroid treatment (including "side" effects) will be conditioned. However, the magnitude or duration of conditioned responses are not as great as unconditioned responses. Therefore, to the extent that certain side effects of a drug may be deleterious, conditioned side effects cannot be as dangerous to the patient as the side effects induced by the drug itself.

This very brief outline refers to only one of several experimental protocols that could be adopted to explore the role of conditioning in the pharmacotherapy of psoriasis. If it can be shown that a partial schedule of reinforcement can approximate the therapeutic effects of a continuous schedule of reinforcement, total drug dose and the costs of medication would be reduced, some (deleterious) side effects would be reduced (which might increase adherence to the pharmacotherapeutic regimen), and the duration of pharmacotherapeutic effects might be extended.

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