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Placebo mechanisms for drug dose reduction: what is the evidence?

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"Recent research has, however, shown that even the knowledge to receive a placebo will generate clinical improvements as long as the patients have had a positive experience (history) with medication and positive expectations are maintained."

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The mechanisms that generate and steer the placebo response in clinical trials and clinical practice are increasingly better understood. Pavlovian conditioning of physiological responses to medication that are associated with the intake of a drug, and expectation-driven evaluation of symptoms and symptom changes by the patient after the intake of a presumed medication, contribute to symptomatic improvement as well after intake of an inert pill (placebo), as long as he/she is unaware of its nature [1]. It has also been shown that the likelihood of receiving active treatment in clinical trials modulates the placebo response [2]. Recent research has, however, shown that even the knowledge to receive a placebo will generate clinical improvements as long as the patients have had a positive experience (history) with medication and positive expectations are maintained [3]. Separating expectancy-mediated and conditioned placebo responses may be feasible in experimental research, but in clinical trials as well as in daily routine, "much like the laws of gravity, the laws of learning are always in effect" [4] and do not allow such isolation.

If expectation and conditioning are ingredients of the placebo response, the quest of how to make use of them in medical practice and research arises. One precondition is to rigorously follow principles of 'associative learning' that were set by Ivan P Pavlov.

This was realized by – among others – Robert Ader (1932–2011), a psychologist at the Rockefeller University (NY, USA) who pioneered psychoimmunology, the investigation of CNS influence and control of immunological functions using Pavlovian conditioning principles since 1975 [5]. In the 1980s, Ader had hypothesized that the placebo effects as seen in clinical studies, specifically with randomized, placebo-controlled crossover trials (a frequently used design until today), may be due to conditioning [6]. He was among the first to propose using a conditioning procedure to partially replace drugs with placebos in tandomized-controlled trials [7], and he even patented a "Method and device for administering medication and/or placebo" to test his hypotheses [101].

In an initial study, the effects of atenolol, a beta-blocker, were investigated in 24 patients with mild or moderate hypertension [6]. Patients received either placebo, followed by the drug, followed by no treatment (Group 1); or the drug, followed by placebo (Group 2); or the drug, followed by no treatment (Group 3); with each period lasting for 1 week. Prior to drug intake, Group 1 did not differ from Group 2 and 3 in the average blood pressure taken daily at home. After 1 week of drug treatment for all, blood pressure and heart rate were significantly lower in the placebo treated group (Group 2) than in the nontreatment controls (Groups 1 and 3), indicating that the placebo response was more than a residual drug effect. This is consistent with a conditioning model of the placebo effect. Such a conditioned response to placebo pills can be achieved if it is preceded by an acquisition period that is sufficiently long and effective.

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Drug treatment could consider 2 to 3 weeks of regular medication intake, followed by periods with interspersed placebo pills during the drug regime, called partial reinforcement (Table 1). Such a strategy might be suitable to reduce the overall dose of drug intake, while maintaining its efficacy. With such reinforcement, treatment effects with interspersed placebos may be even longer lasting than continuous treatment with the corresponding medication [8].

While this idea has been around for quite a while and was tested in a laboratory setting with volunteers and patients [9], it was not until the 1990s that its clinical relevance was demonstrated in drug trials. Again it was Robert Ader and colleagues who published the first such report in 2010 [10].

Table 1. Use of placebo pills in a partial reinforcement design with a 1:1 reinforcement rate.

Treatment day	Treatment
Acquisition period	
1	D
2	D
3	D
4	D
5	D
6	D
7	D
8	D
9	D
10	D
11	D
12	D
13	D
14	D
Maintenance treatment	
15	D
16	P
17	D
18	D
19	P
20	D
21	P
22	P
23	D
24	D
25	P
26	P

D: Drug; P: Placebo.
Modified with permission from [9].

A group of 64 patients recruited at two investigational sites in Rochester (NY, USA) and Stanford (CA, USA), with mild to moderate psoriasis were treated with a standard corticosteroid cream applied twice daily to a selected 'target' lesion on their knees or elbows for 3 to 6 weeks, while a commercial skin moisturizing cream (control) was applied to the respective skin area on the contralateral side. After this baseline treatment, they were randomized in a double-blinded fashion to one of three groups: Group 1 continued treatment with the same corticosteroid concentration (100%); Group 2 received a reduced (50 or 25%) corticosteroid doses (dose control); and Group 3 received the 100% dosage on a 50 or 25% reinforcement schedule (100% dose every second to fourth application) for another 8 weeks. Groups 2 and 3 thereby received the same total amount of corticosteroids overall. The Psoriasis Severity Score was evaluated weekly and showed a similar efficacy of treatments between Groups 1 and 3, while it showed a relapse in severity in Group 2 at the Rochester site. This demonstrates the potential of drug reduction using a partial reinforcement schedule. However, as the data were not replicated at the Stanford site, this also indicates procedural differences between both locations, which corrupted the data.

In a pediatric study in children with attention-deficit hyperactivity disorder (ADHD) [11], Sandler and colleagues from Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill (NC, USA) investigated the possibility of reduced dosing of amphetamine salts for treatment of ADHD. All patients were first randomized to receive either the full dose (FD; 100% = 0.6 mg/kg/day extended release amphetamin salts), the reduced dose (RD; 0.3 mg/kg/day) or placebo, each for 1 week with 1 week wash-out inbetween in a double-blind crossover fashion; this was conducted to assess the optimal dosing per patient. They were then randomized to one of three groups for an open-label study: to receive FD for 2 months (Group 1); to receive FD for 1 month and RD the second month (Group 2); or to receive FD for the first month and then the RD plus a distinct placebo for the second month (Group 3). Standardized parent and teacher ratings of symptom severity were assessed, as were side effects of treatment. Groups 1 and 3 were equally effective in the maintenance of ADHD symptom improvement in comparison with the first 4 weeks, while Group 2 showed significant relapse of symptoms and side effects after the first 4 weeks of treatment.

While these two examples confirm positive short-term effects of conditioning procedures to reduce dosage of common treatments, their potential for reducing drug dosing during long-term therapy must be further investigated. In particular, we currently do not understand which physiological systems are especially prone for conditioning, which reinforcement schedules should be used to achieve optimal effects, and how to prevent habituation/extinction of the learned pharmacological responses. For some conditions, partial reinforcement with FD treatment may provide the most stable effects; while for the others, consolidation of the learned pharmacological response may be achieved through subtherapeutic drug doses [12]. Which psychological and physiological trait and state variables predict facilitated conditioning also needs to be determined in future research.

As Robert Ader has pointed out, "*One could not expect conditioning to occur in replacement therapies, that is, in those situations in which drugs are prescribed to replace what a target organ is unable to provide. However, such a strategy has several possible advantages in a number of other clinical situations. If a partial schedule of reinforcement can approximate the therapeutic effects of a continuous schedule of reinforcement,*

total drug dose would be reduced, some side effects might be reduced (which might, incidentally, increase adherence to the pharmacotherapeutic regimen), dependence problems might be reduced or more easily alleviated, and the duration of therapeutic effects might be extended. Also, the costs of medication would be reduced" [7].

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