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Opinion

# The Role of Expectation in the Therapeutic Outcomes of Alcohol and Drug Addiction Treatments

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## Abstract

Throughout history, patient–physician relationships have been acknowledged as an important component of the therapeutic effects of any pharmacological treatment. Here, we discuss the role of physicians' expectations in influencing the therapeutic outcomes of alcohol and drug addiction pharmacological treatments. As largely demonstrated, such expectations and attitudes may contribute to produce placebo and nocebo effects that in turn affect the course of the disease and the response to the therapy. This article is aimed at discussing the current insights into expectations, placebo and nocebo mechanisms and their impact on the therapeutic outcomes of alcohol and drug addiction treatments; with the goal of informing physicians and other health care providers about the potentially widespread implications for clinical practice and for a successful treatment regimen.

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Treatments for alcohol and drug addiction that have solid evidence for efficacy are currently available, but their use in routine clinical practice is limited. Meanwhile, high relapse and dropout rates are observed among patients engaged in addiction treatments.

A question that arises is what expectations and beliefs physicians and other practitioners have towards their patients and with regard to the efficacy of treatments, and whether these expectations can affect the therapeutic outcomes.

The clinical relevance of this question is based on the finding that the therapeutic effects of pharmacological treatments can be regarded as a composite of two components: one pharmacodynamic, related to the active ingredient contained in a drug, and the other psychosocial, related to the context in which it is given and to the patient–physician interaction (Kaplan *et al.*, 1989). Physicians may induce positive or negative expectations in patients, directly by expressing their views of a medication's efficacy and providing information about possible side effects. Additionally, physicians may induce expectations through

indirect or unintended means that may reflect their perception of medication efficacy. As a result, positive or negative expectations may have a significant impact on therapeutic outcomes (Colloca and Miller, 2011).

Here, we focus on crucial studies showing the relevant implications of expectations, placebo and nocebo effects in modulating the outcomes of alcohol and drug addiction therapies. Our aim is to inform physicians and other health care providers about the valuable use of positive expectations in this therapeutic context, but also about the detrimental consequences that negative expectations may exert on treatment outcomes.

We decided to emphasize the importance of the patient–clinician relationship, given the crucial role of physicians in delivering treatments and also conveying information to patients and the scarcity of literature specifically investigating the effects of expectations and attitudes of physicians with regard to alcohol and drug addiction treatments and their outcomes.

The notion that the physician might influence patient's health independently of diagnostic and therapeutic activities was first suggested by Hippocrates. However, only in recent years the patient–physician interaction and the expectations associated with the therapeutic encounter have been recognized as one of the most important factors influencing therapeutic outcomes. In fact, it is now recognized that expectations delivered and disclosed during routine treatments, may contribute to produce placebo effects and nocebo effects (the negative effects of placebo).

Such effects stem from psychobiological processes consisting of learning and expectation components acting on neurophysiological systems, and their role in influencing the expression and maintenance of various pathological states and their inherent therapeutic interventions, has been largely demonstrated (Enck *et al.*, 2008; Benedetti, 2014).

In particular, Amanzio and Benedetti (1999) were among the first to recognize the specific role of expectations in generating placebo effects. Using an experimental model of pain, they found that expectations were able to induce placebo responses, by acting on the endogenous opioid system, whereas conditioning activated other specific subsystems.

In addition of demonstrating the role of the opioid mechanisms in placebo effects, the authors also show that a simple verbal suggestion (receiving an analgesic vs. receiving an antibiotic) was able to induce in subjects the expectation of pain relief.

This phenomenon was also demonstrated in another elegant study (Pollo *et al.*, 2001), showing that verbal instructions about certain and uncertain expectations of analgesia produced different placebo analgesic effects. In this study, thoracotomized patients were treated with buprenorphine on request together with a basal intravenous infusion of saline solution. However, the verbal instructions regarding the saline infusion was changed in three different groups of patients so that they would expect to receive a potent painkiller or a placebo.

The verbal instructions altered clinical outcomes, not just in terms of pain but also by inducing a dramatic change in behavior, leading to a significant reduction of opioid intake.

Expectations *per se* represent an intriguing theoretical concept which deserves to be explicated briefly. From a general perspective, expectations may be considered as beliefs about the consequence of a given event, and therefore could be aimed at preparing the body to anticipate the event to better cope with it. For example, the expectation of a future outcome and of a future response can be held by an individual about one's own emotional and physiological responses such as pain, anxiety and sexual arousal (Kirsch, 1999). It can then lead to a cognitive reappraisal of the appropriate behavior, with positive expectations leading to adopt a particular behavior, and negative expectations leading to its inhibition (Bandura, 1997).

Furthermore, social cognitive theory differentiates between *self-efficacy* expectations, a belief about one's ability to successfully perform a behavior, and *outcome* expectations, defined as a belief about the likelihood of the behavior leading to a specific outcome (Bandura, 1977). According to this view, the physician's belief to possess the appropriate skills to treat his patients may be seen as a self-efficacy expectation compared to the physician's belief or anticipation that the patient's medical condition will improve by following the prescribed treatment (outcome expectation).

For example the notion of a disease as curable, or that a certain medication is effective and safe, or that a patient will adhere to treatment plans, may induce positive expectations in the physician toward both the patient and the treatment. This may contribute to positive patient–physician interactions and communication that, in turn, may

result in patient's compliance and satisfaction with the treatment, and in the adoption of behaviors enhancing healing processes.

Similarly, the patient's expectation plays a crucial role in shaping outcomes. According to Kirsch's theory (Kirsch, 1985), a patient experiences an outcome because he/she expects it. It is possible to distinguish between '*response expectancies*', defining them as 'anticipations of the occurrence of non-volitional responses' and '*stimulus expectancies*', which 'are anticipations of the occurrence of external consequences'. Expectations of an *outcome* or a *response* are formed through information learned via personal experiences and interpersonal interactions affecting the outcome itself.

This is suggested by a study aimed at evaluating factors affecting treatment outcomes in patients with alcohol use disorders (Dearing *et al.*, 2005). Patient's expectations and the quality of the patient–physician relationship emerged as the most important predictors of a successful treatment experience.

Of course, the influence of expectations on therapeutic outcomes has been demonstrated in several other medical fields but here we suggest that the impact of expectations in patients with alcohol and drug use disorders may offer distinct implications for treatment delivery. In a pioneering study by Marlatt *et al.* (1973), subjects were led to believe that they would be sampling an alcoholic or non-alcoholic beverage. The two beverages tasted almost identically, so it was not possible to detect the presence or absence of alcohol on better than a chance basis. Alcohol-dependent subjects, when expecting to sample a drink containing alcohol, consumed almost twice than those who expected to receive only non-alcoholic beverages, regardless of the actual presence or absence of alcohol in the drink.

Another important contribution supporting the fact that expectations shape outcomes in the field of addiction is illustrated by a recent study by Volkow *et al.* (2003), who investigated the effect of verbal suggestions on brain response to the stimulant drug methylphenidate or placebo in cocaine abusers. In particular, changes in brain glucose metabolism, as measured by [<sup>18</sup>F]deoxyglucose-PET, were evaluated when subjects expected to: (a) receive the drug and indeed received it; (b) receive the drug but received the placebo; (c) receive placebo but received the drug; (d) receive placebo and indeed received placebo. When patients expected to receive the drug, the brain metabolic changes and the subjective effects of the drug were about 50% greater, in comparison with the group of patients who were told they would receive placebo. Thus, it appears clear that in patients with alcohol and/or drug use disorders, the expectation of a reward (alcohol, drugs) affects the response to the reward itself. Furthermore, this study shows that simple verbal suggestions of a positive outcome (receiving methylphenidate) not only enhance the drug-induced brain effects but also the subjective response to the drug with significant greater self-reports of 'feeling high' when patients expected to receive methylphenidate as compared to expectations of receiving placebo when actually the drug was given.

As already suggested, these findings may have valuable clinical implications, especially considering that it has been recently suggested that the expectation of a clinical benefit is comparable to the expectation of a reward and induces brain responses similar to those observed in reward processing (Volkow *et al.*, 2003).

Probability of reward activates dopaminergic neurons by the combination of direct excitatory glutamatergic inputs and indirect inhibitory gamma amino butyric acid inputs. The firing of dopamine-containing neurons reflects both the magnitude of the reward and the probability that reward occurs in addition to motivational state, context-dependence and level of certainty (Fiorillo *et al.*, 2003; Ploghaus *et al.*, 2003; Schultz, 2006). Probability of reward and

expectation of positive outcomes are not mutually exclusive. Redish (2004) provided a measure of expected future reward based upon a specific state and the elapsed time until the reward is obtained, such that the value function discounts rewards that take longer to achieve. Actions are selected by an individual to maximize future rewards. An individual learns a specific behavior path toward the reward. The most recent action is in part shaped by the events of previous states, through a constant re-evaluation of the initial expectation and subsequent selection of actions. Anticipations of reward and expectations elicited by prior individual experience are integrated finely shaping behaviors and clinical outcomes. Brain activations induced by the anticipation of reward and the expectation of positive outcomes may have healing effects, and can also promote 'healthy' behaviors, such as compliance with treatment. The flip side of the coin, however, is that negative expectations can inhibit these behaviors and also exert an influence on the patient's experience of medication efficacy. In fact, several studies have demonstrated that physicians' view of patients with alcohol and drug use disorders impacts the efficacy and quality of care delivered.

Chappel and Schnoll (1977) were the first to report that negative attitudes of physicians toward patients with alcohol and drug use disorders led to delayed diagnosis and poor treatment. Almost 30 years later it seems that little has changed. Data from a survey conducted among primary care physicians in the United States show that physicians continue to perceive the effectiveness of treatments for alcohol and drug as being limited (Lindberg *et al.*, 2006). Also, national data from the specialty addiction treatment system show discouragingly low rates of adoption of effective treatments, despite the fact that significant efforts have been made toward the development of pharmacotherapies for the treatment of alcohol and drug use disorders (Knudsen *et al.*, 2011). Specifically, a mail survey of 135 physicians with addiction specialty found limited use of naltrexone, with approximately 40% of physicians reporting to have prescribed this medication rarely or never (Thomas *et al.*, 2003).

Mark *et al.* (2003) examined naltrexone prescribing patterns using a sample of 1,388 American Society of Addiction Medicine and Association of Persons Affected by Addiction member physicians. Among the most significant barriers to prescribing naltrexone were physicians' concerns about patients' compliance and efficacy of the medication.

Attitudes and expectations toward the medications have been also reported among the factors implicated in limited buprenorphine adoption in substance abuse treatment centers (Wallack *et al.*, 2010).

A common perception is that pharmacological treatments do not work because patients with alcohol and drug use disorders do not get 'cured', despite evidence that the rates of relapse and recovery in addiction treatments are equivalent to those of other chronic medical diseases, such as diabetes or hypertension (McLellan *et al.*, 2000). Similar findings were reported with regard to treatment adherence rates (McLellan, 2000).

Several studies also demonstrated that length of time spent in treatment is related with better outcomes in patients with both alcohol and drug addiction (Stark, 1992).

Although there has been an increased recognition of alcohol and drug addiction as chronic and relapsing diseases since the late 1990, the stigma associated with addiction and the misconception that drug use is the result of bad choices, reflecting a moral failure and primarily managed as a legal problem still lead many physicians to distance them from addiction. The echo of Prohibition, combined with the application of the Harrison Act that prevented physicians from treating opioid dependence, seems to still reverberate in the physicians' view of this medical condition. Indeed, denial, resistance or

manipulations are words still commonly used by physicians to describe the attitude of these patients.

Here, we suggest that these expectations and attitudes do not represent just ideological or ethical barriers, but they also are an *active component* of the pharmacological treatment delivered in routine clinical practice, that may detrimentally influence the therapeutic outcomes.

Therefore, physicians should avoid providing biased opinions or negative expectations toward addiction pharmacotherapies. Instead, incorporating positive framing in disclosure processes, boosting patients' and physicians' positive expectations and tailoring the information to the patient's needs may help increase efficacy, compliance and credibility of any medical treatment in the field of addiction, in which alteration of reward sensitivity and expectations burden brain's inhibitory control circuits thus negatively impacting clinical outcomes (Volkow *et al.*, 2010). As suggested by Volkow and colleagues, mere anticipation of positive outcomes can enhance the brain response to medication as well as the subjective experience and perception of efficacy in these patients (Volkow *et al.*, 2003).

Indeed, expectations can be strategically managed to promote healthy behaviors, compliance with treatment and overall satisfaction with clinical outcomes. Ultimately, as described in social science by the law of self-fulfilling prophecy, people respond the way we expect them to respond.

## CONFLICT OF INTEREST STATEMENT

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