It is well known that expectation can become one of the key elements of drug taking. But sometimes, as experiments have found, expectation can be the only element of getting high. **Professor David Nutt** on whether placebos offer real, or imaginary, effects

High hopes

Whether it's the conman at Glastonbury whose fake acid-soaked playing card tabs proved so popular by word of mouth he had to jump the barrier to buy another deck or the pair of teenagers getting 'off their heads' on banana skins, the power of mind over matter has always been part of drug use. Assuming the purchasers of playing cards and bananas were getting their desired response, why would this be? The best explanation is that they are experiencing the placebo effect.

Placebos are false drugs that look like the real treatment but do not have the key therapeutic ingredient. Placebos are given in an identical way to the active or 'real' treatment, so that the user believes they are receiving an active form of treatment, so is expecting it will work. And it often it does.

The underpinning of the placebo effect is complicated, with several factors being involved. The most important being that of expectation: people get the experience they want or have been told to expect. The placebo effect is especially strong when the user is interacting with others, especially friends and partners, who are reporting the same effects – either from a real drug or a placebo.

This has been well-established in clinical experiments where some subjects were given active drugs and others placebos. Both reported equal effects. This is not surprising, because the psychological effects of a common setting and shared desire for pleasure and fun can be as powerful as 'real' drug effects for substances such as amphetamine, LSD and cannabis. Such pleasurable effects of placebos are generally much stronger in new or relatively naive drug users and less in more drug-experienced people.

Perhaps the most classic study of placebo and recreational drug effects took place in 1955 when a team of researchers, headed by psychiatrist Harold Abramson, examined the subjective responses of 33 adult volunteers expecting to receive a dose of LSD. Instead they were given 75cc of tap water. Of the 33 subjects, only two had taken LSD before, but all were well briefed about the drug's dramatic psychological effects. Subjects were told to anticipate a possible "temporary psychosis" and were given the placebo in small groups

containing at least one extra individual who was given a genuine dose of LSD.

Within 30 minutes of receiving the placebo, subjects began reporting physiological and perceptual changes: 25 per cent said 'yes' to the question "do you feel as if in a dream?", 35 per cent reported feeling anxious and 60 per cent reported that their palms were sweaty. Although the placebo responses were moderate compared to those reported by the LSD takers, the authors concluded that "tap water is capable of eliciting certain responses from certain subjects who believe they have received lysergic acid diethylamide".

Placebos are often called sugar-pills but in medical experimentation an "active" placebo control condition is sometimes used. This is when another drug which produces some pharmacological effects – but different ones to the drug of interest – is given. The object here is to ensure that all subjects experience some effects, so making the 'blinding' of the experiment more secure.

In a study published last year looking at the subjective effects of another psychedelic compound, psilocybin (the active ingredient in magic mushrooms), four of 36 subjects receiving the active placebo methylphenidate, better known as Ritalin, described their experience in such a way that it met the experimenter's criteria for a "complete mystical experience". All subjects said they had not taken a hallucinogenic drug before, but were made aware that they would at some stage receive a moderate or high dose of psilocybin.

Although subjective responses to psilocybin were much more pronounced than those to methylphenidate – 22 of 36 subjects receiving psilocybin met criteria for a complete mystical experience and a third claimed the experience was the single most spiritually significant experience of his or her life – it is interesting that second-hand knowledge of the experimental drug's mind-expanding potential appears to have significantly impacted the psychological response to taking the active placebo Ritalin in a small number of individuals.

It is important to note that placebo effects can be bad as well as good. If a group of people are given a drug and one gets a bad effect, feels ill for example, then others may report the same symptoms. Sometimes this can lead to a sudden outbreak of fear and health anxiety in a group of people who can believe they have been poisoned. Another negative aspect of placebos is that if an experienced drug user inadvertently takes a placebo instead of the real thing they may experience an unwelcome reaction that usually mimics the withdrawal they would get if suddenly stopping drug use.

This is because every time a drug is taken the body reacts in a way opposite to the drug effects to minimise the actions of the drug on the body and brain. These oppositional reactions are one of the main reasons why tolerance develops to drug effects and they begin to kick in as soon as the drug is taken – or even in anticipation of drug use. However if the drug is not taken these oppositional reactions of the body are experienced without the counterbalancing actions of the drug and can lead to quite distressing symptoms such as anxiety, palpitations, shivers and shakes, depending on the type of drug used.

The placebo is a much-mentioned but ill-understood tool in medical research. They can take the form of false treatments, such as those used in psychotherapy, or even a variant of a surgical procedure. It is a drug or other treatment that both the patient and the prescribing doctor or other health professional believes will work. Such a placebo-controlled study is the only way to properly estimate the absolute efficacy of any treatment. Even in fields of medicine where you might not expect 'expectation' to have any real effect, such as diabetes and hypertension, placebo effects are well documented. This is because the brain has a major impact on all body systems in illness as well as in health.

33 adult volunteers expecting to receive a dose of LSD. Instead they were given 75cc of tap water

As said earlier, the placebo effect, whether it is to create a feeling of pleasure or therapeutic relief, seems to depend entirely on anticipation and expectancy. There has been little research on the brain mechanisms for the placebo effect with recreational drugs, but some quite clear neuroscience insights have been found with studies of placebos used in pain relief.

The placebo effect on pain has been known for many years. When the brain's natural opioids, the endorphins, were found in the 1970s, they became an obvious candidate for the mediators of the placebo effect. That they did play a role was shown in another classic 1983 experiment, *Partial antagonism of placebo analgesia by naloxone*, where the opioid antagonist naloxone was given to people with pain from dental extractions who were experiencing placebo-induced pain relief. Researchers Grevert, Alpert and Goldstein found the antagonist reduced the degree of pain-relief produced by the placebo – suggesting that a component of the placebo effect is due to the release of endorphins.

It is likely that endorphins or other chemical messengers in the brain play a role in other placebo effects, but this has not yet been systematically studied. However, a pointer in this direction can be found in the 2001 study *Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease* on patients with Parkinson's disease – a disorder in which the neurotransmitter dopamine is markedly depleted in the brain, and so is treated with drugs that increase dopamine function. In patients expecting to get a form of dopamine replacement but given a placebo, an increase in dopamine function was noted. Intriguingly when this effect was studied using the technique of PET scanning, that allows measurement of changes in dopamine release in the brain, it was found that *anticipation* of treatment lead to the release of dopamine.

Based on this study it may be that dopamine is the missing link between the placebo effect and drugs that lead to a degree of pleasure. Whether or not placebo LSD works through the release of endogenous psychedelics is less likely, but could be studied using similar imaging techniques.

Professor David Nutt is Head of the Department of Community-Based Medicine, Psychopharmacology Unit, University of Bristol. He is also an ACMD member
Robin Carhart-Harris is a PHD student at the Department of Community-Based Medicine