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Medicine's inconvenient truth: The placebo/nocebo effect

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Abstract

Placebo and nocebo effects are often regarded by clinicians as either a quaint reminiscence from the pre-therapeutic era, or simply as a technique for establishing the efficacy of therapeutic interventions within the locus of evidence-based practice. However, neither of these explanations sufficiently account for their complexity or their persistence and impact in clinical medicine. Placebo and nocebo effects are embedded in the very fabric of therapeutic relationships and are both a manifestation and outcome of the rituals that characterise clinical practice. They are also a stark reminder of the many personal and environmental factors, including the attitudes, beliefs and expectations of both doctor and patient, that shape the outcomes of health professional-patient interactions. We describe how recent biological and neuropsychiatric data have clarified the operation of placebo and nocebo effects in clinical practice – demonstrating the ability of the therapeutic context to modulate endogenous biological processes in a targeted manner. This, in turn, illustrates the potent philosophical and sociocultural aspects of medical praxis.

Keywords: placebo; nocebo; context effect; medical therapeutics; medical practice; medical ethics

Introduction

Placebo and nocebo effects are often regarded as either a quaint reminiscence from the pre-therapeutic era,[1] or simply as a technique for establishing the efficacy of therapeutic interventions within the locus of evidence-based practice. Neither of these explanations, however, sufficiently account for its complexity or significance. Rather, these are wide-ranging phenomena that reflect the 'interplay between the patient and the disease', which if not acknowledged, can lead to a 'complete decontextualisation of patient, disease, doctor and technology'.[2] It is 'the epistemological and theoretical junction where the insufficiency of the mechanistic model for understanding therapeutic phenomena becomes obvious'.[3] Further, clinical interactions and their outcomes are not simply a manifestation of medical science, but are shaped by physicians' and patients' attitudes, values, beliefs, preferences and expectations.[4]

In other words, medical treatment is not conducted in a therapeutic vacuum, but rather in a context that is rich in meaning for any given patient in a particular time and place.[5]

Understood this way, the placebo and nocebo terminology can be re-conceptualised as a 'meaning response'[6] or as a 'contextualised healthcare response'.[7] This does not change the wording or meaning of placebo effects, but places a focus on what is observed when a patient receives a placebo. In this case, giving a placebo simply simulates a routine clinical interaction (without the actual index treatment), and the outcome is due to the effect of the therapeutic context or healthcare environment.

In this article, we suggest that a closer examination of placebo and nocebo effects allows for the appreciation of the power of the therapeutic context on the outcome of a given therapy.

Placebos and nocebos

Broadly understood, a placebo (from the Latin, 'I shall please') is a substance or procedure that has no therapeutic effect and is used as a control in testing new drugs or prescribed to provide psychological benefit rather than for any physiological effect, although the latter is now known not to be true. The placebo effect is the beneficial effect produced by a placebo, which cannot be attributed to the properties of the placebo itself,[8] but rather what the administration of a placebo is simulating (a specific therapeutic context).

Placebos have been further categorised as active when verum medications are given in sub-therapeutic doses, and impure when active agents are used in a context where they could not have an effect,[9] although in both cases it is the simulation of the therapeutic context which is the key factor.

In contrast, a nocebo (from the Latin, 'I shall cause harm') is an agent whose administration results in a noxious or detrimental effect on health that cannot be attributed to the properties of the substance or intervention itself.

Nocebo effects therefore are noxious effects arising from the administration of a placebo or treatment which, 'cannot be explained on the basis of the known pharmacology of the drug, are idiosyncratic and not dose-dependent',[10] and may manifest as biologically implausible negative effects of active therapies.

A number of conclusions can be drawn from these definitions. The first is that there is an inherent contradiction in that both placebos and nocebos are defined as inactive, but both have an effect.

The second is that because these substances are defined in terms of their effect, there is likely to be no substance or intervention that is truly inert, or lacking capacity to exert an effect.

The third, therefore, is that placebo and nocebo effects are likely to be evident across different diseases, illnesses and modalities of treatment,[11] and may have variable manifestations in different patients and/or in different sociocultural contexts.[6] The key to these definitions is the notion that it is not the content of the placebo that elicits an effect, rather that administering a placebo (or performing a sham procedure) simulates a real clinical interaction. The variables in this interaction can modulate symptoms in positive or negative directions.

For these reasons, clinicians, irrespective of their age, gender, experience or area of practice, may be uncertain of the potential operation of these effects in their day-to-day practice.[12] As a consequence some practitioners – by definition – may consciously employ placebos in their work, some may do so unconsciously,[13] while others may not recognise that the nature of their practice may exert placebo or nocebo effects.[14] This variation in knowledge, attitudes and practice is significant, because placebo and nocebo effects may be important determinants of health outcomes since they may result from almost any aspect of medical care.

What aspects of medical practice can result in a placebo and nocebo effect?

Given that placebo and nocebo effects are present in routine clinical care, even when a placebo is not given, it is unsurprising that almost every facet of health professional–patient interactions may modulate the placebo and nocebo component of a given treatment. Initial interactions, investigations, diagnosis, the ritual of medication prescription, surgical or other physical interventions are all potentially important modulators, not to mention practitioners themselves. A diagnosis has far-reaching medical, social and often medico-legal implications,[15] particularly in patients with hitherto medically unexplained symptoms;[16, 17] a diagnosis which gives meaning to

the patient's illness is a form of treatment per se,[18] with the potential for either placebo[16] or nocebo effects.[17] If diagnoses are supported by the weight afforded by laypersons to 'high technology' investigations,[19] diagnoses are not purely a matter of potentially fallible human speculation; rather, they are an important component of the therapeutic process and outcome.[20]

Other elements of the therapeutic context have been studied. Coloured pills have more of an effect than white,[21-23] injections are more effective than tablets in selected populations, whereas the reverse is seen in others,[22, 24-26] and treatments administered in the emergency department are more effective, presumably due to the acute nature of the context.[27] Recent studies have shown that higher priced items are judged to be more effective than cheaper ones,[28, 29] and branded pharmaceuticals appear to be more effective than generics.[30] Two placebos given together are more effective,[21] and adding a placebo to a verum medication can result in augmented results.[31] Interestingly, generic substitutes for brand-name drugs may be associated with a higher rate of nocebo responses than the branded alternative.[32]

These findings are not only limited to pharmacological agents. Surgery has also been associated with significant placebo effects, with placebo, 'sham' or ineffective surgery being associated with a reduction in ischaemic chest pain,[22, 33] lumbar pain,[22] symptoms of Meniere's disease,[22, 34] and symptoms of cardiac failure following insertion of inactive pacemakers in patients with hypertrophic obstructive cardiomyopathy.[35] Placebo responses have also been described with non-conventional physical interventions, particularly acupuncture, with an extensive literature describing a range of benefits from various sham techniques.[36]

These many findings emphasise the importance of the psychosocial context around a patient, as it is clear that factors other than the biomedical component of treatment may influence the patient's outcome. This commences with the 'therapeutic meeting between a conscious patient and a doctor'.[37]

Enthusiastic practitioners and their beliefs about the nature of a treatment[38, 39] can have an effect even when clinicians are told that a patient might be receiving a placebo or an active medication, without disclosing this information to the patient.[40] A physician who explores a patient's needs and expectations is also likely to elicit a higher placebo response.[41, 42] This has been demonstrated with decreased narcotic use and shorter hospital admissions in anaesthetic practice.[43]

The administration of medication appears to be more effective in the context of a therapeutic ritual,[3, 6, 44, 45] and 'pure social interaction can, in some circumstances, be as powerful as the action of a pharmacological agent',[46] influencing the outcomes of acupuncture,[47] opioid analgesia[48] and the administration of benzodiazepine anxiolytics.[49] In contrast, malign rituals in traditional healing may represent an extreme form of nocebo effect.[50]

There is a number of reasons why physicians and their interactions with patients may promote placebo and nocebo effects during routine therapy. Some have explained the physician's personal capacity to influence illness and health outcomes by reference to their 'power',[51, 52] specifically, their 'social power' (derived from the status afforded to physicians and their vocation), 'charismatic power' (derived from the personal characteristics of the practitioner) and 'Aesculapian power', which 'the physician possesses by virtue of her training'.[51]

This characterisation of the placebo effect in terms of power seems accurate because the medical consultation undoubtedly occurs within a socially constructed asymmetrical power relationship,[53, 54] which – by way of its stylised form and rituals – is likely to create placebo effects.[44, 55, 56] In this regard, it is noteworthy that religious metaphors and dramaturgical considerations abound in clinical medicine[55, 57] and the more elaborate the ritual, the more likely it is that a placebo effect will occur.[44, 45, 58, 59]

However, medical consultations should not be considered as purely political acts[60] or malevolent exercises in power,[61] as sickness and illness inevitably create problems with meaning, and the ceremonies and rituals that characterise medicine may function, in part, to restore order by facilitating 'meaning and expectancy for the patient'.[46] The relational or interpersonal aspects of the therapeutic relationship may also function to generate trust – which may, in turn, provide the basis upon which care proceeds and explain something of the impact of placebos and nocebos. A range of physician behaviours, such as listening, spending appropriate time, being informative and encouraging involvement in the decision-making process, can engender trust.[62] Consequently, these behaviours may engender a placebo effect, while a betrayal of trust may be associated with a nocebo effect.[63, 64]

Despite these observations, there has been a historical tendency to consider placebo (and more recently nocebo) effects as 'white noise' – something to be eliminated from scientific medicine[65] – or simply as an invalid means of healing associated with quackery and deception both in research[66, 67] as well as in clinical practice.[14, 68, 69]

In recent years, however, an emerging body of research has provided more sophisticated insights into the operation of placebo and nocebo effects.

Some suggest that making a conclusion of the existence of a placebo effect may be erroneous because the placebo effect may simply be the refection of phenomena such as regression towards the mean,[70] or the evolution of the natural history of a condition.[65, 71] Such effects can be contrasted to those that occur as a result of inter-related psychological phenomena and neurobiological changes. However, well-designed experiments using natural history controls have contradicted such ideas.

Mechanistic explanations of placebo and nocebo effects

Psychological explanations of the placebo effect in clinical situations suggest a degree of classical conditioning attending the process of diagnosis, investigation and treatment (the therapeutic ritual), possibly mediated through immuno-endocrine mechanisms;[72] if the prior results of medical interactions and treatments have been positive, then a placebo effect may occur with future treatments, and the converse is true with nocebo effects for ineffective or poorly tolerated treatments.[59]

Anticipatory 'response expectancies',[66] analogous to rewards, are mediated through dopaminergic pathways in the mesolimbic and mesocortical systems.[72, 73] Expectation also favours anti-nociception,[74] variably.[75]

Patients may formulate positive predictive analogies after an initially positive encounter with a new clinician,[76] or responses to interventions that initiate both conditioning and expectation responses.[72] It is clear that verbal suggestion affects both placebo and nocebo responses[77]

Neurobiological mechanisms have been identified in the context of placebo analgesia,[78] due to naloxone-modifiable opioid[79, 80] and non-opioid dependent systems. Cholecystokinin (CCK) inhibits placebo analgesia, which is involved with nocebo hyperalgesia,[78] while its effect is reversed by the CCK antagonist, proglumide.[81] These mechanisms appear to operate locally rather than generally[82, 83] and can be verified by functional magnetic resonance imaging (fMRI)[84, 85] and PET scanning.[86]

Dopaminergic and opioid activity increases in the nucleus accumbens in association with some placebo effects; in contrast, nocebo effects are associated with a reduction in activity.[87] The prefrontal cortex has been found to exert an inhibitory influence on executive control, with placebo-related expectation responses stimulating this area of the brain, and neuronal degeneration in this area – as may occur in Alzheimer disease – leads to a loss of placebo responsiveness.[72] Although there is rostral processing of placebo responses demonstable by fMRI in the context of visceral

placebo analgesia,[88] not all processing occurs at the cortical level because it has been demonstrated that enhanced spinal cord responses invoked by nocebo are measurable in the ipsilateral dorsal horn at the appropriate dermatomal level.[89]

Other research indicates that oxytocin levels appear to be correlated with a state of trust; exogenous administration of oxytocin increases trusting behaviour in economic gaming situations,[90, 91] with ritual appearing to be central to this phenomenon.[92]

Genetic factors: Although it is generally acknowledged that one cannot identify typical 'placebo responders',[72] polymorphism of the serotonin transporter-linked polymorphic region and the tryptophan hydroxylase-2 gene promoter regions have been linked to placebo responses in those with social anxiety disorder,[93] and recent evidence suggests that those persons homozygous for the catechol-O-methyltransferase val158met polymorphism demonstrate more pronounced placebo responses than heterozygotes.[94]

These diverse, interrelated and arguably interdependent quantifiable mechanisms[95] may be invoked when we undertake patient care, thereby affecting the responses of patients to our treatments and cause a 'Hawthorne effect'.[96] Hence, it is appropriate to reflect upon how we, by the simple means of our agency, may affect our patients' treatment outcomes.

Discussion

Miller and Colloca suggest that that the 'placebo effect operates predominantly on illness rather than disease';[68] in other words the placebo effect manifests phenomenologically as a subjective manifestation of patient experience, whereas disease is an objective biological state. Recent research that provides some bio-physiological explanations of the placebo and nocebo effects suggest, however, that it is a mistake to simply designate certain patient experiences as a 'placebo effect' as this dissociates some possible results of therapeutic interventions from pathophysiological causality, thereby stigmatising these results as incredible and invalid alternatives to 'the deterministic claims of bio-medicine'.[97] This simply creates a false dichotomy in clinical practice.

Others, such as Grunbaum, have recognised that placebo effects are possible with any form of medical intervention, the so-called 'generic placebo notion'.[98] Thus, any medical interaction, any point at which a physician is present, may create placebo and nocebo effects – meaning it is not contradictory to be simultaneously a 'scientific physician and a walking placebo'.[99] Such bio-semiotic interpretations of the placebo effect[100] more clearly align with the notion of the 'meaning effect',[6] and the idea that aspects of patients' life experience might contribute to the production of placebo and nocebo effects.[101] For this reason, some have suggested that the term 'placebo effect' should be recast as a phenomenon determined by the 'psychosocial context or therapeutic environment on a patient's mind, brain, and body'[102] in which medical interventions may manifest with pleasing or displeasing results.

Although it has been poorly understood, the notion that patients' values, beliefs and expectations will influence the outcomes of treatment is familiar to many clinicians. To lay persons, the trope of a bitter but efficacious medicine[103] is culturally well understood,[104] and hence patients often anticipate adverse effects from effective treatments; the anticipation of benefit or harm has important psychological and neurobiological implications relevant to the nocebo effect.[105] Such misattribution responses are highly relevant to clinical medicine, as they are often the cause of treatment discontinuations.[106] Non-specific symptoms can be elicited from nearly 75% of unmedicated persons over a 3-day period.[107] Nearly 90% of persons receiving a placebo will report at least one biologically implausible, non-specific symptom.[108] These effects, and the patient who experiences 'side-effects' with all medications[109] are part and parcel of clinical practice.

Nocebo responses are contextualised,[110] potentially learnt or conditioned, and are dependent on negative expectation setting. Providing an exhaustive inventory of potential adverse effects in a

context irrelevant to the patient, while fulfilling the duty of truth telling, may not serve patients' best interests[110] as ‘mere information about potential harm is likely to be harmful in itself’.[111] Importantly, information about therapies is not simply provided by medical practitioners but is increasingly gained from different sources including friends, relatives, support groups and all forms of media. The Internet, for example, can be an important source of positive and negative information, and the patient may have already developed clear expectations about a treatment[111] on the basis of their prior enquiries.

While the placebo effect is an integral part of medical practice, unethical and deceptive uses of placebos, or the disingenuous use of impure placebos in clinical practice should be deplored.[68, 112] Unfortunately, deceptive use of active placebos, such as sub-therapeutic doses of antimicrobials, are commonly employed, as are impure placebos such as antibiotics or vitamins for coryzal illnesses.[9, 113] Patients may be deceived by experiencing adverse effects; using an impure placebo with actual adverse effects, even if mild, will amplify placebo responses. Taken together, the use of either a classic placebo or a real medicine in a placebo dose (or for an incorrect usage) can be considered an exploitation of the psychosocial context without the desire to administer a targeted biological therapy. This is, in fact, tantamount to administering a placebo, as it is the psychosocial context that is delivered alone, without the active treatment, and this is what constitutes a placebo; the delivery of the treatment ritual and context (through simulation), without the active treatment.

Ethical practice requires that we attempt to provide benefit and avoid harm to our patients. We recognise that our actions may have either effect, or both, and that these may operate through mechanisms outside of simple pathophysiological explanations. We might ask then, where is the harm in engaging in non-deceptive behaviours that may benefit our patients?

There are several clinician actions that might augment positive patient responses, without engaging in deception: speaking positively and truthfully about therapy; empowering the patient through encouragement and education; developing a compassionate, empathic and trusting relationship; reassuring the patient; reinforcing the importance of interpersonal relations; learning about the specifics of the particular patient; assisting the patient in exploring their own ideas and values about health and finally; creating ceremony and ritual to imbue the interaction with meaning and expectancy specifically relevant to the particular patient.[7]

Nocebo effects have particular importance in considerations of informed consent, and in the attribution of malign effects from medical interventions, although ‘information can be self fulfilling … humans have a tendency to perceive what they expect to perceive’.[110] The potential for a nocebo effect clearly is present when informing patients of the risks and benefits of treatment, there is a nexus between the moral and ethical duty to inform (and by informing, not to do harm), and these are relevant to the legal concept of informed consent operational in Australia, particularly in relation to explaining both obvious and material risks.[114, 115]

Given the existence and influence of a pervasive societal dialogue of risk that affects one's ontological security,[116] information regarding treatments derived from sources other than the practitioner must be appreciated and acknowledged,[111] but ultimately, the notion of contextualised consent should consider how much information a patient wishes to receive, recognising that this is an iterative process,[102] with a compromise between unfettered patient autonomy[117] and unjustified paternalism.[118]

Although it is enormously challenging to discuss the risks of therapy without creating anxiety and by invoking a nocebo effect precipitate the experience of adverse effects, it is possible to engage patients in conversations that respect autonomy, avoid undue paternalism and recognise that serious, material side-effects will be disclosed regardless.[119] However, explaining that the potential for, the expectation of, and resultant increased surveillance for, adverse effects can create a situation where the full benefits of treatment may not be realised, and misattribution of side-effects can lead to unnecessary treatment terminations.

Conclusions

The contextual elements of medical practice modulate clinical outcomes, and placebo and nocebo effects arise simply through the practice of medicine. Like climate change, this is something of an inconvenient truth, because it is undermines the rigid biomedical determinism that increasingly tends to characterise contemporary medical practice.

We suggest that, in their day-to-day practice, clinicians should be mindful that their presence in the therapeutic relationship has agency over and above the effects of the drugs they use or the procedures they perform. This is critically important because it is a reminder that the context in which medical care is delivered influences important patient outcomes including treatment adherence, the experience of adverse effects and the efficacy of care.

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