SCANDINAVIAN JOURNAL OF PRIMARY HEALTH CARE, 2016
VOL. 34, NO. 4, 428–433
http://dx.doi.org/10.1080/02813432.2016.1249065

Taylor & Francis
Taylor & Francis Group

DISCUSSION

OPEN ACCESS

Context as a drug: some consequences of placebo research for primary care

P. Lucassen[a] and F. Olesen[b]

[a]Department of Primary and Community Care, Radboud University Nijmegen Medical Centre, the Netherlands; [b]Research Unit for General Practice, Department of Public Health, Aarhus University, Aarhus C, Denmark

ABSTRACT

Objective: On the basis of emerging research evidence, this review aims to discuss the importance of the context surrounding the doctor–patient encounter for the success of treatment.
Design and setting: Discussion paper based on placebo–nocebo and pain studies conducted in the western world.
Main outcome measures: Literature-based theory about impact of communication elements on seriousness of symptoms in clinical practice.
Results: The therapeutic outcome seems to be impacted by rituals around a clinical encounter and by the doctor patient communication and relation. A warm, friendly and empathic attitude is crucial in the first contact with the practice and during the consultation as it influences the patient's perceived outcome. It is important to raise positive expectations when discussing the prognosis, conducting treatment and prescribing medications as the effect may be reduced if the physician expresses doubt about the effectiveness of the medication. Additionally, overly focus on side effects in the doctor–patient conversation about proposed treatments seems to influence the magnitude of perceived side effects in the patient. Thus, shared decision-making might be a desirable tool for ensuring better expectations in the patient and successful symptom relief.
Conclusions: The context of the doctor–patient interplay matters. Placebo–nocebo research provides strong evidence for this link. The therapeutic context induces biomedical processes in the patient's brain that may enhance or reduce the effects of chosen interventions. The context thus works as a drug, with real effects and side effects.

KEY POINTS

- Increased awareness of the context drug may help GPs alleviate symptoms and better motivate patients for treatment.
- Treatment is affected by multiple types of context, as also confirmed by placebo–nocebo research.
- The therapeutic context influences the biomedical processes, which may enhance or reduce intervention effects on symptoms.
- The impact of context should be considered in daily general practice as it may serve as a drug, with real effects and side effects.

ARTICLE HISTORY
Received 25 May 2016
Accepted 15 August 2016

KEYWORDS
Placebo; nocebo; context; doctor–patient relation; symptoms; shared decision-making; general practice; Denmark

Prologue

There are these two young fish swimming along, and they happen to meet an older fish swimming the other way, who nods at them and says, "Morning boys. How's the water?" And the two young fish swim on for a bit, and then eventually one of them looks over at the other and goes, "What the hell is water?" (*David Foster Wallace*).[1]

Introduction

In primary care, our work is to diagnose and treat patients. We use focussed questions and provide targeted treatment; we prescribe drugs, we give injections, we propose referrals. This is the core of what we have learned when we qualified as general practitioners (GPs), and this toolbox has brought us great success. However, we tend to forget that each treatment is conducted in a specific context.

As the fish may forget the importance of the water, we may forget the role of the context in which our activities take place. Think about the context in the GP's consultation room or the context around a surgical procedure, for instance an arthroscopy.[2] Here, we shall define context as the strength of the relation in

CONTACT P. Lucassen peter.lucassen@radboudumc.nl Radboud University Nijmegen Medical Centre, Department of Primary and Community Care, PO Box 9101, 6500 HB Nijmegen, the Netherlands

the meeting between the doctor and the patient, and the environment in which specific interventions are applied to the patients. Thus, by context, we mean the doctor–patient relation, the different rituals around treatment and the total environment surrounding the doctor–patient encounter.[3,4]

Context has received increasing attention over the last decades. For example, Di Blasi et al. concluded 15 years ago that "one relatively consistent finding is that physicians who adopt a warm, friendly and reassuring manner are more effective than those who keep consultations formal and do not offer reassurance".[5] Likewise, in the field of psychotherapy, Wampold showed that contextual factors such as empathy, alliance, collaboration and goal consensus often exceeded the effects of the specific ingredients of treatments.[6]

Our initial interest for performing the current analysis was sparked by the emerging evidence of the importance of context, particularly from placebo–nocebo research. Although this new evidence may have great importance in clinical general practice, the results from this line of research tend to go unnoticed; this is probably because placebo use is often linked with deception,[7] because of the confusion around the concepts placebo and placebo effects and because the role of placebo is generally restricted to randomized controlled trials as a means to control for bias.[8]

We have known for a long time that symptoms can be alleviated by drugs, for instance pain killers. The new research shows that symptoms, which are always processed emotionally and/or cognitively before they are perceived, can also be heavily modified by the context around the treatment. The effect of context often exceeds the effect of the specific treatment, and a recent meta-analysis suggests that both context and specific effects should be reported in future clinical trials on symptom alleviation.[9] Another important new finding is that the effect of the context can be seen in different types of brain scans, and we now know that the effect is mediated through biomedical processes and transmitters in the brain.[8] Context is not deception; the biomedical effect is now well proven.

We will here present important findings from recent research in this field and discuss their usefulness in different phases and aspects of the primary care consultation. These findings are based on a search of the literature with the text words "placebo" and "nocebo". This yield of this search was enriched with articles found by checking references of retrieved publications.

Results

Ensuring a supportive atmosphere

Placebo research has contributed significantly in evidencing the impact of the atmosphere in the clinical consultation. A randomized controlled trial, including 262 adult patients with irritable bowel syndrome (IBS), compared patients allocated to the waiting list with two other groups of patients; both groups were treated with sham acupuncture.[10] In the first group (limited interaction), the therapist carried out the procedure in limited interaction with the patients; the therapist introduced himself shortly, stated that "he knew what to do" and that he had been "instructed not to converse with patients". He placed the sham needles (blinded for the patient, who was unaware that it was not real acupuncture) and left the room for 20 min. In the other group (augmented interaction), the therapist discussed symptoms and consequences of IBS with patients and did so in a warm, friendly and emphatic manner while providing positive expectations about the results of the procedure. The patients in the augmented interaction group scored better on all outcomes. For example, 62% experienced adequate relief compared to 44% in the limited interaction group and 28% in the waiting list group.

Several studies have compared the effect of sham acupuncture with real acupuncture, including traditional Chinese acupuncture.[11] In general, they all conclude that symptoms are alleviated, but no difference is found between real and sham acupuncture; this indicates that it is the acupuncture ritual that mediates the effect, and this effect can be seen in brain scans.[8] Similar results have been demonstrated in a randomized controlled trial (RCT) including 77 rheumatoid arthritis patients. This RCT showed that homeopathic consultations, but not homeopathic remedies, were effective in improving pain management, objectively assessed swollen joint count and mood.[12] Homoeopathic consultations were highly patient-centred and individualized, and patients had ample time to discuss relevant issues.

This is in line with what is generally witnessed by experienced clinicians in general practice: a warm, friendly and empathic attitude and a professional behaviour around procedures is not only important during the consultation; it is also crucial in the first contact with the practice as this contact may be determinant for the success or failure of an encounter and the patient's perceived outcome of treatment.

Being positive

Expectation is considered to be one of the main mechanisms by which the placebo effect exerts its influence. Already in 1987, Thomas showed that a "positive consultation", that is, the patient has been given a firm diagnosis and been told that s/he would be better in a few days, effectively influenced the outcome.[13] In a study of the effectiveness of acupuncture in 455 patients with osteoarthritis of the knee, patients in the high expectations group (therapist saying, "I think this will work for you") had significant improvements in pain and satisfaction compared with patients in the neutral expectations group (therapist saying, "It may or may not work for you" or "It really depends on the patient").[14] A meta-analysis of 27 studies confirmed the effectiveness of raising expectations on pain relief.[15] It showed that verbal suggestions ("This treatment is effective") have a significant and large effect (effect size: 0.75) on patients' pain relief. Recent research has even shown that pain alleviation during surgical procedures, such as arthroscopy for arthrosis, is largely a context-mediated effect connected to expectation and the treatment ritual.[2]

Being positive and raising positive expectations is important during the consultation when the GP discusses the prognosis with the patient and when s/he prescribes medication. Obviously, in daily practice, it is not always possible to be positive, but GPs should be aware of when to be positive and to use this awareness consciously.

Analogous to the findings that positive expectations give better outcomes (placebo effect), negative expectations tend to result in worse outcomes (nocebo effect). In a study with 22 healthy volunteers, experimentally induced heath pain was blocked with a potent opioid agonist consisting of remifentanil in different expectancy conditions: no expectancy, positive expectancy (suggestion of analgesia) and negative expectancy (suggestion of hyperalgesia), all induced by verbal suggestions.[16] Positive expectancy enhanced (doubled) the analgesic effect, whereas participants in the negative expectancy group experienced no analgesic effect. Meta-analyses show that the magnitude of this nocebo effect in clinical practice is variable; sometimes small,[17] sometimes considerable (effect size: 0.62–1.03).[18]

These findings suggest that physicians may (possibly unknowingly) reduce the effect of their prescriptions by expressing doubt about the effectiveness of the medication.

Nocebo effects are frequently the unintended consequences of negative suggestions. Hauser provided an interesting list of short sentences with negative suggestions causing uncertainty ("This medication may help"), ambiguity ("We'll just finish you off" as preparation for surgery), emphasizing the negative ("That always hurts a lot"), focusing attention ("Are you feeling nauseous?") or ineffective negation and trivialization ("It's just going to bleed a bit"); sometimes the use of jargon provokes nocebo effects ("We looked for metastases – the result was negative").[19]

The influence of positive and negative suggestions has been amply demonstrated in patients with pain. There are, however, indications that the placebo and nocebo effects induced by verbal suggestion also apply to patients with itch,[20] fatigue, nausea and hypokinesia in patients with Parkinson's disease.[8]

Giving information

GPs often give information, for example about adverse effects or about expected pain, before a procedure involving injections. Many GPs perform minor surgical interventions, such as treatment of an ingrowing toenail or removal of a sebaceous cyst involving subcutaneous injection of a local anaesthetic. Most physicians will warn their patient just before the needle pierces the skin. But does this warning help patients? Is the phrase "You will feel a big bee sting; this is the worst part" a good one just before the local injection? Varelman tested this in 140 healthy pregnant women at term gestation requesting epidural anaesthesia. The women were randomized to a group receiving the "bee sting" phrase and a group being told that "we are giving you a local anaesthetic that will numb the area, and you will be comfortable during the procedure". The pain score immediately after the procedure was 5 (scale: 0–10) for the bee sting phrase and 3 for the gentler words ($p < 0.001$).[21] Warning the patient for pain or other undesirable experiences and sympathizing with the patient during painful experiences does not – contrary to common belief – make patients feel better. Instead, patients are generally more distressed.[22]

Information about adverse effects of prescribed medicines is part of the regular consultation and considered necessary because the patient has the right to know. We consider this an element of good practice, but is it always appropriate? We may induce aggravated side effects of drugs by expressing concerns about side effects. It makes a difference when the GP says to patients with benign prostatic hyperplasia, "You will receive a drug with proven effectiveness" rather than "You will receive a drug with proven effectiveness; it sometimes has adverse effects, such as

erectile dysfunction, decrease of libido or problems with ejaculation, but these side effects are rare". More than 40% of patients in the second group experienced side effects compared to 15% in the first group.[23] So, words do harm! Another example is from patients with unstable angina pectoris who were prescribed aspirin. In one centre, they received a leaflet without information about gastrointestinal side effects. In two centres, the leaflet contained information about gastrointestinal side effects of aspirin; for example, "Side effects are not anticipated beyond occasional gastrointestinal irritation". Significant differences were found between these groups. The frequency of major gastrointestinal side effects was not significantly different, but the frequency of minor gastrointestinal side effects was (16% in the no information group versus 44% in the information group). Moreover, the number of dropouts because of gastrointestinal side effects was six times higher in the information group.[24]

The decision of giving no information about side effects is a difficult one. There is substantial overlap between symptoms that are most commonly experienced in the community and symptoms that are most often reported as side effects.

The strength of the GP's focus on side effects in the conversation about proposed treatments heavily influences the degree of the perceived side effects in the patient.

Sharing decision-making

Although shared decision-making is undisputed in this era of patient-centred medicine, placebo–nocebo research provides additional evidence for why shared decision-making should be promoted. Involving patients in the decision-making may modify their expectations in a positive way, as also confirmed in a study by Bartley et al. [25] Sixty-one university students were randomly assigned to two groups: a choice group and a no-choice group. The participants were told that the purpose of the study was to examine the effectiveness of two types of beta-blocker medication on pre-examination anxiety called Muprolol and Metotrol; both were placebos. All participants obtained information on both types of beta-blockers concerning mechanism of action, effects on the body and potential side effects. All participants were then asked to indicate their preference for one of the two beta-blockers. After this procedure, the participants were randomized; participants in the choice group took their preferred beta-blocker, participants in the no-choice group were randomly assigned to a beta-blocker. Before the test procedure (i.e. three cognitive tests to simulate an exam), the researchers measured their pre-exam anxiety. After the test procedure, questionnaires were completed about physical symptoms, side effects and level of anxiety. Participants in the choice group had an increased placebo effect (greater heart rate reduction), whereas participants in the no-choice group had an increased nocebo effect (more side effects of the medication). This effect of choice on outcome is particularly relevant in people who desire control over treatment alternatives.[26]

These findings add evidence to the effectiveness of shared decision as a tool to raise better expectations and thereby promote better symptom relief. Yet, we should also realize that not every patient wants to be involved in the decision-making. Rather, forced involvement might introduce anxiety and nocebo effects.

Our understanding of the context may help us better understand and treat patients with medically unexplained symptoms (MUS), a group of patients which is often seen in general practice. The most severely affected MUS patients have many serious symptoms. A common hypothesis is that the handling in the brain of bodily sensations is disturbed in these patients and that biomedical processes in the brain enhance or diminish the perception of symptoms from the body.

The placebo–nocebo research shows that context can considerably modify symptom perception in the normal brain, but many questions still remain unanswered. Do patients with MUS have a disturbance in the brain processes that can be influenced by context effects? And does this serious disturbance impact the way the brain filters symptoms before they are perceived? We know that treatment of MUS aims at readjusting these processes.[27]

As stated earlier, we are now able to visualize the described medical placebo and nocebo effects by new types of brain scans. We also know more and more about the transmitters involved in the symptom-modifying processes, but a detailed description of the underlying biomedical mechanisms is outside the purpose of this paper.[3,8]

Conclusions and implications

The quality of the doctor–patient relations does matter. Words matter. Choices matter. Expectations matter. Atmosphere and behaviour matters. One could also say: context matters. Placebo–nocebo research provides strong evidence for this link.

The therapeutic context induces processes that enhance or reduce the effects on symptoms of our interventions (drugs, surgery or cognitive behavioural therapy).[4] We must learn to use this context

consciously in daily general practice because it works as a drug with a strong influence on the magnitude of perceived symptoms and this "drug" has real effects and real side effects. Physicians using the context drug will be more effective in alleviating symptoms and motivating patients to rely on a beneficial natural course of many symptoms.[4]

The new research shows that it is due time to create a renaissance for the value of the personal doctor, who is well aware that s/he induces effects that can be biomedically detected and clinically measured. Placebo–nocebo research is context-based research,[4] and context is the water in which we administer specific treatments. We should be more aware of the quality of our water.

Acknowledgements

We would like to thank Lone Niedziella for her linguistic help.

Ethical approvals

According to Dutch and Danish legislation, approval by an ethical committee is not required.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding

The work was supported by the Research Unit for General Practice, Department of Public Health Aarhus University.

References

[1] Loxterkamp D. Complicating relationships; the water that doctors breathe. BMJ. 2015;351:h4185.
[2] Harris I. Surgery, the ultimate placebo: a surgeon cuts through the evidence. Sydney: New South Books; 2016.
[3] Finniss DG, Kaptchuk TC, Miller F, et al. Biological, clinical, and ethical advances of placebo effects. Lancet. 2010;375:686–695.
[4] Olesen F. Beyond the placebo: understanding the therapeutic context. Br J Gen Pract. 2015;65:6–7.
[5] Di Blasi Z, Harness E, Ernst E, et al. Influence of context effects on health outcomes: a systematic review. Lancet. 2001;357:757–762.
[6] Wampold BE, Imel ZE, The great psychotherapy debate. The evidence for what makes psychotherapy work. New York: Routledge; 2014.
[7] Bishop FL, Howick J, Heneghan C, et al. Placebo use in the UK: a qualitative study exploring GPs' views on placebo effects in clinical practice. Fam Pract. 2014;31:357–363.
[8] Benedetti F. Placebo effects. Oxford: Oxford University Press; 2014.
[9] Zou K, Wong J, Abdullah N, et al. Examination of overall treatment effect and the proportion attributable to contextual effect in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis. 2016;75:1964–1970.
[10] Kaptchuk T, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ. 2008;336:999–1003.
[11] Cherkin DC, Sherman KJ, Avins AL, et al. A randomized trial comparing acupuncture, simulated acupuncture, and usual care for chronic low back pain. Arch Int Med. 2009;169:858–866.
[12] Brien S, Lachance L, Prescott P, et al. Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: a randomized controlled trial. Rheumatology. 2011;50:1070–1082.
[13] Thomas K. General practice consultations: is there any point in being positive? Br Med J (Clin Res Ed). 1987;294:1200–1202.
[14] Suarez-Almazor ME, Looney C, Liu Y, et al. A randomized controlled trial of acupuncture for osteoarthritis of the knee: effects of patient-provider communication. Arthritis Care Res (Hoboken). 2010;62:1229–1236.
[15] Peerdeman KJ, van Laarhoven AI, Keij SM, et al. Relieving patients' pain with expectation interventions: a meta-analysis. Pain. 2016;157:1179–1191.
[16] Bingel U, Wanigasekera V, Wiech K, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011;3:70ra14.
[17] Mistiaen P, van Osch M, van Vliet L, et al. The effect of patient-practitioner communication on pain: a systematic review. Eur J Pain. 2016;20:675–688.
[18] Petersen GL, Finnerup NB, Colloca L, et al. The magnitude of nocebo effects in pain: a meta-analysis. Pain. 2014;155:1426–1434.
[19] Hauser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. Dtsch Arztebl Int. 2012;109:459–465.
[20] Bartels DJ, van Laarhoven AI, van de Kerkhof PC, et al. Placebo and nocebo effects on itch: effects, mechanisms, and predictors. Eur J Pain. 2016;20:8–13.
[21] Varelmann D, Pancaro C, Cappiello EC, et al. Nocebo-induced hyperalgesia during local anesthetic injection. Anesth. Analg. 2010;110:868–870.
[22] Lang E, Hatsiopoulou O, Koch T, et al. Can words hurt? Patient-provider interactions during invasive procedures. Pain. 2005;114:303–309.
[23] Mondaini N, Gontero P, Giubilei G, et al. Finasteride 5mg and sexual side effects: how many of these are related to a nocebo phenomenon? J Sex Med. 2007;4:1708–1712.
[24] Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects. Clin Pharmacol Ther. 1987;42:250–253.

[25] Bartley H, Faasse K, Horne R, et al. You can't always get what you want: the influence of choice on nocebo and placebo responding. Ann Behav Med. 2016;50:445–451.

[26] Geers AL, Rose JP, Fowler SL, et al. Why does choice enhance treatment effectiveness? Using placebo treatments to demonstrate the role of personal control. J Pers Soc Psychol. 2013;105:549–566.

[27] Kuzminsky R, Impaired sensory processing in patients with multiple functional somatic symptoms [PhD thesis]. Aarhus: Faculty of Health Sciences, University of Aarhus; 2008.