

Placebo effects in children

“...placebo effects in medicine in children do follow similar rules than in adults and may – even if not larger in effect size – be easier to elicit and may have long-lasting effects throughout life.”

Keywords: adolescents • children • doctor–patient relationship • placebo effects • trials

Placebo effects play a central role in medicine, whether in clinical routine in private practice or in a hospital setting, or during a clinical trial – with or without placebo application – or even without a doctor or other healthcare professional being around physically. Placebo effects are an immanent component of all and any treatments of any disease or condition [1].

As we do know that expectancy and especially learning play a crucial role in generating placebo effects, an interesting question arises with respect to placebo effects in children [2]: does less learning experience on the one hand, but higher learning capacity on the other hand result in lower or higher placebo responses in children compared with adolescents, and in adolescents compared with adults?

Placebos in clinical studies

In randomized, placebo-controlled trials of novel drugs and other interventions that included children, response rates in the placebo arm were reported to be higher in children compared with adolescents and adults, for example, for attention-deficit hyperactivity disorder, in epilepsy and in depression [2], while drug effects usually are reported to be similar between children and grown-ups. However, across all medical conditions age-related differences in the placebo response in trials have only been found for a few diseases [3].

Despite such differences in effect sizes, it can in general be assumed that the placebo responses are mediated by similar mechanisms in children and adults, that is, learning

and expectations. It has been shown that placebo responses may also be learned by social learning (observation of effective treatment in others) [4], and it is well established that such social learning also contributed to the type and severity of symptoms within families [5].

It can be questioned whether children below age 12 years truly understand the concept of giving a placebo during a randomized controlled trial, or the applied drug : placebo ratio. Children appear to assume in general that they will receive the drug rather than placebo irrespective of the true probability to receive placebo in the trial [6]. It has also been noted that study unblinding occurs more frequently because of the observation of children by their parents. Rather than via own expectations, children respond to the expectation (and subsequent behavior) of their parents. Therefore, the time spend with the doctor during a treatment trial may well be a predictor of the size of the placebo response in adults, but not in children [7]. It has not yet been shown that the amount of contacts between parents and physicians determines the size of the placebo response of pediatric patients.

The concept that expectations and experiences of others (parents, siblings, relatives, friends) rather than ones own expectations generate the placebo response, has been called ‘placebo by proxy’ [8]. It should, however, be noted that improvement reports noted by proxies should not be mixed up with reports noted by the patient himself or herself, even and especially in case of children: it may well be that patients or teachers change their



Katja Weimer
University Hospital, Department of Internal Medicine VI: Psychosomatic Medicine & Psychotherapy, Tuebingen, Germany



Paul Enck
Author for correspondence:
University Hospital, Department of Internal Medicine VI: Psychosomatic Medicine & Psychotherapy, Tuebingen, Germany
paul.enck@uni-tuebingen.de

expectations in response to a treatment, subsequently alter their behaviors, and this in turn alters the child's behavior that – falsely – is attributed to the medicinal intervention.

Placebo research in children

Except for the conductance of placebo-controlled trials that are occasionally done in children – frequently, head-to-head trials (comparative effectiveness research) are preferred for ethical reasons – genuine placebo research is rarely done in children for obvious reasons: placebo experiments usually include deceptive procedures (false information given) and while this may be acceptable in adults under certain circumstances (intellectual ability to understand the reasoning when disclosed after the experiment) children (as well as other persons with limited abilities to agree in experiments) may not be able to appreciate why such deception is necessary, and are therefore under specific protection of law and ethics, as is acknowledged in the Declaration of Helsinki. Even ‘authorized deception’ that may be an ethically acceptable procedure and has been shown to not affect the outcome of experiments [9] is not easy to employ in pediatric experiments because of the need to debrief after the experiment.

“...the model of social learning of adequate coping with symptoms following diagnostic or therapeutic manipulations may be easiest to install when using familiar models...”

When performed in direct comparison, placebo analgesia has been shown to be equally effective in children, adolescents and adults, arguing against the evidence of higher placebo response rates in children that were demonstrated in some clinical conditions [2]. However, little is known about the operating mechanisms, and it is still to be elucidated whether this holds true for all other clinical and nonclinical conditions that are simulated in experiments. Such experiments would also need to explore whether and to what degree expectations of parents and other proxies do influence these placebo responses.

Placebos in clinical routine

Beyond the use and usefulness of placebo effects in medical and experimental conditions, for utilizing and maximizing the placebo effect in everyday medical routine it may be of advantage if children would exhibit higher placebo response rates than adults. For one, many parents (and presumably also many pediatricians) provide homeopathic medicines to children that are in our opinion pure placebos. By doing so, they utilize the placebo effects for minor and mild diseases and conditions that otherwise would be treated with more invasive

drugs that produce adverse events. Parents also interrupt for chronic medication intake of their children, for example, for attention-deficit hyperactivity disorder at weekends, and rely – maybe even without knowing – on the conditioning and partial reinforcement procedures after repetitive drug–placebo cycles [10]. Unfortunately, this holds also true for other (in-pure) placebos given frequently in children, for example, the use of antibiotics in viral infections. Finally, the model of social learning of adequate coping with symptoms following diagnostic or therapeutic manipulations may be easiest to install when using familiar models, for example, parents, siblings, friends and peers, instead of unfamiliar ones, but this may not be a *conditio-sine-qua-non* [11].

Placebo effects may also be implemented and improved with strategies to optimize patients' expectations via cognitive strategies:

- Developing a positive outlook on treatment results that should however be realistic with respect to timing and extend, since too high expectations may provoke disappointments;
- Allow positive learning experiences, and strengthen and reinforce goals already reached, thereby enhancing self-efficacy and the feeling of having reached ones own goals with ‘internal’ resources;
- Provide positive models, for example, during treatment of groups of patients with similar conditions or by demonstrating efficacy via video or internet streaming. Also, verbal reports of other patients may be helpful;
- Create rituals, for example, by repeating behaviors to allow stimulus-response pattern to develop, such as during Pavlovian conditioning. This will enhance the belief that similar responses will be evoked in the future.

In summary, placebo effects in medicine in children do follow similar rules than in adults and may – even if not larger in effect size – be easier to elicit and may have long-lasting effects throughout life. Their exploration in experimental research and their utilization in everyday medicine are still at an early stage.

Financial & competing interests disclosure

The paper was supported by a grant from Deutsche Forschungsgemeinschaft. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- 1 Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? *Nat. Rev. Drug Discov.* 12, 191–204 (2013).
- 2 Weimer K, Gulewitsch MD, Schlarb AA, Schwille-Kiuntke J, Klosterhalfen S, Enck P. Placebo effects in children: a review. *Pediatr. Res.* 74, 96–102 (2013).
- 3 Weimer K, Colloca L, Enck P. Age and sex as moderators of the placebo response – an evaluation of systematic reviews and meta-analyses across medicine. *Gerontology* doi:10.1159000365248 (2014) (Epub ahead of print).
- 4 Colloca L, Benedetti F. Placebo analgesia induced by social observational learning. *Pain* 144, 28–34 (2009).
- 5 Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. *Gastroenterology* 121, 799–804 (2001).
- 6 Rothner AD, Wasiewski W, Winner P, Lewis D, Stankowski J. Zolmitriptan oral tablet in migraine treatment: high placebo responses in adolescents. *Headache* 46, 101–109 (2006).
- 7 Rutherford BR, Sneed JR, Tandler JM, Rindskopf D, Peterson BS, Roose SP. Deconstructing pediatric depression trials: an analysis of the effects of expectancy and therapeutic contact. *J. Am. Acad. Child Adolesc. Psychiatry* 50, 782–795 (2011).
- 8 Grelotti DJ, Kaptchuk TJ. Placebo by proxy. *Brit. Med. J.* 343, d4345 (2011).
- 9 Martin AL, Katz J. Inclusion of authorized deception in the informed consent process does not affect the magnitude of the placebo effect for experimentally induced pain. *Pain* 149, 208–215 (2010).
- 10 Enck P, Klosterhalfen S. Placebo mechanisms for drug dose reduction: what is the evidence? *Clin. Invest.* 2, 1069–1071 (2012).
- 11 Hunter T, Siess F, Colloca L. Socially induced placebo analgesia: a comparison of a pre-recorded versus live face-to-face observation. *Eur. J. Pain* 18(7), 914–922 (2014).