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Pain and placebo in pediatrics: A comprehensive review of laboratory and clinical findings

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Abstract

Pain modulation by placebo mechanisms is one of the most robust and best-studied phenomena, yet almost all research investigating the mechanisms and implications of the placebo analgesia are based on adult research. After highlighting crucial aspects that need to be considered in studying pain modulation in children, this comprehensive review examines studies related to pain modulation with an emphasis on factors such as age, neural development and pain measures. Psychological mechanisms underlying placebo effects including: 1) verbally-induced expectations; 2) conditioning and learning mechanisms; 3) child-parent-physician interactions are critically discussed. Taken together, research suggests that placebo mechanisms can impact therapeutic outcomes and potentially be exploited clinically to improve clinical outcomes in pediatric population. Recommendations for further investigating the mechanistic bases and harnessing placebo effects for supportive therapeutic applications are given.

Keywords

Age; Analgesia; Children; Clinical applications; Conditioning; Development; Expectations

Laboratory research on placebo effects has provided extensive evidence about mechanisms underlying these neuropsychosocial phenomena, which produce behavioral changes and

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potentially pain and other symptom improvement [13; 28; 22; 14]. Placebo research, defined as the investigation of the mechanisms underlying suggestive and conditioned healing processes [14], has been mostly done in adults and it remains unclear how and to what extent children form placebo effects [9; 77]. On one hand, there is evidence from clinical studies that placebo responses are present in a variety of pediatric conditions including Attention-deficit hyperactivity disorder (ADHD) [65], asthma [5], atopic dermatitis [67], seasonal allergic conjunctivitis [51]; autism [38], depression [12], epilepsy [60], functional gastrointestinal conditions [66], chronic fatigue syndrome [62], hypertension [68], migraine [69], and syncope [64]. On the other hand, it is important to understand whether the placebo mechanisms that have been explored so far are uniquely important for adults as opposed to children. In adults, placebo analgesia occurs via anticipation of pain relief, first-hand analgesic experiences via conditioning, observing pain reliefs in others and interpersonal interactions [15]. Verbal suggestions of benefit (e.g. reduction of pain) induce positive expectations (e.g. analgesia) that can activate top-down mechanisms and culminate in outcome improvements. Typically, in adults, direct experience of benefit via conditioning induces stronger placebo analgesic effects as compared to verbal suggestions alone [18; 19; 17]. When conditioning paradigms involve repetitive exposure to pharmacological treatments, a placebo given after painkillers (e.g. morphine, ketorolac) produces effects mirroring the behavioral and therapeutic changes associated with the drug administration in both humans and animals. Interestingly, observation of a benefit in another person produced placebo effects that are similar to those induced by directly experiencing the benefit. Broadly, psychosocial cues and the entire set of interpersonal interactions (e.g. parents, peers, or proxy) contribute to induce expectations and potentially recall memories of analgesia. Although placebo effects by proxy are based on reports of parents and may reflect report bias rather than real benefit in the children, the phenomenon by which physician–child–parent interactions triggers placebo mechanisms is relevant for clinical outcomes [16; 49; 3]. In this paper, we discussed methodological aspects related to pain modulation in early stage of life and primarily reviewed studies related to pain modulation with an emphasis on factors and psychological mechanisms triggering placebo analgesia. We briefly compared placebo analgesic effects with other conditions and finally, we identified gaps in current knowledge about placebo effects in pediatrics.

Methodological considerations

When considering a complex psycho-neurobiological phenomenon such as the placebo effect as opposed to a disease process, it is important to take account of the fact that age and neural development not only impact enormously upon overall cognition [44] but also on nociception, pain experience and measurement. Infants and children respond to noxious stimulation from birth (and before birth [26]) and nociceptive and pain responses derive from neural development at different levels of the central nervous system. In fact, nociceptive activity produces reflex movements, autonomic and metabolic responses that are distinct from the pain experience characterized by sensorial, discriminative and affective components arising from neural activation of brain central regions. In this review, we discuss both nociceptive and pain responses starting with infants to first years of childhood

to adolescence by presenting studies of conditioned nociception in infants as well as studies on verbally-induced expectations in children and adolescents.

At the heart of all the pain and placebo studies discussed in this review is the issue of how pain (or reduction of pain) is measured over the age ranges tested. Pain is an elusive experience that poses unique measurement challenges. For adults, pain measurement usually consists in verbal reports of the individual temporal, spatial and emotional pain experience. In infants, the impossibility to communicate verbally might preclude the assessment of pain experience. A broad variety of pain measures has been developed and validated and observational pain scoring in children differs greatly with age, from infancy through the first years of childhood [47]. Self-report of pain can be obtained in children age 3 years and older, though establishing whether children are able to understand and use the self-report scales can be difficult. However, when it is obtainable, self-report is widely considered the main source of pain experience and takes priority over observation, reports by proxies including family members, biochemical and cortical markers, as well as clinician observation. Parental reports can be flawed and in conflict with children reports. Parental expectancies have also a significant influence on both reports of child behavior and parent-child interactions. For example, manipulation information provided to the mothers who believed their sons to be behaviorally “sugar sensitive” changed mothers’ perceptions of behavior [34]. Children were given a sweet but sugar-free drink and the mothers’ perceptions of behavior, physical activity of the child (using wrist and ankle actometers) and mother-son interactions were assessed. Mothers who were incorrectly informed that their sons had ingested sugar rated them as more hyperactive and less compliant than those provided with accurate information [34]. Relationships between subjective and objective measures are often low, with subjective measures typically showing greater improvements in situations where parents have positive expectancies for outcomes (for a review, see ref. [76]). Finally, in determining a placebo effect, confounding factors such as regression to the mean, report biases and natural history need also to be factored out in determining the presence and magnitude of placebo effects (for a review, see [13; 28]).

Psychological mechanisms

Verbally-induced placebo effects

Suggesting to a child that a treatment (actually a dummy treatment) is going to relieve his or her pain can cause the child to believe that the treatment is effective, expects analgesia and potentially activate top-down placebo analgesic mechanisms. Suggestibility can influence expectations and therefore, placebo effects. The degree of suggestibility appears to be modulated by age. Approximately 80% of children are considered suggestible compared to 15% in the adult population [55]. Although suggestibility levels remain high throughout the elementary school years [10], 8 year old children are more suggestible by the influence of adults compared to 12 year old children [53]. However, adults with higher suggestibility traits are prone to form larger placebo responses. In adults, individual differences in suggestibility contribute significantly to the magnitude of behavioral [20] and brain placebo analgesic responses [35].

Krummenacher and colleagues have recently compared the impact of suggestions on pain perception and placebo analgesia in healthy children and adults in a heat-pain paradigm. Half of the 49 healthy right-handed children aged from 6 to 9 years stratified for magical thinking [61] and gender were randomly assigned to verbally-induced expectation group or a control condition (Krummenacher et al.[42]). The placebo cream was a blue hand disinfectant and children were told that the cream was a painkiller that would alleviate the painful heat sensation. Pain sensation was assessed using the Faces Pain Scale-Revised, a common metric in pediatric pain measurement [33] showing face expressions ranging from no pain (smiling) to maximum pain (crying). The findings demonstrated that verbal suggestions induce significant placebo analgesic responses on tolerance and threshold pain levels with girls being more placebo-responsive for heat pain threshold in relation to the control group [42]. The magnitude of these effects was overall more than 5 times (heat pain tolerance) and 3 times (heat pain threshold) larger than those found in healthy adults in a recently published similar heat pain paradigm [41].

Two studies have further illustrated the contribution of verbally-induced expectations to enhance placebo analgesia and improve clinical pain outcomes in pediatrics.

Children with cancer were studied for potential benefit of EMLA, a eutectic mixture of lidocaine and prilocaine, given prior lumbar puncture [36]. Twenty-eight children were enrolled in either an open crossover study comparing EMLA versus no treatment (5-15 year old) or a double-blind placebo controlled study (4.5-11 year old). Children and nurses who scored the pain were either outright informed by the provider that they were receiving an analgesic medication (open-label) or were unaware, as was the provider, if they were receiving active medication or placebo (double-blind manner). Pain was assessed using a 100 mm VAS as well as a VAS showing face expressions ranging from no pain (smiling) to maximum pain (crying). There was no correlation between patients' ages and pain scores. Children and nurses overtly informed about the analgesic medication showed net analgesic benefit as compared to no treatment with EMLA reported to be invariably effective. By contrast, those who received active analgesic medication in a blinded manner showed lower analgesic effects with two cases in which EMLA was scored lower than placebo by both children and nurses. These findings suggest that expectations boost the intrinsic actions of the analgesics but also the necessity of having placebo-randomized controlled studies in children [36].

In another study, 117 children aged from 3 to 17 years, stratified by age (3-7, 8-11, 12-17), received needle venipuncture along with an inert cream and they were either told that the cream would help reduce the needle pain or were not told anything. A control group received no cream (natural history group) [31]. The placebo cream was a disinfectant, odorless, thick, white foam hand-wash with no anesthetic properties. Pain was measured with a face pain scale. The child was asked to choose which of the series of seven faces best predicted the level of pain he/she would feel from the needle and expected pain was assessed before the procedure. After the venipuncture, each child was asked how much pain he/she felt during the venipuncture. Eighty-three percent of the children who were told that the cream would help alleviate pain stated that they believed it did, while only 33% of those told nothing believed that cream alleviated pain. Children's pain self-reports tended to be lower

for both the two placebo cream groups relative to the natural history group but no difference between the group receiving cream plus suggestion and cream alone was found. Using a placebo cream might have reduced child's expectation of pain and anxiety with a potential beneficial clinical outcome. A video was taped beginning immediately after the cream application and ending after the needle was removed without including the phase in which children were given their self-report of pain. An observer blind to the placebo intervention of the design and procedures rated each child's pain behaviors. The observer reported less pain-related behaviors in the group of children who were told they were given an analgesic cream [31].

Further studies are necessary to understand how these behavioral effects are underpinned by distinct neural developmental substrates.

Conditioning and learning mechanisms

Developmental age is intimately related to placebo mechanisms. Verbally-induced placebo effects are likely going to become more effective with increasing age, whereas conditioned analgesic and hyperalgesic responses are likely to be present in early stages of life and be a much stronger feature of infancy.

Notably, we found several studies in infants suggestive of conditioned positive and negative effects. For example, a case study of an infant with complex cardiopathy and agenesis of the trachea demonstrated that repeated, frequent bronchoscopies performed under the effects of midazolam and fentanyl, yielded a conditioned analgesic response. After 61 bronchoscopies, each performed by the same clinician, it was found that neither medication was needed being that the patient indicated no signs of distress. Further, the infant began demonstrating compliant behavior by positioning her body to receive treatment and anticipating the treatment by watching the movement and preparation of the personnel [2]. These findings suggest that a conditioned anti-nociceptive response, through repetition, can strongly affect behavior and clinical outcomes.

Conditioning and memory can also affect nociception and pain negatively as shown by some observational studies of infants. Hospitalized full-term infants of diabetic mothers underwent repeated venipuncture (heel lancing without anesthesia) for monitoring blood glucose concentration in the first 24 to 36 hours. After the first day of life, the infants exposed to frequent heel lancing showed more pain, or signs of increased distress, than normal infants following venipuncture for newborn screening only. Further, the mere action of cleaning the skin elicited pain behaviors in the infants of diabetic mothers, suggesting that skin cleaning repetitively associated with venipuncture, became a conditioned stimulus for conditioned aversive hyperalgesic responses [71]. Likewise, the infants learned to anticipate painful stimulations.

Similar findings provide evidence of association-based effects for conditioned hyperalgesia. Full-term, male, newborn infants aged five days or less participated in a study aimed at investigating whether neonatal circumcision altered pain response at 4-month and 6-month vaccination compared with uncircumcised boys who served as controls. The study also tested whether pre-circumcision treatment with lidocaine-prilocaine cream (EMLA)

influenced the subsequent response to vaccination by randomly randomizing infants to placebo or EMLA. Infants were video-taped during the vaccination and pain responses were assessed from the videotape by a researcher unaware of the study purpose, circumcision and treatment status. Three validated behavioral measures were used to assess infant's pain: infant facial action, cry duration, and visual analogue pain scores. Circumcised infants showed a stronger pain response (percentage facial expression, cry duration and VAS scores) to subsequent routine vaccination than uncircumcised infants. Those circumcised with EMLA had attenuated response to vaccination than those who received placebo, indicating that negative pain responses can impact future responses to pain and can be prevented with adequate management of pain in the neonatal period [70].

The impact of inadequate pain treatment in early stages of life is further supported by another study in children with cancer who had participated in a placebo-controlled, randomized study [78]. In children younger than 8 years undergoing painful procedures (bone marrow aspiration, lumbar puncture, or both), mean pain ratings during each subsequent procedure were consistently higher for those who had received placebo in their initial treatment compared to those who received the active drug, despite both groups receiving fentanyl in all subsequent treatments. Older children did not show this pattern indicating that sub-sequential learning effects in therapeutic contexts may be influenced by age [78].

Collectively, these findings indicate that that prior experiences and memory of pain markedly shape behaviors even when the impossibility to communicate verbally preclude to process painful stimulation through verbal suggestions, suggestibility and beliefs.

Another important open question to be addressed is how and when the unique neurobiology of placebo analgesia and capability to activate self-healing processes is influenced by development. Are developing children more prone than older children and adults to learned associations between medication and therapeutic efficacy leading to robust placebo effects? Although we are not able yet to provide a definitive answer, it appears that neural development can influence conditioned pain modulation (CPM) also known as diffuse noxious inhibitory controls referring to the ability to change the perceptual intensity of one painful stimulus through modulation of a second, conditioned, stimulus placed on another part of the body. Importantly, CPM is thought to reflect the descending inhibition of nociceptive signals [80; 81].

Recently, Tsao et al. studied the role of age in CPM in a cohort of 133 healthy children aged from 8 to 17 years [73]. Pressure test stimulus was tested before, during, and after the application of cold water conditioning stimulus and CPM was assessed by a reduction in pressure pain ratings during cold water administration. Older children (age: 12–17 years) showed greater CPM than younger children (age: 8–11 years) suggesting a role of neural development stage in descending pain inhibitory mechanisms. However, other factors may play a role as well. It has been reported that maternal anxiety for pain and children's sex influence responses to CPM. One hundred thirty-three children and adolescents aged 8-17 years and their mothers were enrolled to examine CPM responses and influences of sex and maternal anxiety. CPM responses, children's anticipatory anxiety and pain-related fear were

measured. Maternal pain anxiety was also assessed. The magnitude of CPM was influenced by neither age nor maternal anxiety over pain in both boys and girls. Greater maternal pain anxiety was significantly associated with greater CPM anticipatory anxiety and pain-related fear in girls, but not in boys [24].

In parallel to these findings in children, a recent study has explored CPM in adults randomized to 20-40, 41-60 and 61-80 year old sub-groups and found that CPM capability decreased with age, indicating greater CPM in the youngest participants.

Further consideration is needed to probe the possibility that the activation of the endogenous inhibitory systems varies during life span and what the modulatory factors are.

Parent-patient-physician interactions

The patient-physician relationship influences placebo effects [7; 8]. Aspects of the style of communication and the relationship, between the physician and patient, may contribute to placebo effects in children, but likely based on different components. Some studies have specifically characterized the unique relationship between physicians and pediatric patients. Physicians who engage in “joking” relationships decreased pain, fear and anxiety in their children [72]. For example, physicians who dressed as clowns significantly decreased pre-operative anxiety, measured by an observational behavioral checklist, in 5 to 12 year old children [74], suggesting that interactions between children and their physicians might contribute to modulate pain and associated-symptoms in clinical contexts.

Child-clinician relationship are often complex also due to the reliance on parental influence in the clinical setting [72]. Parents’ expectations alone can impact care provided by pediatricians. For example, it has been demonstrated that parental expectations positively correlate with the likelihood of their child being prescribed antibiotics (n=10 physicians, 306 parents) [45]. Moreover, a survey in parents of 95 children with otitis media (age ranging from 6 months to 12 years) identified that parental satisfaction of physicians’ meaningful explanations, care and control in the encounter correlated with ear related symptoms and quality of life [54]. Importantly, the contribution of the child-physician relationship to the placebo effects in a pediatric setting includes a parent-physician dynamic. This dynamic may be dependent on different pediatrician styles of communication and engaging the parent. A physician’s ability to engage the parent through effective communication can improve outcomes in developing children [39]. Moreover, a survey of 107 parents indicated that parents preferred pediatricians to demonstrate interpersonal sensitivity (or “bedside manner”) and partnership with the parent, above receiving medical information or independently directing their child’s care [79].

In clinical practice, pediatricians could learn from our understandings of the impact of their interactions with their young patients and their parents. While interactions with physicians could affect placebo and clinical outcomes, children and adolescent may not be able to fully understand the meaning and significance of the information being provided to them by the physician and physicians may believe that they will not be able to comprehend the information being provided [63]. This indicates the need for physicians to vary and match –

verbal and nonverbal –communication strategies with patients of younger age to optimize potential for positive health outcomes and their parents. A meta-analysis of 28 studies, in patients from 2 week to 18 year old, showed that the simple presence of parents during medical procedures (n=1256) reduces patient distress and anxiety in children as compared to no parental presence (n=1025) [58]. The parental presence did not affect health care provider work or procedure complications overall.

Placebo effects are also influenced by the behavior of others whose behavior is altered by knowing that the patient is receiving therapy [32]. This circular relationship may be especially important in younger children, where a change caused by placebo cannot be explained by the child's knowledge of treatment. Placebo effects induced by proxies can be due to the 1) parental perception (i.e. parents may believe that administering a medication will produce an effective change in their child and thus begin to perceive change independent of the pharmacologic effects of medication), or 2) a change in the parent's behaviors, which leads to objective changes in the child's behavior, or 3) an interaction between the two (i.e. changes in parental perception alter parental behavior, which then alters the child's behavior).

Interestingly, children whose parents promote positive coping behaviors, display less catastrophizing and functional disability secondary to painful insult [75] suggesting that parental actions improve health outcomes, enhance coping, and influence pain modulation. Infants and children may also be influenced by immediate behavior through affect-mirroring, a theory that the caretaker's facial and voice expressions impact the child's level of distress and, further, that the child may then exhibit similar behavior [30; 52]. Application of the affect-mirroring theory can be seen in a recent study that identified a correlation between parents' reassurance and children's distress during painful medical procedures. One hundred 5-10 year old children and their parents (86 mothers, 14 fathers) participated in a study investigating how children perceive their parents as fearful when they actually reassure. Children had to score vignettes whereby facial expression (happy versus fearful), vocal tone (rising versus falling), and content (informative reassurance versus uninformative reassurance versus distraction) were manipulated. In response to the vignettes, the children provided higher ratings of fear during reassurance than distraction. Children's perceptions of fear of their parents based on facial and verbal cues increases distress during painful medical procedures, despite parental reassuring behavior [48].

In sum, the parent-patient-physician dynamic impacts distress and perception of pain emphasizing that parent and patient beliefs, expectations and, importantly, non-verbal communication can lead to improvement on health outcome modulation.

Randomized Clinical trials: Is there any relation between placebo responsiveness and age?

An alternative way to examine the relation between placebo responsiveness and age is related to the existing literature on meta-analyses of randomized clinical trials. The findings provide conflicting information regarding the role of age. For example, a meta-analysis of randomized control trials for antiepileptic drugs reported that children (age < 18)

experienced a higher rate of alleviation of epileptic symptoms from placebos compared to adults (age 18) [60].

Chronicity of disease and its severity influence placebo responsiveness. Longer duration of disease (e.g. depression and anxiety) influences placebo responsiveness negatively [46; 11]. Conversely, a meta-analysis of trials for migraines (41 trials; n=5199; age 0-18 years) found that acute treatment in children and adolescents were not associated with age. Children and adolescents showed very low therapeutic gain due to a high placebo rate with verum response rates very similar to those seen in adulthood trials [25].

Recently, Enck and colleagues extracted 74 systematic reviews, meta-analyses, and meta-regressions in major medical areas (neurology, psychiatry, internal medicine) known for high placebo response rates from a literature database of approximately 2500 papers. These meta-analyses were then screened for predictors including age of the placebo response across multiple RCTs. 15 of the 74 studies indicated that younger age is associated with higher placebo responses, and this trend was predominant in psychiatric conditions but not in depression, and internal medicine but not in gastroenterology [23].

The inconsistencies of the literature in identifying a relationship between age and placebo responsiveness may be due to the heterogeneity of neurocognitive and affective developmental stages and additional confounding variables such as duration of disease, baseline symptom severity, patients versus physicians' ratings (and parents' versus teachers' ratings), comorbidities, the cultural context of the health care system, peer behavior, sample size and study design. Finally, other characteristics of the pediatric study population that may contribute to placebo responsiveness include female gender, smaller body surface area [31] as well as level of care received during study and socioeconomic status [11]. The many potential contributors to placebo responsiveness related to age and development indicate a need for further differentiation of subgroups and investigation in the neurodevelopmental stages and mechanisms of the placebo effect in children. There may also be notable differences in medication efficacy between adults and children, attributable, for example, to differences in developmental physiology, pharmacodynamics and pharmacokinetics [37].

Ethical considerations

Though there is clearly a need for laboratory and placebo-controlled research in pediatrics, there are ethical considerations and challenges of study design in conducting such trials. In particular, the deceptive nature of placebo studies and the ethics of using placebos in children who cannot consent are continuously debated.

Federal regulations stipulate that children be included in pharmacological research; still, it remains unclear under what circumstances it is ethical for children to be included in placebo-controlled trials [50]. Firstly, there is no consensus on the ethics of using placebo-controlled trials. Some researchers believe that is unethical to treat patients with an intervention that is inferior to a known efficacious treatment [50]. However, comparison to placebo may be necessary to identify therapeutic efficacy of investigational interventions.

According to the federal regulations, children may be included in research if one of the three conditions is met. The first two regulations include 1) the child is at minimal risk or no greater risk than would occur in daily life or, 2) the child is at more than minimal risk, but will receive direct benefit from participating in the research. The third condition states that if the child will experience greater than minimal risk, and no direct benefit, three additional conditions must be met. These include 1) the risks are only slightly higher than minimal, 2) the research procedure is similar to the experience that subject will have outside a research environment, and 3) the subject's participation will contribute to the generable knowledge about the disorder or disease [50].

These conditions permit children to be included in non-pharmacological research assuming that, procedures and safety measures must be taken for including children in placebo-controlled trials.

Due to the fact that children are considered a vulnerable population, the American Academy of Pediatrics (AAP) established ethical guidelines for including children in placebo-controlled trials [56]. Although children are able to assent to participation in research, they may not fully understand the associated risks or benefits. This is of particular concern considering that children are more suggestible than adults [55]. As a result, the AAP declared that children could participate in placebo-controlled trials if the placebo does not cause the child's condition to deteriorate or if the placebo does not cause greater risk to the child [21]. Therefore, children may participate in placebo research if: 1) there is no consensus on accepted treatment within in the field, 2) the effectiveness of established treatment is in question, 3) the established treatment has higher risks and side effects and significantly lower benefits, 4) the placebo is used to determine the natural course of the disorder or disease and is later added to an established regimen, 5) the effectiveness of therapy has not yet been established and within the disease process the patient enters in and out of remission of the disorder or disease [21].

Even when children are included in placebo based studies, as previously mentioned, methodological challenges to conducting studies in children pose problems to sound research. For example, data collection is often based on parental and self-report, which makes interpretation of negative findings difficult. Further, it provides a discussion point regarding the need for improved research methods in young children. Relying on more objective measures, such as clinician ratings rather than subjective patient or parent reports, potentially decreases placebo response. Objective measures can be based on behavioral assessment or on physiologic parameters. This may involve assessing cooperative behavior and measuring heart and respiratory rate changes in analgesic studies, for example. Such additional outcome measures are especially necessary when evaluating infants or cognitively impaired children [31; 59]. The implementation of ethical non-deceptive, double-blind, immediate-recue designs using patient-controlled analgesia or nurse controlled analgesia, implicitly measuring analgesic dose savings instead of pain scores might contribute to improved reliability and validity in clinical pediatric pain study protocols [4; 40].

Harnessing Placebo Effects for Supportive Therapeutic Applications

Given that children may demonstrate robust placebo responsiveness, it is worth considering if this can be harnessed for supportive therapeutic application. Understanding placebo effects in children may allow us to cultivate strategies for relief of pain, anxiety and fear in certain conditions and circumstances. Further, applying the dose extender model in a clinical setting may allow for reduced drug intake in certain pediatric conditions.

A study of post-operative pain treatment in children after tonsillectomy showed that placebo treatment accounted for a 5.6 unit decrease in reported pain, which was 3 units further reduction than the predicted pharmacologic efficacy of acetaminophen [1]. Although the placebo responsiveness was considered attributable to possible environmental confounders such as spontaneous pain resolution, enhanced behavioral coping mechanisms, and clinician indiscrimination of pain from other phenomena, this study indicates both the profound potential therapeutic applications of the placebo effect in children and also the need to understand what factors contribute to it.

We have illustrated how placebo effects may predispose children to therapeutic outcomes in placebo analgesic responses. Also, we have discussed how psychosocial stressors as well as environment can influence therapeutic outcomes. This demonstrates potential clinical applications for targeting and harnessing these processes in pediatrics. Deliberate harnessing of positive thought and emotion and using them for the purpose of enhancing health can help alleviate distress and potentially reduce pain in medical procedures such as those done in an emergency setting or in the context of chronic disease and cancer treatment [57; 43; 27].

This concept has been also applied to children undergoing chemotherapy who experience recurrent side effects including food aversion and nausea and vomiting that develop into pre-chemotherapy aversive reactions, or conditioned negative placebo effects, that can be induced simply by conditioned stimuli including the arrival at the clinic setting, placement of the IV, and so forth. One study showed that giving children various flavored candy after chemotherapy and before meals significantly improved meal intake compared to a group where no candy was given [6]. Another group of researchers proposes to apply this methodology to investigate if candy can be used to avoid pre-treatment nausea and vomiting [29]. These lines of research serve as further examples of need for more rigorous studies integrating placebo mechanisms with clinical outcomes.

Clinical examples of the conditioned placebo effects, described above, serve as further support of harnessing placebo effects for therapeutic applicability in pediatrics. Moreover, conditioned stimuli can be used to elicit stronger responses thereby allowing the conditioned responses to potentially serve as a “triggers” for boosting placebo analgesia.

Conclusion

Taken together, research suggests that placebo mechanisms can impact therapeutic outcomes and potentially be harnessed clinically to improve pain and other clinical outcomes in pediatric population. In daily practice, it is reasonable to suggest that clinicians use trustful care, allow control for the patient and caregiver, implement joking, play and reward, and

promote positive encounters and expectation of treatment effectiveness where appropriate. Further, overt schedule of conditioning with patients and caregivers transparently informed, may be appropriate for certain conditions amenable to boost therapeutic response while risks and harms are minimized. Moreover, research on mechanisms of the placebo effect should be encouraged promising to shed light on optimization of clinical trial designs and improve knowledge on self-healing processes in children.

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Synopsis

Are developing children more prone than older children and adults to form placebo analgesic effects? We address this issue providing a comprehensive analysis of both nociception and pain modulation in pediatrics.