Maturitas 79 (2014) 389–400

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Should placebo be used routinely for chronic pain in older people?

Steven M. Savvas*, Leah M. Zelencich, Stephen J. Gibson

National Ageing Research Institute, Victoria, Australia

ARTICLE INFO

Article history:
Received 5 September 2014
Received in revised form
16 September 2014
Accepted 17 September 2014

Keywords:
Placebo
Placebo analgesia
Placebo mechanisms
Chronic pain
Persistent pain
Older people

ABSTRACT

As research expands our understanding of underlying placebo mechanisms, interest turns to the clinical application of placebos. Whether placebos are appropriate and effective in the management of chronic pain in older people deserves considerable attention. The evidence suggests that adults of any age are responsive to placebos, and that placebo treatments can be effective for many conditions prevalent in older people. Though placebos in general already seem to be used with some regularity in medical practice, the use of placebos alone for chronic pain is probably unjustified unless other treatments are inadvisable or have been exhausted. However maximising the mechanisms that underpin placebo analgesia such as expectancy or the psychosocial context should be encouraged and would be considered a feature of good clinical practice. It would also be anticipated that older people may see an additional benefit with placebo treatments when such treatments reduce existing or planned medication regimes, as older people typically experience more comorbidities, increased susceptibility to adverse drug reactions, and altered pharmacological responses to drugs. Further research is still needed in placebo-related treatment paradigms for the management of chronic pain in older people.

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* Corresponding author at: National Ageing Research Institute, 34-48 Poplar Road, Parkville, VIC 3052, Australia. Tel.: +61 401386386.
E-mail address: s.savvas@nari.unimelb.edu.au (S.M. Savvas).

http://dx.doi.org/10.1016/j.maturitas.2014.09.006
0378-5122/

1. Introduction

1.1. Placebos

Placebos come by many names – placebo, obecalp ('placebo' backwards), cebocap (or sugar pill), pure or impure placebos, dummy and sham treatments. An exemplar is the administration of an inert sugar pill with no active pharmacologic agent, although placebos do not need to be medications as interventions such as sham surgeries also have demonstrable placebo effects. Whatever the form, placebos may improve a patient's condition due to a variety of biopsychosocial factors, including patient expectancy of therapeutic benefit, prior conditioning, and the psychosocial context of the setting such as the patient–doctor relationship. Placebos also have a fundamental role in research as a foundation of modern clinical research design. This is complemented by a growing body of work on the precise underlying mechanisms of placebo response. However, opinion still diverges on the clinical use of placebos in the course of treatment, so this overview examines and contextualises placebos for chronic pain in older people.

Benedetti et al. [1] defines the placebo effect as a "psychobiological phenomenon occurring in the patient's brain after the administration of an inert substance, or of a sham physical treatment such as sham surgery, along with verbal suggestions (or any other cue) of clinical benefit [2]". Vase et al. [3] defines placebo response as "the reduction in symptoms as a result of factors related to a subject's/patient's perception of the therapeutic intervention". Regardless of nuances in definition, the common salient points are that there is no specific pharmaco-active ingredient in the medication (or targeted physiological mechanism when using a non-pharmacological intervention) that accounts for the treatment response, and that the improved outcome is principally due to a biopsychosocial response. Regarding placebos for pain relief, placebo analgesic effect is interchangeable with placebo effect, and in clinical trials is the reduction in pain report in a group administered a placebo treatment compared to a group offered no treatment. Most clinical trials lack the inclusion of a 'no-treatment' group and so the actual 'placebo effect' is usually not measured.

1.2. Measuring placebo effects

Potential pitfalls exist in evaluating placebo effects of clinical trials as most trials are designed to compare an 'active' treatment group with a placebo group. Though this design has merit for assessing the active treatment, estimating the placebo response is problematic due to bias from unrelated factors uncontrolled with this methodology. For example, patients often are included in trials when pain is at its worst and chance alone dictates that pain will more likely be less extreme next time (referred statistically as the regression to the mean). Therefore, some of the placebo effect may be accountable to this regression. Placebo effects may also be conflated when improvements in pain relief may be expected as part of the natural course of the disease, so that pain will likely lessen as part of the disease progression.

To avoid these biases, placebo effects can instead be evaluated by comparing the placebo treatment group with a 'no-treatment' or 'usual care' group. Most clinical trials are however not designed to include a third arm (active, placebo, and no-treatment) and for those that do, the placebo effect may still be moderated as even this methodology has limitations. These trials typically inform patients of an equal chance of receiving either active or placebo treatment, with the implication that placebo treatment will be ineffective in improving the condition treated. Therefore any potential placebo effects that may be related to known placebo effect mechanisms such as verbal suggestion and expectation are muted. Another alternative design are trials that specifically measure the placebo effect and these methodologies often include manipulation of known placebo mechanisms such expectancy or conditioning procedures to elicit a placebo response. A more recent methodology incorporates an open/hidden paradigm with either the patient aware of treatment administration (open) or unaware of administration as the treatment is obscured within the procedure itself (hidden). The difference in treatment outcome between open and hidden administration is thought to reflect the placebo effect [1].

2. Mechanisms of placebo analgesia

A number of mechanisms have been proposed to account for placebo analgesia, including psychological processes like expectancy and classical conditioning theory or the role of emotions and psychopathology in modulating placebo responses. Neuroscience also has established the involvement of neurotransmitter systems and brain regions during placebo analgesia responses using various brain imaging techniques. Evidence suggests altered activity in brain regions relevant to pain pathways during placebo analgesia, including cortical (rostral anterior cingulate cortex, anterior insular), sub-cortical (amygdalla, hypothalamus, thalamus), midbrain (periaqueductal gray), medulla (rostral ventral medulla) and even spinal sites [4–9]. The general conclusion is that placebos regulate pain-related activity via top-down processing in brain regions and neurotransmitter activation (endogenous opioid systems, CKK receptor systems, mesolimbic dopamine systems, and more recently the cannabinoid system) that correlates with reduced pain experience (see Benedetti et al. [1]), though bottom-up processing may also be involved [10].

2.1. Expectancy and conditioning

Two principle biopsychological constructs that arise from placebo treatment to show placebo effects are expectancy and conditioning. Expectancy theory proposes that a person's expectation of an outcome will influence the outcome itself. Numerous early studies have demonstrated that pairing lowered pain stimulus with placebo administration results in placebo analgesia [11] and