PLACEBOS AND PSEUDOTHERAPIES. A LITERATURE REVIEW AND CONCEPTUAL ANALYSIS

A. Pértega-Gomes¹, M. Araújo², E. Gonçalves¹, A. Norton², N. Vila-Chã³

¹Centro Hospitalar Universitário do Algarve, ²Hospital Magalhães Lemos. ³Centro Hospitalar Universitário do Porto

OBJECTIVES: To establish a chronological evolution of the concepts of **placebo**, and **pseudo-therapy**, as well as a reflection on how these terminological considerations profoundly determine the potential for the clinical translation of laboratory research.

BACKGROUND AND AIMS: pharmacological compounds present both positive and negative effects that do not relate to their pharmacodynamics or pharmacokinetic properties. These effects are known as placebo and nocebo and result from a complex body-mind interaction. Recent neurophysiological studies revealed some neurotransmitter pathways, but the mechanisms underlying are far to be fully understood.

MATERIAL AND METHODS: The authors' searched the databases Pubmed, PsycInfo and Google Scholar, applying the search terms placebo effect, pseudotherapy and pseudoscience.

RESULTS:

In order to promote a more accurate understanding of mechanisms associated with placebo effects, some authors advocate for a reconceptualization of the phenomenon, namely as **“contextual healing”** effect.

1. PSYCHOLOGICAL MECHANISMS:

Two major processes interact to create and maintain placebo effects:

	Precognitive associations	Appraisals
Mechanism	Learned associations that can operate without cognitive intervention .	Interpretations/ cognitive evaluations of the meaning of events in a given context.
	Reactive responses to events. Largely invariant to cognitive context and goals.	Conceptual acts. Constructed interpretations.

2. NEUROBIOLOGICAL MECHANISMS:

Picture from "Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. NATURE REVIEWS. 2015;16". AMY, amygdala; dmPFC, dorsomedial prefrontal cortex; Hipp, hippocampus; HYP, hypothalamus; NAc, nucleus accumbens; IOFC, lateral orbitofrontal cortex; PAC, periaqueductal grey; RVM, rostromedial medulla; vmPFC, ventromedial prefrontal cortex.

VENTROMEDIAL PREFRONTAL CORTEX

seems to play a central role in placebo effect, integrating different elements (social information, interoceptive assessment of one's body state, expectancies and memories) and triggering a response at other processing levels.

HISTORICAL OVERVIEW

Negative connotations of the word Placebo - «*Placebo Domino in regione vivorum*», a religious chant used by hired/fake mourners in mediaval ages. Later, the name of a character in the Canterbury Tales, the opposite of Justinus, the fair one. First medical ditionaries enfazise that is «**any medicine adapted more to please than to benefit the patient**». Early 19th century descriptions of "A 'polychromatic assortment of sugar pills' was routinely quaffed by patients."

Mesmer – first use of “placebo” as **control** for therapeutic trials

Beecher's 1955 study – a systematic review of the therapeutic effect of iv and sc saline injection and lactose pills in conditions such as **angine pectoris, common cold, post-operative pain**.

Pervasive recognition of placebo effects - a large resistance by biomedical physicians to engage in a discussion about – **a phenomenon restricted to first person accounts? Not quite!**

-Explosion of research – more than 80.000 published studies

-Potential interfaces: neurovegetative system; neuroendocrine pathways; Immunology.

-Central to the process – **expectation pathways** coordenated in the VmPFC; example, loss of placebo effect in Alzheimer's with PFC dysfunction AND superiority of overt vs. covert administration.

Is Placebo a fake medical intervention = pseudotherapy?

Evidence suggests otherwise. The exploration of variables involved in the healing context may prove valuable in the future personalized care. Semantic disambiguation may help disentangle in practice.

What are the limits and risks? Where to draw the line?

A good point made in the Madrid Declaration of Pseudotherapies is that, in order to avoid the search for pseudotherapeutic practises, expertise on communication must be developed by physicians.

What can we expect of the area in the future?

Several groups are adressing the placebo effect from many angles, including context manipulation, communication and personality issues, and genome studies (with recent «placebome» identification»). Conceptual issues will benefit from broad reflection on the meaning of disorder and healing.

CONCLUSIONS: Scientific interest in this topic has grown. Nevertheless, translational research is currently hampered by confusing and misleading conceptualization of these phenomena. The demarcation of therapy vs. pseudo-therapy echoes the question of what constitutes a medical disorder or not, which raises ethical and epistemological concerns. Additional conceptual and empirical research is necessary.

References: Amanzio, M., Pollo, A., Maggi, G., Benedetti, F. (2001). Response variability to analgesics: a role for non-specific activation of endogenous opioids. Pain. 15;90(3):205-15. Amanzio, M., Benedetti, F. (1999) Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J Neurosci. Jan 1;19(1):484-94. Beecher, HK. (1955). The powerful placebo. J Am Med Assoc. Dec 24;159(17):1602-6. Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., Rainero, I. (2003). Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J Neurosci. May 15;23(10):4315-23. Colagiuri, B., Schenk, LA., Kessler, MD., Dorsey, SG., Colloca, L. (2015) The placebo effect: From concepts to genes. Neuroscience. 307:171-90. de la Fuente-Fernández, R., Ruth, TJ., Sossi, V., Schulzer, M., Calne, DB., Stoessl AJ. (2001). Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science. Aug 10;293(5532):1164-6. Geuter, S., Koban L., Wager, TD. (2017). The Cognitive Neuroscience of Placebo Effects: concepts, Predictions, and Physiology. Annu Rev Neurosci. Jul 25;40:167-188 Hadamitzky, M., Sonderrmann, W., Benson, S., Schedlowski, M. (2018). Placebo Effects in the Immune System. Int Rev Neurobiol. 138:39-59. Lidstone, SC., Schulzer, M., Dinelle, K., Mak, E., Sossi, V., Ruth, TJ., de la Fuente-Fernández, R., Phillips, AG., Stoessl AJ. (2010). Effects of expectation on placebo-induced dopamine release in Parkinson disease. Arch Gen Psychiatry. Aug;67(8):857-65