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SIG Chair Report

It is with pleasure that I write to you in the second SIG on Pain and Placebo e-newsletter of 2010. The feature of the April newsletter is a paper by Professors Paul Enck and Manfred Schedlowski, who write about trends in research on placebo over the last 50 years. This is a very interesting paper which identifies many of the key moments in research on placebo over this time. Perhaps of more interest is the ability to take a step back and look at what progress has been made and areas where more attention is needed.

It is on this note that I can update you on the progress made towards our SIG satellite meeting in Montréal, Sunday, August 29th. This will be a one-day meeting focusing on some specific areas of research on placebo, particularly future directions in clinical trial design and interpretation and applications of placebo mechanisms to clinical practice. Confirmed speakers to date include: Fabrizio Benedetti, Don Price, Ted Kaptchuk and Wayne Jonas. We are hopeful of confirming Irving Kirsch and Robert Temple soon. There will be additional speakers and panelists to make the day both interesting and engaging for participants.

Damien Finniss

Guest Editorial

The waxing and waning of placebo research over the last 50 years

Paul Enck & Manfred Schedlowski

Running a PUBMED search with the search term “placebo” brings about approximately 138,000 references as of today (April 1, 2010), with increasing numbers over the years, since the beginning of PUBMED in 1953. These are, of course, all placebo-controlled trials that have been published ever since, but among all the papers we also will find about 2000 papers (1.5%) that specifically address and discuss the placebo response per se, excluding letters, editorials and comments. This is our current knowledge base of the placebo response in general and its specifics in various clinical areas of interest, with the majority of papers dealing with “placebo analgesia,” the most thoroughly studied phenomenon in placebo research.
Looking at the publication years of these 2000 papers over the past 50 years (Figure A), a number of things become evident: For one, the number of publications increased substantially starting 1994. Secondly, three "waves" of publications can be identified, with peaks around 1964, 1989, and 2002 – these "waves" appear more pronounced when the scaling is logarithmic, as in Figure B. Finally, the number of papers appears to drop again when 2010 is taken into account (not included in the figures): the first three months of 2010 have seen 22 papers, estimating the 2010 total record to be around 90, the lowest number over the last few years. Therefore, let us have a closer look at these five events.

1. The first "peak", though small in numbers around 1964, was mainly due to a series of studies on psychological and psychiatric papers discussing personality issues or concepts of the placebo response. The paper that may have found most attention was Howard Shapiro's landmark paper in JAMA (1). These psychological concepts have dominated and driven the placebo research for almost 20 years.

2. The second wave of publications peaked in 1989: this year's studies addressed the placebo response in many diseases, such as in otology, urology, rheumatology, gastroenterology, neurology, psychiatry. The key paper of this year certainly was Robert Ader's paper on conditioned immune response as the mechanism of the placebo response, one of the first linking the Pavlovian conditioning procedure to pharmacotherapy (2). From there to the very recent finding (3) to utilize Pavlovian conditioning procedures to partially substitute drug treatment in immune diseases demonstrates the long way experimental placebo research has travelled to prove its clinical relevance, beyond the planning of randomized placebo-controlled trials.

3. The substantial increase in placebo oriented research since 1994 was probably initiated by a series of placebo papers and comments in Lancet (4-11), in JAMA (12) and in the New Engl J Med (13). They addressed all major diseases and clinical conditions that have dominated the discussion ever since, especially in pain and depression.

4. The third wave had its maximum in 2002; it most likely was initiated by an NIH-sponsored scientific workshop with more than 500 participants earlier in 2000 (14). Two years later, the first brain mapping studies on the placebo response in Parkinson's Disease (15), in depression (16) and in pain (17) were published that were quickly followed by many other studies using PET, fMRI and other neurophysiological techniques to investigate the central processing of the placebo response "on line". This has substantially broadened our understanding of the neurobiological and biochemical mechanisms underlying the placebo response (18), as well as directing our focus towards more specific experimental designs of its investigation, e.g. exploring mechanisms of reward and learning. The latest advances in this development have been involvement of spinal processing in placebo analgesia (19) and the use of transcranial magnetic stimulation to block expectancy-induced analgesia at the level of the prefrontal cortex (20).

The increased availability of these tools certainly has contributed to the rapid rise in placebo studies. At the same time, it has led to increased discussion of the ethics of the use of placebos in clinical trials and the search for alternative study designs avoiding or minimizing the use of placebos.

5. The presumed decline of relevant placebo papers in these days (2010) may indicate that another paradigm shift in placebo research is needed. While we appear to know that placebo mechanisms in different diseases involve different biological mediators (21), transferring this knowledge into clinically relevant management strategies – from novel study designs to test new drugs to utilizing the placebo response in the medication therapy of patients – is still lacking. Furthermore, any attempt to identify personality traits in subjects receiving placebo treatment – the starting point of placebo research 50 years ago - has failed so far, probably due to a lack of specificity of psychological constructs such as optimism (22), suggestibility (23) or trust (24). Instead, first observations have linked the placebo response phenotype to genetic predisposition (genotype) (25) – we may expect much more of this type of research in the near future with genome-wide scanning techniques becoming more and more available for routine testing.

In summary, almost 50 years of placebo research in medicine and beyond reveals progress as well as drawbacks, paradigm shifts as well as missing links, and points towards the need of developing novel strategies of transferring recently acquired knowledge into future clinical routine.

References