Placebo effects in medicine: A bibliometric analysis

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Abstract
Objective: It was the aim of this bibliometric analysis to identify all publications dealing with so-called ‘context effects/placebo effects’ to bring some organisation into the publication landscape of the past 35 years.
Design: An electronic database search was carried out in Pubmed from its inception to November 2011.
Participants: Already published articles and their participants were included.
Setting: This review was carried out at an academic institution.
Main outcome measures: Condition, country, year, journal, number of authors, type of publication and main focus of the publication.
Results: There are slight differences in the focus and the origin of research. Although the subject is multidimensional and covering all areas in healthcare, only a few research disciplines cover the field of placebo effects. The research field is shrinking as evident by the smaller number of researchers publishing in this field. It is suggested that the discussion regarding placebo and context effects is getting more homogenous and is turning into a specific field by itself. There is an increasing concentration of placebo effects being reproduced in experimental settings.
Conclusion: It is debatable whether the complexity of the broad range of what produces placebo effects can be successfully detected in a randomized controlled trial setting.

Keywords
Context effects, placebo effects, non-specific effects, meaning response, bibliometric analysis, review

Introduction
Medical outcome partly depends on the context in which the treatment takes place.1 There are a large number of determinants contributing to the general terminology of the concept of so-called ‘placebo effects’, some of which are not yet fully understood, whereas it is likely that others have not yet been identified. Research in context effects, placebo effects and their interactions has shown that the overall effect of multi-component treatments is not a simple addition of singular components plus ‘placebo effects’, but that it can be far more complex.2–5

It was the aim of this bibliometric analysis to identify all publications dealing with so-called ‘context effects/placebo effects’ in order to bring some organisation into the publication landscape of the past 35 years. We have two main objectives: (1) to provide a bibliometric overview, which is to serve as a base to (2) then only select experimental studies in order to explore the actual content of these studies in-depth with the help of content analysis.

The present publication only covers the first objective.

Methodology
An electronic database search was carried out in Pubmed from its inception to November 2011. Search terms consisted of a search strategy adapted from a Cochrane Collaboration protocol on practitioner communication.6 In order to identify relevant publications an already existing and published search strategy was used which was adapted from a protocol published by the Cochrane Collaboration regarding ‘The effect of varying practitioner communication on patients’ health status and treatment outcomes’.6 This search strategy consists of 61 search terms, including ‘MeSH’, ‘*’ and ‘[All Fields]’. In 2001, the same author team already published a systematic review regarding the influence of context effects on health outcomes.7 In 2003, their contribution to the research field was expressed in their publication ‘Context Effects: Powerful Therapies or Methodological Bias?’.8 Experts in the field of placebo research were directly contacted. Randomized controlled trials (RCTs) and data from other clinical (controlled, uncontrolled) and non-clinical trials (cohort studies, case reports, case series) were included in the literature review as well as reviews and meta-analyses. Retrieved abstracts were hand searched and categorised to describe the condition, country, year, journal, number of authors, type of publication and main focus of the publication.

Statistical Package for the Social Sciences (version 19) was used to compute frequencies of variables, means and
Table 1. Extracted data classified according to place of origin and year of publication.

| Condition | Origin | Year | ≤2000 (n = 122) | >2000 (n = 179) |
|-----------|--------|------|-----------------|-----------------|
|           | America (n = 147) | Europe and Rest (n = 154) |                  |                  |
| Healthy   | 34 (23.1%) | 43 (27.9%) | 19 (15.6%) | 58 (32.4%) |
| Depression| 14 (9.5%)  | 18 (11.7%) | 11 (9.0%)  | 21 (11.7%) |
| Various   | 5 (3.4%)   | 10 (6.5%)  | 5 (4.1%)   | 10 (5.6%)   |
| Hypertension | 8 (5.4%) | 4 (2.6%)  | 10 (8.2%)  | 2 (1.1%)   |
| Migraine  | 6 (4.1%)   | 5 (3.2%)   | 3 (2.5%)   | 8 (4.5%)   |
| Irritable Bowel Syndrome | 5 (3.4%) | 3 (1.9%)  | 0           | 8 (4.5%)   |
| Panic disorder | 3 (2.0%) | 4 (2.6%)  | 5 (4.1%)   | 2 (1.1%)   |
| Main focus | Placebo effects | 36 (24.5%) | 30 (19.5%) | 46 (37.7%) | 20 (11.2%) |
|           | Placebo response | 30 (20.4%) | 22 (14.3%) | 24 (19.7%) | 28 (15.6%) |
|           | Placebo responders | 4 (2.7%) | 10 (6.5%) | 4 (3.3%) | 10 (5.6%)   |
|           | Placebo effects, expectation | 8 (5.4%) | 4 (2.6%) | 0 | 12 (6.7%) |
|           | Placebo analgesia | 4 (2.7%) | 4 (2.6%) | 1 (0.8%) | 7 (3.9%) |
|           | Placebo effects, expectancy | 4 (2.7%) | 4 (2.6%) | 7 (5.7%) | 1 (0.6%) |
|           | Placebo effects, placebo response | 4 (2.7%) | 4 (2.6%) | 6 (4.9%) | 2 (1.1%) |
| Journal type | Specific condition | 28 (19.0%) | 26 (16.9%) | 34 (27.9%) | 20 (11.2%) |
|           | Pain | 23 (15.7%) | 17 (11.0%) | 14 (11.5%) | 26 (14.5%) |
|           | Psychiatry | 17 (11.6%) | 16 (11.7%) | 18 (14.8%) | 17 (9.5%) |
|           | Psychopharmacology | 6 (4.1%) | 14 (9.1%) | 10 (8.2%) | 10 (5.6%) |
|           | Neurology | 13 (8.9%) | 11 (7.1%) | 5 (4.1%) | 19 (10.7%) |
|           | General Medicine | 9 (6.1%) | 10 (6.5%) | 10 (8.2%) | 9 (5.0%) |
|           | Research | 8 (5.4%) | 10 (6.5%) | 3 (2.5%) | 15 (8.4%) |
| Publication type | Meta-analysis | 17 (11.6%) | 29 (18.8%) | 8 (6.6%) | 38 (21.2%) |
|           | SR | 12 (8.2%) | 5 (3.2%) | 7 (5.7%) | 10 (5.6%) |
|           | RCT | 49 (33.3%) | 58 (37.7%) | 37 (30.3%) | 71 (39.7%) |
|           | CCT | 37 (25.2%) | 32 (20.8%) | 43 (35.2%) | 25 (14.0%) |
|           | UCT | 21 (14.3%) | 21 (13.6%) | 20 (16.4%) | 22 (12.3%) |

SR: systematic review; RCT: randomized controlled trial; CCT: clinical controlled trial; UCT: uncontrolled clinical trial.

*aIncludes the whole continent.

bTop most frequent items represented, therefore % does not add up to 100.
to measure associations between dependent and independent variables by applying the Chi-square test.

Results

A total of $n = 301$ publications were included in this bibliometric analysis. Part of the results of the bibliometric analysis can be seen in Table 1. In the analysis, it was distinguished between two factors. One was the separation of trials according to their origin. Here, the data were split into the continents ‘America’ and ‘Europe and the rest’ of which ‘the rest’ comprised of only a few countries outside of America or Europe and ‘America’ included the whole continent. Splitting the data that way distributed them almost equally between the two categories. Furthermore, trials were separated according to whether they were published before or after the year 2000. Factors such as investigated health condition of included participants, main focus of studies, journal and publication types were investigated closely.

Condition

The results found that approximately half of all included studies concerned healthy participants, which given the general topic of ‘placebo effects’ or ‘context effects’ was not surprising. There was no great difference in localisation of origins. However, the inclusion of healthy subjects in studies of this type has doubled after 2000. About 20% of participants were diagnosed with depression, both before and after 2000 and across continents. Hypertension patients have participated less often in placebo effects studies after 2000 in both locations of origin.

Main focus

The main focus of the articles was very wide-spread and ranged from attention/belief/communication/expectancy to mechanism of placebo effects/responder rate/nocebo – only to mention a few. The most frequently represented topics were all dealing with placebo effects or the placebo response. Generally, the main focus of studies about ‘context effects’ in America seems to differ from the one in ‘Europe and rest’.

Journal type

Over half of the articles were published in journals featuring specific conditions, but more than a quarter were in journals focusing on pain. Publications in journals with the focus on psychiatry have been constant throughout the years and across locations of origin. Twice as many publications were found in the area of psychopharmacology in ‘Europe and rest’ compared to America. Publications in generally labelled neurology journals have tripled after 2000.

Publication type

Three quarters of all articles were meta-analyses and their publication has more than tripled since 2000. Apparently, the publication of meta-analyses is more popular in ‘Europe and rest’ compared to America. About 70% of included publications are randomised controlled trials. The realisation of randomised controlled trials has slightly increased, whereas those of uncontrolled clinical trials have decreased since 2000 and there were slightly more randomised controlled trials from ‘Europe and rest’ compared to America. Chi-square test revealed an association between publication type and the year (before 2000 versus after; $\chi^2 > 0.001$).

T-tests

T-tests revealed a highly significant difference for the number of authors before and after the year 2000 ($p = .001$). Before 2000, the mean number of authors was 4.76 (SD 2.41), whereas after 2000 the mean was 3.85 (SD 2.02). Furthermore, there was a slightly significant difference ($p = .04$) for the origin and year of publication. In Europe and the rest, there were slightly more publications covering the topic of context effects after 2000 with a mean of 2001.46 (SD 7.37) compared to the mean of America 1999.52 (SD 8.96).

Conclusion

This bibliometric analysis of publications in the field of placebo effects is the first of its kind and has shown the broad variety of main foci, journal types, publication types and conditions of participants included in articles. It has been shown a decade ago that there can be cultural variation in the response of control groups to inactive medication for conditions such as anxiety, hypertension and ulcers. In our analysis, there are slight differences in the focus and the origin of research, which will be further investigated in the second, more in-depth context analysis of all publications of the experimental studies to be published soon. A significant shift has occurred for conditions that have been investigated, the publication and journal type and the main focus of the articles from before to after the year 2000. It seems that although it is a multi-dimensional subject, covering all areas in medicine and healthcare, only a few research disciplines cover the field of placebo effects. Furthermore, this analysis showed that the research field is shrinking,
evident by the smaller number of researchers publishing in this field. Thus, it is suggested that the discussion regarding placebo and context effects does not become more and more heterogeneous but rather homogenous and is turning into a specific field by itself.

The analysis also showed that there is an increasing concentration of placebo effects being reproduced in experimental settings, namely in randomised controlled trials. It is debatable whether the complexity of the broad range of what produces placebo effects can be successfully detected in such settings. In our next publication, we will be selecting all experimental studies and explore the content of these studies in-depth with the help of content analysis.

**Declarations**

**Competing interests:** None declared

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**Ethical approval:** No ethical approval was necessary because this bibliometric analysis was comprised of a collection of previously published data.

**Guarantor:** KB.

**Contributorship:** KB devised the project idea in agreement with all other contributors. All co-authors devised a draft protocol of the project. KB designed data collection tools, monitored data collection for the whole trial. TO wrote the statistical analysis plan, cleaned and analysed the data, and all co-authors drafted and revised the paper.

**Provenance:** Not commissioned; peer-reviewed by Padmanabhan Badrinath.

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