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Case reports and case series from *Lancet* had significant impact on medical literature

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Abstract

Background and Objectives: Case reports and case series are often the first evidence of innovative treatment, but clinical trials need to follow to substantiate this evidence. The objective of this article was to evaluate case reports or case series describing innovative treatment concerning their impact.

Methods: Case reports and case series ($n \leqslant 10$) from a high-impact journal, *The Lancet*, published from 1 January 1996 to 30 June 1997, were evaluated according to predefined criteria. To assess publication impact, Pubmed, Science Citation Index, the Register of Current Controlled Clinical Trials, and the Cochrance Controlled Clinical Trials Register were searched.

Results: Sixty-four case reports and 39 case series were identified. They were cited in average 17 times (median 6,5; range 0–336). Twenty-Four follow-up trials were identified, nine in the register of current controlled clinical trials.

Conclusion: Case reports and case series can be well received, and have significant influence on subsequent literature and possibly on clinical practice. Many were followed by clinical trials. Often, though, they report rare conditions for which trials may not be feasible, and more or less explicitly transfer established treatment into other conditions. Overall, there is a strong publication bias favoring positive results, and opportunity should be created for publication of follow-up reports.

Keywords: Case reports; Case series; Clinical trials; Clinical research; Review; Impact factor; Publication bias

1. Introduction

Although interest has increased recently, case reports and case series are usually not objects of investigations but targets of criticism. However, most of the current treatment in medicine is not supported by evidence from controlled clinical trials [1], but based on the best available evidence, which may well be uncontrolled or observational studies. At the same time, case reports and case series are likely to account for the greatest part of discarded treatments in medicine [2]. It is a great achievement of evidence-based medicine (EBM) to have pointed to this problem and to insist on more solid evidence, but we are not aware of research that assesses what stimulates clinical trials, except if the trials are the outcome of research projects, for example, in the pharmaceutical industry.

For a clinical trial to be funded, there must be preliminary evidence on which to base the belief that a treatment may be efficacious. Case reports and small uncontrolled series are often this first line of evidence [3]. There has been recent interest in case reporting from a wider variety of angles. The most comprehensive coverage of the issue is the book by Jenicek [3], which defines the place of case reports within EBM. Vandenbroucke defended case reports and case series because of their high sensitivity for detecting unexpected novelty. Frequently, discovery of therapeutic advances in medicine happens only serendipitously through unanticipated side effects; therefore, case reports and series remain a cornerstone of medical progress. Sildenafil is a famous current example [4]. Greenhalgh's work on case reports focused on narrative medicine [5] and its benefit for medical education and quality improvement [6] as well as on the integration of qualitative research into EBM [7].

We wanted to know what happened to case reports and case series that were published in the last general medical journal to find them worthy of publication? Were they cited and did they stimulated other reports? How frequently were they followed by to clinical trials?

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2. Methodology

We used the following inclusion criteria to select case reports and case series:

1. The paper was published between 1 January 1996 and 30 June 1997 in *The Lancet*.
2. The number of patients in case series was <11.
3. No external comparison group was reported, but literature references to historical controls were permissible.
4. Innovative or unusual treatment was described either as primary focus or as a secondary recommendation of the paper.

For each case report of case series, we documented:

1. The number of patients.
2. The category of treatment used.
3. The outcome of the reports was categorized as success, improvement, or failure. Success was the full clearance of all symptoms; improvement was defined as clinical improvement without elimination of the disease. Failure of treatment was lack of clinical improvement or worsening of the condition.

To assess the impact of the papers, we determined the frequency at which case reports or case series were cited and whether controlled clinical trials followed them by searching the following databases:

1. The Science Citation Index. (Alexander Meves [A.M.], Joerg Albrecht [J.A.])
2. www.pubmed.gov. The disease as quoted from the title of the report (usually there is no abstract) and therapy as found in the title. All searches had to be repeated if the report itself did not turn up (A.M.).
3. Cochrane Controlled Clinical Trial Register (J.A., A.M.).
4. Current Controlled Clinical Trials (J.A.)
5. The references of each paper to identify case reports or series. Case reports or case series were identified by their title, by their abstracts in Medline, or by their description in the paper themselves, if neither was applicable the original paper was reviewed (J.A.).
6. For papers for which we could not agree of whether the published trials were based on the report we contacted the author (J.A.)

Assessment of inclusion criteria and data extraction were independently performed by J.A. and A.M.—unless otherwise indicated. The results were entered in an Excel/Access database. All disagreements were resolved by discussion.

3. Results

We identified 64 case reports and 39 small case series published in *The Lancet* between 1 January 1996 and 30 June 1997 (Tables 1 and 2).

3.1. Trials of the intervention reported

Of the 64 reports 11 (17%) were followed by clinical trials, 4 (6%) of which are still found in the Register of Current Controlled Clinical Trials. Small case series were followed by trials 13 times (33%); 5 (13%) of which could still be found in the Current Controlled Clinical Trials Register.

3.2. Impact

Of the 64 case reports surveyed, 16 (25%) were cited a minimum of 21 times and 5 (8%) more than 50 times. For the small case series the picture was similar, with nine (23%) cited at least 21 times and three (8%) cited 51 times or more. Thirty-five (55%) case reports and 21 (54%) of the case series referenced other case reports or case series.

3.3. Outcome

Sixteen (25%) of the case reports reported clear success, 44 (69%) documented improvement of their patients, and 3 (5%) reported treatment failure. Case series also usually report improvement or cure (31, 79%), only 4 (10%) reported mixed results in which the treatment failed in one or more cases and 4 (10%) reported straightforward failure of the therapy suggested.

4. Discussion

4.1. The need for case reports and case series

Whereas there has been increased recent interest in case reporting, little is known of the impact of case reports and case series on the literature or the percentage of case reports of innovative treatment that are eventually substantiated by controlled clinical trials. We conducted a survey of case reports and case series to determine how often they are cited and how many are followed by clinical trials. Our survey was limited to *The Lancet* because it is the only high-impact medical journal that still publishes case reports and case series of new and innovative treatments regularly. Sometimes the publications concerned recently introduced treatments and their use for the treatment of ''off-label'' diseases; for example, there were four reports using the recently marketed mycophenolate mofetil for different indications in 1997 [8–12].

Funding for clinical trials is often difficult or impossible to obtain, especially in small specialties, for rare diseases or for trials that compare new expensive treatments with inexpensive and established ones. However, even if evidence is missing, physicians are free to use new and off-label treatment where appropriate. The declaration of Helsiniki endorses this freedom but urges physicians to publish their experience. Although off-label use is widespread [13], places to publish the therapeutic experience is sparse.

Table 1
Summary of characteristics of case reports (n = 64)

	Number	Percentage
Frequency of being cited by other publications		
0	5	(8%)
1	8	(13%)
2–5	19	(30%)
6–10	9	(14%)
11–20	7	(11%)
21–50	11	(17%)
51–100	4	(6%)
336	1	(2%)
Reports that quote other reports or case series		
Yes	35	(55%)
No	29	(45%)
Case reports that were followed by published trials		
Yes	11	(17%)
No	53	(83%)
Case reports thatwere followed by trials in the current controlled clinical trials register (11/2002 ?)		
Yes	4	(6%)
No	60	(94%)
Outcome (overall impression)		
Success (total clearance of disease)	17	(27%)
Improvement	44	(69%)
Failure	3	(5%)
Reference to other case reports (or case series)		
Yes	35	(55%)
No	29	(45%)

Some reports translate established and evidence based treatments of more common conditions into rare diseases, for example, Gottlieb's publication of Doxorubicin in classic Kaposi sarcoma [14], or cure of a duodenal ulcer after the eradication of *Helicobacter heilmannii* [15]. Other cases may identify coincidental outcomes of a therapy that is hard to initiate, for example, bone marrow transplantation for autoimmune hepatitis, hepatitis B, or rheumatoid arthritis [16–19]. We found some papers that substantiated previous observations by long-term follow up, for example, one patient who received bone-marrow transplantation for Langerhans' cell histocytosis 12 years prior to the second report [20]; or a case series that extended a clearly successful case report of a treatment success previously published in *The Lancet* by the same author. This series of four patients, who received aspergilloma treatment endoscopically, demonstrated mixed outcomes, a result that is helpful to judge the treatment in a more balanced way [21]. Whereas a case report or small case series is not sufficient evidence to establish efficacy of a therapeutic intervention, large trials in these conditions are unlikely to be performed [22]. In the absence of trials, it would be desirable to have access to the experiences of physicians who have treated similar cases. Dedicated space that allows submission of second or third reports is missing. This space could be easily created on the Web in the form of a registry. A first such registry is currently being developed by Gracyznki et al., who have set up a Web site for the reporting of unusual cases, which is called the World Library of Case Reports (www.WLoCR.com). Before the advent of the Web, similar registries have been suggested, for example, for new surgical interventions.

4.2. Impact of case reports and case series

Reports and small case series published in *The Lancet* have considerable influence. They are certainly read and cited. We found that the 103 papers we surveyed were cited on average 17 times (median 6.5). Only seven papers were not cited at all. One paper, which reported a patient from a dose-finding trial of eight patients, was cited 336 times [23]. Whereas this paper was an exception, 25 (24%) of the papers were cited a minimum of 20 times and 8 (8%) 51 times or more. Some editors assume that case reports ''are never read'' and ''never cited'' [24], and refrain from publishing them; however, for *The Lancet*, this assumption is not true. An average number of 17 quotations over a period of 6 years is impressive, but slightly lower than *The Lancet*'s impact factors for 1996 and 1997, which were17.9 [25] and 16.1 [26], respectively. The Journal Citation Report's (JCR) impact factor is calculated by dividing the number of citations of papers in the 2 years after publication by the number of ''substative manuscripts'' published in the journal. That *The Lancet*'s impact factor could be harmed by the reports has been predicted elsewhere [26], and indeed, it sank to 10.2 [25] in 1999 as a reflection of the increased room devoted to research letters. However, the papers we examined still had substantial impact on the medical literature.

Table 2
Summary of characteristics of case series (2 to 10 patients); (n = 39 case series)

	Number	Percentage
Frequency of being cited by other publications		
0	2	(5%)
1	5	(13%)
2–5	10	(26%)
6–10	4	(10%)
11–20	9	(23%)
21–50	6	(15%)
51–69	3	(8%)
Reports that quote other reports or case series		
Yes	21	(54%)
No	18	(46%)
Case reports that were followed by published trials		
Yes	12	(31%)
No	27	(69%)
Case reports that were followed by trials in the current controlled clinical trials register (11/2002)		
Yes	5	(13%)
No	34	(87%)
Number of patients		
2	11	(28%)
3	6	(15%)
4	3	(8%)
5	5	(13%)
6	3	(8%)
7	2	(5%)
8	3	(8%)
9	2	(5%)
10	3	(8%)
Not reported	1	(3%)
Case series that reported mixed response including patients where the treatment had failed		
Yes	4	(10%)
Case series that reported failure of treatment only		
Yes	4	(10%)
Case series that report improvement or cure, without failure		
Yes	31	(79%)
Reference to other case reports (or case series)		
Yes	17	(44%)
No	22	(56%)

Fifty-six (54%) of the papers referenced other case reports or case series, and 87 (84%) discussed some results of bench research to lend more credibility to their findings. This reliance on external evidence is understandable. Although a pathophysiologic model lends credibility to the clinical results, the reference to other reports or series helps to understand why certain interventions were chosen and how the idea that a treatment may work was developed.

4.3. Controlled clinical trials

We found 23 published controlled clinical trials that were based on or evaluated treatment of the case reports or case series surveyed, with nine trials, some of which were duplicates of published trials, still to be found in the register of current controlled clinical trials. After a period of sometimes only 5 years after publication (until June 2002, when we began the survey) 22% reports were followed by clinical trials. This percentage is an impressive proportion, especially considering the rarity of some of the treated conditions.

4.4. Publication bias

The papers we surveyed stimulated optimism. Only three reports (5%) and four case series (10%) reported treatment failure. Publication bias is well known in medicine. Medical editors have acknowledged the low number of negative trials published, and called for ''an amnesty of unpublished trials'' to register unpublished small often negative trials [27,28]. One survey of published clinical research found a strong bias towards positive results. This bias was stronger in observational than controlled studies, and more prominent in smaller rather than larger trials [29].

4.5. Limitation

This survey only reflects the impact of papers published in *The Lancet*, and does not allow generalizing these findings to other journals. It is also strictly limited to papers that report on treatment benefits, and does not include reporting of treatment associated adverse events, which are

sometimes not identified in clinical trials. However, *The Lancet* is the only high-impact journal that still publishes case reports and case series, and therefore, it seemed not possible to find comparable journals to supplement our observations. Also, we cannot evaluate the impact that case reports and case series have on clinical practice. Most importantly, though, the survey cannot enlighten us on what proportion of the treatments that were suggested are useful and how many may be more harmful than beneficial.

4.6. Reporting quality of case reports and case series

There are papers on reporting of case series most notably by Moses [2] and Abel [30,31] and Jenicek's excellent recent book [3]. They suggest, in essence, the following guidelines that need to be considered when writing and conducting case series:

1. Case series should be longitudinal, according to a predefined protocol. The protocol should define eligible patients, dosage, and treatment regime as precisely as possible. This reflects the thought process that should precede any treatment innovation.
2. It must explain why they have been observed, thus outlining basic inclusion and exclusion criteria. The reader has to understand why patients have been chosen. Patients selected due to failure of previous treatments and untreated volunteers have a different chance of cure; thus, the protocol must allow for these differences and analysis must be separate, if necessary.
3. All patients in a department/an institution fulfilling the criteria and consenting should be treated according to plan.
4. The diagnosis of the patients must be well-documented and open to scrutiny
5. All patients should be observed with respect to outcome, which needs to be clearly defined and measured as objectively as possible, even those that may refuse the innovative treatment. An intention to treat analysis should be considered standard for nonrandomized studies [31].
6. There should be some indication of treatment success rate in untreated or differently treated patients.
7. The place of treatment should be described, indicating differences of patient collectives, for example, between primary and tertiary centres.

Case series that are carefully designed and, of course, very similar to clinical trials, are likely to minimize bias and maximize the information that can be deduced from a limited numbers of patients. Case reports are essentially the beginning of what, through duplication elsewhere, or in by the same physician, can become a case series, and should therefore follow these rules where possible.

Numerous guidelines are available to guide medical reporting. We have demonstrated that case reports and case series can have substantial impact on the literature, but that controlled clinical trials did not follow published case reports and case series even published in a high-impact journal more than 75% of the time. For many treatments, case reports and case series are the only available evidence. Therefore, we suggest that a guideline for case reporting based on the successful CONSORT statement (*CON*solidated *S*tandards *O*f *R*eporting *T*rials) [32] should be developed and space should be given to follow-up reports. Despite the space constraint in medical journals, this may improve the quality of reports and help to substantiate their results.

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