



Original Research Paper

Integrative medicine case series: A clinician's guide to publication

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ABSTRACT

Case series, while considered low on the research hierarchy, have been a valuable method of informing medical practice for as long as medicine has been practised. Case reports can generate hypotheses, uncover original observations, novel diagnostic and therapeutic approaches, unusual, new or uncommon diseases and complications of medical treatment. Despite their importance, and contemporary trends supporting their further use, publishing case series can be a difficult task for many clinicians and researchers. Preparing a case series for publication can be both a professionally and personally rewarding endeavour for clinicians. This article describes practical and academic insights into writing a case series for publication.

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1. Introduction

A case series is a descriptive, uncontrolled study based on a group of patients with a particular condition or disease who undergo a particular treatment [1–5]. Among study designs, case series are generally considered one of the least methodologically robust, however, they occupy a strategic and useful niche in the research hierarchy. Case series are most commonly used in some modalities or conditions where technical or ethical reasons limit controlled trials but overall case series are a under-utilised resource [6]. A case series does not generally determine treatment efficacy but provides evidence of management, safety, complications, and generalises the management of a condition. From the findings in cases series, hypotheses are often generated and/or proof (or disproof) of a concept, which are then tested in a larger and more structured research designs [7].

2. Difference between a case report and case series

Advances in Integrative Medicine has previously published guidelines for publication of integrative medicine case reports [8]. Many of these recommendations will extend to case series, but there are also some additional and unique requirements. The development of guidelines for case series has been somewhat complicated by the fact that there is no universal agreement on

what separates a case series from a case report. The number of cases has been used as a distinguishing feature with case reports typically not including more than three cases whereas case series include more than three cases [9]. Others suggest that the minimum for a case series is five [10]. Case series are also sometimes conflated with uncontrolled trials. However, this representation is inaccurate. Uncontrolled trials investigate a specific research question without the use of a control group, but do so in a controlled non-clinical research setting, whereas case series focus on the presentation of data collected in clinical settings.

The reporting intent has also been postulated as a potential differentiation between case reports and case series. It has been suggested that case reports tend to be best used for communicating rare diseases and a case report includes an individual medical report for each patient [9,10]. Case series, on the other hand, are suggested to be best used to present characteristics of new diseases, to formulate hypothesis for later studies, to present results of new therapies or therapies for rare conditions, to report rare adverse effects in common conditions or to present new findings on the management of a condition and data about individual is pooled together [9,10]. For example, case series on alternative methods for treating hip fractures have been used to generate a hypothesis for a number of higher level randomised controlled studies [11]. Case series have identified, in clinical practice, a trend of greater safety through a reduction in bleeding and re-admission for dehydration for children who underwent a powered intracapsular tonsillectomy – in this case used to confirm if initial clinical findings observed in practice regarding the safety

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of this procedure were correct [12]. Case series have been used to present rare complications of the use of mesh for crural repair in hiatal hernia repair [13]. Case series can also often be the first published indications of emerging epidemics – a 1981 published case series was particularly influential, for example, reporting on the syndrome that was soon to be known as AIDS [14].

3. Why case series matter

Whilst considered 'low' on the evidence hierarchy (case series are a level IV on the scale of evidence, placing them lower down than studies that have a control of some kind), they remain an instrumental resource in increasing knowledge and disseminating clinical information [1]. Historically case series have been used to raise links about side effects to medication/treatment such as liver adenomas and the contraceptive pill, and toxic effects of high concentrations of oxygen on the optic nerve in newborn infants [10]. Case series have been used to identify novel treatments, or uncover novel uses for existing treatments. Case series have also been used to identify conditions such as polycystic ovarian syndrome, identify etiological causes of conditions such as the aetiology of osseous metaplasia and identify new treatments such as anterolateral thigh and fibular flaps [3,9]. Case series provide valuable information in the medical field for new innovations and treatments for many conditions that cannot be researched in another way due to technical and/or ethical reasons, examples of this include fracture healing, heart surgery and child birth [6]. Like case studies, case series may also provide initial evidence of safety, or proof of concept, of new and emerging treatments, which may be validated by larger trials. In a field such as integrative medicine, with an emerging but not yet developed research capacity [15], case series may be a useful tool to build research capacity, whilst also building the nascent evidence base for integrative medical treatments.

4. Building research capacity in integrative medicine

A well-written, rigorous case series can significantly inform evidence-based practice. However, poorly written and/or irrelevant case series can negatively influence treatment decision-making and decrease the value of case series [9]. Therefore it is essential that issues of quality and rigour are fully considered when developing case studies. In addition to informing evidence-based practice, case series are a way in which clinicians can develop both their clinical and research skills and enhance reflective practice [16]. The whole process of designing, planning, conducting, analysing, writing and receiving feedback from journal editors can also be satisfying on a personal level and the clinician can develop new skills that may improve their clinical practice.

Scholarly writing, as done through publication of case reports, systematic reviews and case series can offer valuable learning experiences for clinicians, offering insights into their own practice that result in improved clinical care for their patients, obliging mental and practical discipline in reflective practice [17]. Peer-review can offer valuable feedback and provides insights to clinicians beyond their training or clinical practice experiences. In addition to professional benefits, clinicians partaking in scholarly writing activity can also help develop their fields.

In integrative medicine particularly, which historically lags other fields in ability to fully engage with research activity, the active involvement of clinicians in research is particularly important [15]. Clinician involvement is necessary, for example, to reflect the realities of clinical practice in the field or discipline that is being studied [18]. However, it is equally essential that clinicians engage with research in a meaningful and rigorous way.

For case series to appropriately inform evidence-based practice, they must be presented in a scientifically rigorous manner.

5. Case series guidelines

Whilst a number of guidelines are available for the reporting of various research methodologies (such as the CARE statement for case studies, or PRISMA for systematic reviews), there are no standardised reporting guidelines for case series. Many publications use the terms case reports and case series interchangeably, or include case series in the guidelines for case reports. However, case reports and case series are different methodological approaches and case report literature frequently does not include the additional reporting, ethical issues and methodological complexities that occur when undertaking and reporting on a case series. The methodology of a case series includes the generation of a hypothesis, inclusion and exclusion criteria for cases, a time period for collection, and a method of analysing the case series. A case report will have none of these methodological inclusions (though may generate a hypothesis in the discussion). When reporting a case series the hypothesis, the time frame for collecting data and the analysis of the data is to be included, whereas a case report only has a time frame for care or treatment and no hypothesis or analysis section.

6. Discipline specific guidelines

As with most methodologies, each integrative medicine practice will bring with it unique challenges and considerations for accurate and rigorous reporting. For this reason, a number of disciplines have developed guidelines for the reporting of case series, even though no international standard for the reporting of case series has been developed. Specific guidelines have been developed for the fields of plastic surgery [3], oncology [5], ophthalmology [7,19], acupuncture [16], psychology [4], as well as general instructions [1,2]. In addition to following the case series guidelines for specific disciplines, any international guidelines for the reporting of individual modalities or disciplines – such as the acupuncture specific STRICTA publication guidelines [20] – should also be adhered to. Given the lack of standardised international guidelines on the reporting of case series, it is highly recommended that general instructions, specific case series guidelines and international guidelines for the reporting of individual disciplines be followed. Where there is overlap with case study requirements, the use of the CARE statement should also be followed.

7. Ethical approval and case series

There are a number of issues that make it difficult for clinicians to engage in and conduct a case series. The definition of what is observational versus what is interventional research is not always clear-cut and as such there is no definitive answer on the need for ethical approval for case series. Generally, observational research (i.e. documenting treatment as it is practised, without any alteration to naturalistic practice) will not require ethics approval, whilst interventional research (i.e. altering a treatment strategy to fit within a research project's protocol) will. Different organisations, authors and fields have differing definitions for when a case series is classified as research. Some authors consider ethics is needed for a case series when it is prospective but not when it is retrospective [9]. Many journals use the Duke University Health System Case report guidelines for defining 'research' and the need for ethical approval [21]. The definition of research Duke uses involves "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalisable knowledge" [21]. Thus any case series that has a

systematic data collection *beyond that which is part of routine clinical practice* would be classified as research. Duke however also states that any research, regardless of the method of collection (i.e. prospective or retrospective) that has more than three cases meets the definition of research [21]. Presentation of cases at teaching conferences or continuing education seminars however is not considered research and nor is publishing case series as an editorial piece that clearly states it is the authors personal experience. Authors of case series need to ensure their case series meets the ethical requirements of where it is going to be presented.

Many journals have standardised consent forms for case series that are 'case report' consent forms. Many of these are not suitable for a case series as they are designed specifically for the needs of the individual in a case report and commonly they do not take into account the larger numbers of participants in a case series or the differing reporting and methodology of a case series. Having ethics approval for conducting a case series would ensure there was a consent form that specifically suits the case series being undertaken. If ethics approval is not needed it would be advisable to contact the journal for planned submission of the case series to guarantee a suitable and acceptable consent form can be used. Even in instances where ethics approval is not necessary, a statement that the research (and practice) has met national ethics guidelines is necessary. Where ethics approval has not been granted, this can be demonstrated by inserting a statement to this effect – e.g. ethics approval was not deemed necessary in accordance with institutional guidelines, however the project was conducted in accordance with national ethical guidelines on research projects.

8. How should case series be designed?

Many authors purport the primary purpose of a case series is a 'first step', and should be focused on the generation of a hypothesis, which can later be tested with a more rigorous methodology [6]. Others suggest that case series have a more important evidence-building role in-and-of themselves by systematically documenting the treatment and management of a condition in real world clinical settings [7,9]. Both uses are valid, and ultimately the most important consideration is that a case series should be designed to add valuable information to the current body of knowledge. This means that it is not sufficient for case series to merely document treatment, but they must also serve an educational purpose. Just as case reports published in generalist journals such as *Advances in Integrative Medicine* need to be 'notable' (i.e. serves a *novel* learning activity for the reader).

Less novel case series – such as these that document treatment in accordance with standard professional guidelines – are valid and may play an important role in developing an evidence-base (particularly in nascent disciplines such as integrative medicine), though may be more appropriate for publication in specialist 'case report' journals (these do exist, usually in journals which require a fee for publication – such as *Clinical Case Reports*, *Journal of Medical Case Reports* or *BMJ Case Reports*). The primary reasons for rejection of case series or publication are poor reporting – which can be remedied by following reporting guidelines – or lack of suitability for the intended journal – which can be remedied by ensuring the target journal is appropriately identified beforehand.

Case series must start with a hypothesis – a purpose (for example, high dose *Passiflora* spp. reduces anxiety). From the hypothesis it is determined how the data is to be collected and reported. Case series design should include clear definitions of what cases are to be included and excluded (i.e. consecutive patients presenting with anxiety aged 18–70) and if the data is to be collected retrospectively or prospectively. To avoid selection bias, observational data should collect consecutive cases and this

should be stated in the methodology. Any reasons for deviating from collecting consecutive cases should be planned and clearly stated (this could be the presence of potentially confounding comorbidities or medications or refusal of consent, for example). Development of the hypothesis and the methodology of data collection must be done prior to collecting the data.

9. Statistics in case series

Case series may have a number of limitations such as small patient numbers, no internal control, variable follow-ups and or selection bias (non-consecutive cases), which impact on the appropriate statistical analysis of case series. The use of descriptive statistics such as mean, medians and interquartile ranges (IQR) are descriptive statistics that present the data and do not overstate or confound case series findings. Presentation of data in this way also allows for future synthesis or combining of data from several case-series [19].

It is recommended that case series discuss how the results compare with an appropriate external comparison group [7]. This recommendation is for a discussion rather than a statistical analysis. If an analysis is to be undertaken with a comparison group then it is important that the correct statistical analysis is undertaken. Statistics need to evaluate the potential contribution of random error and assumption of equal event risk should not be assumed especially if follow up times differ with study patients or the collection of study data occurred in vastly different time periods [7,19]. Confidence intervals and risk estimates should be used to present data comparing studies as this limits authors over-interpreting or misinterpreting the data [7,19].

When reporting and analysing frequencies in case series data on the proportion at presentation (or study entry) and the rate during follow up should be reported [19]. Rates should be expressed as person-years as this allows comparison with other studies. This is particularly important for case series with variable follow-ups as combining both proportion and rates does not account for the effect of time [19]. If the case series is looking at events that can occur more than once in a given patient then differentiation between the event rates and rate of patients being effected should be reported.

No comparative tests should be done that yield a *p* value for a number of reasons: (a) case series are unlikely to have the necessary sample to create a *useable p* value, (b) case study methodology does not allow for testing of efficacy, e.g. comparing treatment A against treatment B as there is no comparison group thus no statistical analysis should be undertaken such as *t*-tests, analysis of variance/covariance such as ANOVA or ANCOVA or regression analysis should be undertaken.

10. What should be reported and how should it be reported?

A chief criticism for the use of case series is poor reporting which leads to conclusions that over-reach the case series methodological design or misleading or difficult to interrupt findings [6,7,9]. The flaws in poor reporting could often be easily rectified, allowing proper interpretation of the data and reliable conclusions to be made.

Journals have differing requirements for headings and sections of case series. Most journals advise compliance with the CARE guidelines for reporting case studies [22]. Whilst case series do have some unique considerations, the requirements for reporting are broadly consistent with the CARE statement. They commonly include an abstract, title, keywords, introduction, methods, results, discussion and conclusion. When reporting the results of a case series the following should be included:

Title: The title should include the word case series and describe the aspect of the case series, which is of greatest interest to the reader such as the presentation, the intervention, outcomes, safety or the diagnosis.

Hypothesis: The report should explicitly state the hypothesis under consideration. A hypothesis should have a study population, the intervention and the outcome. The outcome covers risk/safety, rarity and or management of a condition. The hypothesis must also suit a case series design.

Ethics approval: If ethical approval was obtained then state this and the ethics approval number. If ethics was not obtained then a statement about why ethics was not needed and the process of ensuring patient anonymity is needed and details that consent was obtained from the patients.

Definition of condition being investigated and inclusion/exclusion criteria: The method section should include a clear definition of the condition being investigated so that readers can compare the cases presented to their own clinical practice. Inclusion and exclusion criteria should also be clearly stated and the rationale for inclusion or exclusion should also be stated.

Time frame and method for collecting patient data: Authors should present clear details about the time frame for collecting of the cases for the case series and also if the collection was retrospective or prospective. A statement should be included describing how the cases were collected i.e. if continuous cases were collected or if not the reasons for intermittent case collection.

Patient characteristics: Authors need to describe the cohort in enough detail that the study findings are relevant to other clinicians. These include, but are not limited to, age, gender, education disease/injury/presentation, socioeconomic status and or complicating factors.

Intervention: A detailed description of the intervention and any co-interventions administered is paramount so that other clinicians/researchers can repeat the treatment. Is it important to remember that what is standard treatment/care for you may not be standard for others especially in different cities and or countries.

Outcomes: Report on how any outcome data was collected and where possible collect both clinical measures as well as patient's perceptions. Validated questionnaires, such as the Short Form 36 questionnaire, are reliable and sound tools for measuring patient satisfaction.

Details about follow up: Authors should include criteria for the length of the time frame for follow up and ensure that it is realistic and appropriate for the condition being investigated, for example tibial fractures can improve for up to a year so a six months time frame would not be realistic or appropriate. Any patient loss to follow up should also be included.

Blinding: Authors should state if there was any blinding of either the collectors of the data and or the outcome assessors.

Analysis: Descriptive statistics only should be used. No comparative tests should be done that yield a *p* value, as case series are unlikely to have the necessary sample to create a *useable p* value. For this reason it is also not appropriate for a case series to 'compare' treatment A against treatment B.

Discussion of the results: Results should be discussed in relation to other external comparison groups where possible as case series lack internal controls. External comparison groups need to be relevant to the case series and justification for the comparison provided.

Acknowledgement of limitations of methodology: Authors should address the limitations of the case series methodology including the presence of chance, other lifestyle factors and any bias.

Conclusions: No absolute conclusions about the presented treatment should be stated, as a case series methodology is not appropriate for determining the efficacy of an intervention. Case

series are not about hypothesis being tested but about the generation of hypothesis or the management of a condition. As such, statements about X treatment being better than Y treatment, or even X treatment is effective are not valid or appropriate. Conclusions should be descriptive and reflect the findings in a way that is cognisant with the case series.

11. Writing style

The writing style for case series should suit the intended audience; a report or educational presentation (or article submitted to a journal targeted at researchers) would differ in the writing style to an article for publication in a medical journal (whose audience may be more predominantly made up of clinicians). As with all submissions to medical and research journals, articles written for publication should be written in an academic or scholarly prose. 'Clinical' phrases (e.g. "on examination", "presents with" or "of note") should be removed, and replaced with their academic counterparts (e.g. clinical signs are either present or absent, not positive or negative). Journalistic phrases are useful when developing copy for a lay audience, but are not appropriate for a medical or research journal. *Advances in Integrative Medicine* is an international journal, and therefore writing style should be suitable for an audience in which English is not their native language. Time-poor and over-burdened clinicians and researchers for whom English is their first language will also appreciate a more simplified writing style. Empty prose should be avoided, and the results and findings described as succinctly as possible.

12. Summary

Case series are an important and instrumental resource that can lead links about side-effects, identify new treatments and or identify previously unidentified conditions. A criticism for the use of case series is poor reporting which leads to misleading or difficult to interpret findings. The development of a strong case series methodology including the generation of a hypothesis, inclusion and exclusion criteria for cases, a time period for collection, and a method of analysing the case series provides the basis for a rigorous case series that can then provide the pillar for publication, and a strong foundation for developing an evidence base.

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