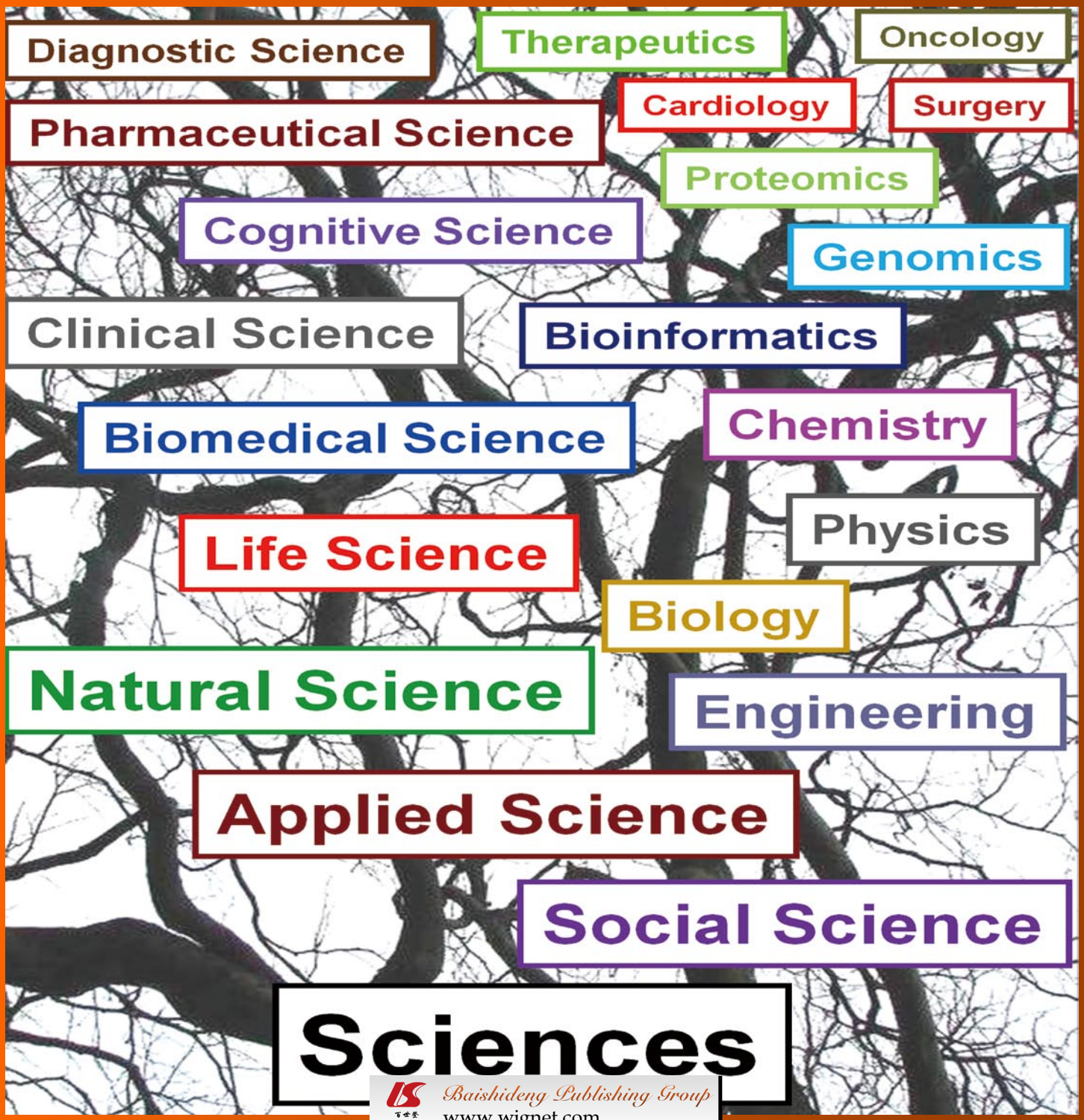
ISSN 2222-0682 (online)

World Journal of *Methodology*

World J Methodol 2011 September 26; 1(1): 1-26



Baishideng Publishing Group
www.wjgnet.com

World Journal of Methodology

A peer-reviewed, online, open-access journal of methodology

Editorial Board

2011-2015

The *World Journal of Methodology* Editorial Board consists of 238 members, representing a team of worldwide experts in methodology. They are from 41 countries, including Argentina (2), Australia (7), Austria (3), Belgium (4), Brazil (3), Canada (10), China (27), Croatia (1), Cuba (1), Czech (3), Denmark (2), Egypt (1), France (6), Germany (4), Greece (3), Hungary (2), India (8), Iran (3), Israel (1), Italy (18), Japan (12), Lithuania (1), Malaysia (1), Mexico (2), Netherlands (2), New Zealand (1), Norway (3), Pakistan (2), Poland (2), Portugal (3), Romania (4), Russia (2), South Korea (3), Spain (17), Sweden (1), Thailand (2), Turkey (2), United Arab Emirates (1), United Kingdom (10), United States (57), and Uruguay (1).

Hans Sanderson, *Roskilde*

Egypt

Nervana S Bayoumi, *Cairo*

France

Marc Y Bardou, *Dijon*
Mohammed M Bettahar, *Nancy*
Olivier David, *Grenoble*
Florian Lesage, *Sophia Antipolis*
Patrick Maison, *Creteil*
Sandrine Marquet, *Marseille*

Germany

Harald Hampel, *Frankfurt/ Main*
Frank Peinemann, *Cologne*
M Lienhard Schmitz, *Giessen*
Alfons Schnitzler, *Duesseldorf*

Greece

Konstantinos P Economopoulos, *Athens*
Demosthenes Panagiotakos, *Athens*
Issidora Papassideri, *Athens*

Hungary

Péter Halász, *Budapest*
András Komócsi, *Pécs*

India

Dipshikha Chakravortty, *Bangalore*
DK Dhawan, *Chandigarh*
R Jayakumar, *Cochin*
Abdul Viqar Khan, *Aligarh*
Geetha Manivasagam, *Vellore*
Jacob Peedicayil, *Vellore*
YS Prabhakar, *Lucknow*
Rakesh Kumar Sinha, *Ranchi*

Iran

Mehran Javanbakht, *Tehran*
Enayat Kalantar, *Sanandaj*
Shekoufeh Nikfar, *Tehran*

Israel

Dan Frenkel, *Tel Aviv*

Italy

Giuseppe Biondi-Zoccai, *Modena*
Carlo Bonanno, *Vicenza*
Paolo Borrione, *Turin*
Filippo Cademartiri, *Monastier di Treviso*
Alberto Chiesa, *Bologna*
Annamaria Cimini, *L'Aquila*
Giovanni Di Leo, *San Donato Milanese*
Giovanna Ferraioli, *Milan*
Irene Floriani, *Milan*
Landoni Giovanni, *Milano*
Stefano Girotti, *Bologna*
Paola Irato, *Padova*
Mario Mascalchi, *Florence*
Patrizia Mecocci, *Perugia*
Germano Orrù, *Cagliari*
Carlo Riccardi, *Perugia*
Mauro Valtieri, *Rome*

Japan

Kohei Akazawa, *Niigata*
Subash CB Gopinath, *Tsukuba*
Koichi Hattori, *Tokyo*
Satoshi Hirohata, *Okayama*
Masahiro Kohzuki, *Sendai*
Yoshinori Marunaka, *Kyoto*
Kenji Miura, *Tokorozawa*
Ryuichi Morishita, *Suita*
Mitsuhiko Noda, *Tokyo*
Yurai Okaji, *Tokyo*
Hirosato Seki, *Osaka*
Hisanori Umehara, *Kahoku-gun*

Lithuania

Giedrius Barauskas, *Kaunas*

Malaysia

Iis Sopyan, *Kuala Lumpur*

Mexico

Martha Rodríguez-Moran, *Durango*
Julio Sotelo, *Mexico*

Netherlands

Bart J Polder, *Emmeloord*
Frank Twisk, *Limmen*

New Zealand

Valery Feigin, *Auckland*

Norway

Cato Grønnerød, *Fredrikstad*
David F Mota, *Oslo*
Tore Syversen, *Trondheim*

Pakistan

Muhammad A Noor, *Islamabad*
Yasir Waheed, *Islamabad*

Poland

Piotr Dziegiel, *Wroclaw*
Tadeusz Robak, *Lodz*

Portugal

Nuno Lunet, *Porto*
Hugo Sousa, *Porto*

Romania

Elena Moldoveanu, *Bucharest*
Monica Neagu, *Bucharest*
Florin-Dan Popescu, *Bucharest*

Russia

Galina B Bolshakova, *Moscow*
Sergey V Dorozhkin, *Moscow*

South Korea

Sang Soo Hah, *Seoul*
Chang-Yong Lee, *Kongju*

Spain

Salvador F Aliño, *Valencia*
Mohamed Farouk Allam, *Cordoba*
Alejandro Cifuentes, *Madrid*
Miren Lopez de Alda, *Barcelona*
Joaquin de Haro, *Madrid*
Emma Garcia-Meca, *Cartagena*
Mónica H Giménez, *Zaragoza*
M de la Guardia, *Valencia*
Josep M Guerrero, *Barcelona*
Fernando Marin, *Madrid*
José A Orosa, *A Coruña*
Jesús Osada, *Zaragoza*
Soledad Rubio, *Córdoba*
Helmut Schröder, *Barcelona*
Jesus Simal-Gandara, *Ourense*
Gabriela Topa, *Madrid*
Miguel A Vallejo, *Madrid*

Sweden

Jenny Selander, *Stockholm*

Thailand

Amporn Jariyapongskul, *Bangkok*
Bungorn Sripanidkulchai, *Khon Kaen*

Turkey

Ferda E Percin, *Ankara*
Aysegul Yildiz, *Izmir*

WJM

World Journal of Methodology

Contents

Bimonthly Volume 1 Number 1 September 26, 2011

AIM AND SCOPE

World Journal of Methodology (*World J Methodol*, *WJM*, online ISSN 2222-0682, DOI: 10.5662) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 23 experts in methodology from 41 countries.

WJM aims to rapidly report the most recent results in medical diagnostics, therapeutic techniques and equipment, clinical medical research, clinical and experimental techniques and methodology. It provides a platform to facilitate the integration of clinical medicine and experimental techniques and methodology to help clinicians improve diagnostic accuracy and therapeutic efficacy. The journal publishes original articles and reviews on the following topics: (1) Clinical medical techniques, including but not limited to those for pharmaceutical medicine, laboratory medicine, radioactive medicine, medical imaging, nuclear medicine, physical therapy, pathology, surgery, disinfection, nutritional therapy, transfusion and medical equipment; (2) Clinical medical research on etiology, epidemiology, pathogenesis, morphology and function, signs and symptoms, clinical trials, and evidence-based medicine; and (3) Laboratory methodology, including but not limited to techniques in DNA/RNA sequencing, preparation and transformation of competent cells, PCR, protein biochemistry, cell biology, genetics and epigenetics, immunology, microbiology, animal models of human pathologies, bioinformatics, and laboratory equipment manipulation and control.

NAME OF JOURNAL
World Journal of Methodology

LAUNCH DATE
September 26, 2011

EDITING
Editorial Board of *World Journal of Methodology,*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: wjm@wjgnet.com
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Co., Limited
Room 1701, 17/F, Henan Building,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: +852-3115-8812
Telephone: +852-5804-2046
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

FREQUENCY
Bimonthly

PUBLICATION DATE
September 26, 2011

ISSN
ISSN 2222-0682 (online)

EDITOR-IN-CHIEF
Yicheng Ni, *Leuven*

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Journal of Methodology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: wjm@wjgnet.com
http://www.wjgnet.com

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2222-0682/g_info_20100722180909.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/2222-0682office

World Journal of Methodology

Online Submissions: http://www.wjgnet.com/2222-0682office
wjm@wjgnet.com
doi:10.5662/wjm.v1.i1.1

World J Methodol 2011 September 26; 1(1): 1-3
ISSN 2222-0682 (online)

EDITORIAL

What is the purpose of launching the *World Journal of Methodology*?

Yicheng Ni

Yicheng Ni, Department of Radiology, University Hospitals, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium
Author contributions: Ni Y solely contributed to this paper.
Correspondence to: Yicheng Ni, MD, PhD, Professor, Department of Radiology, University Hospitals, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium. yicheng.ni@med.kuleuven.be
Telephone: +32-16-330165 Fax: +32-16-343765
Received: August 31, 2011 Revised: September 1, 2011
Accepted: September 19, 2011
Published online: September 26, 2011

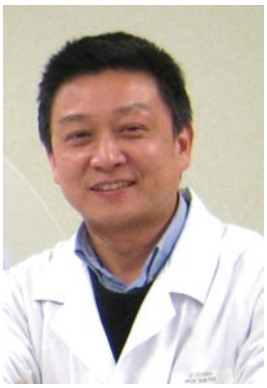


Figure 1 Editor-in-Chief of the *World Journal of Methodology*. Yicheng Ni, MD, PhD, Professor, Department of Radiology, University Hospitals, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium.

Abstract

Congratulations to the publisher, members of the editorial board of the journal, all the authors and readers for launching the *World Journal of Methodology* (*WJM*) as a new member of the World series journal family! Scientific advances and important breakthroughs have been facilitated by well developed methodologies or techniques and any misleading findings and theories are exclusively attributable to certain methodological defects. Thus, the role of appropriate methodologies in the development of science and technology cannot be overemphasized and the need for inaugurating this new journal is self-evident. The *WJM* is a peer-reviewed open-access periodical centered in biomedical sciences but with multidisciplinary coverage. If you want to share any new methodologies, any experiences of the application or improvement of such methodologies and any methodology-related academic issues with your peers, you will find the *WJM* a good media to publish your papers!

Key words: Methodology; Biomedical sciences; Peer-reviewed; Open-access; Journal

Peer reviewer: Alberto Chiesa, MD, Institute of Psychiatry, University of Bologna, Viale Carlo Pepoli 5, 40123 Bologna, Italy

Ni Y. What is the purpose of launching the *World Journal of Methodology*? *World J Methodol* 2011; 1(1): 1-3 Available from: URL: http://www.wjgnet.com/2222-0682/full/v1/i1/1.htm DOI: http://dx.doi.org/10.5662/wjm.v1.i1.1

I am Yicheng Ni (Figure 1), a full professor from University of Leuven, Belgium and the editor-in-chief of *World Journal of Methodology* (*WJM*). It is my great honor to introduce the *WJM* as a new forum for exchanging thoughts and experiences about any methodological approaches to solving problems in research in both fundamental and clinical medicine. Congratulations to the publisher, members of editorial board of the journal, all the authors and readers for this memorable event!

I am very pleased to announce that the first issue of the *WJM*, on which preparation was initiated on April 5, 2011, is officially published on September 26, 2011. The *WJM* Editorial Board has now been established and consists of 238 distinguished experts from 41 countries. What is the purpose of launching *WJM*? And what is

the scope and how are the columns designed? These are some of the subjects I would like to address hereunder.

The word methodology refers to a process involving definitions, explanations and procedures applied as a guideline to collect, store, analyze and present information in the practices of a particular research discipline. Methodology addresses how to solve problems with specified components such as tasks, tools, techniques, methods, phases, *etc*.

Historically, scientific advances and important breakthroughs have all been facilitated by well developed methodologies or techniques[1-5]. Likewise, any findings, conclusions and theories that temporarily predominated but later were proved wrong and misleading can be attributed to their methodological defects[6-8]. Therefore, the role of appropriate methodologies in the development of science and technology cannot be overemphasized and the need for inaugurating this new journal is without any doubt.

The *WJM* aims to rapidly report the most recent results in medical diagnostics, therapeutic techniques and equipment, clinical medical research, clinical and experimental techniques and methodology. It provides a platform to facilitate the integration of clinical medicine and experimental techniques and methodology to help clinicians improve diagnostic accuracy and therapeutic efficacy. The journal publishes original articles and reviews on the following topics: (1) Clinical medical techniques, including but not limited to those for pharmaceutical medicine, laboratory medicine, radioactive medicine, medical imaging, nuclear medicine, physical therapy, pathology, surgery, disinfection, nutritional therapy, transfusion and medical equipment; (2) Clinical medical research on etiology, epidemiology, pathogenesis, morphology and function, signs and symptoms, clinical trials, and evidence-based medicine; and (3) Laboratory methodology, including but not limited to techniques in DNA/RNA sequencing, preparation and transformation of competent cells, polymerase chain reaction, protein biochemistry, cell biology, genetics and epigenetics, immunology, microbiology, animal models of human pathologies, bioinformatics, and laboratory equipment manipulation and control. Since biomedical science stems from natural science as a relatively young branch and has been fostered by the methodologies of almost all other science branches, the scope of the *WJM* can be immensely broad or virtually unlimited as illustrated by a few examples in Figure 2.

The columns in the issues of the *WJM* include: (1) Editorial: to introduce and comment on major advances and developments in the field; (2) Frontier: to review representative achievements, comment on the state of current research and propose directions for future research; (3) Topic highlight including the following three formats (A) 10 invited review articles on a hot topic; (B) a commentary on common issues of this hot topic; and (C) a commentary on the 10 individual articles; (4) Observation: to update the development of old and new

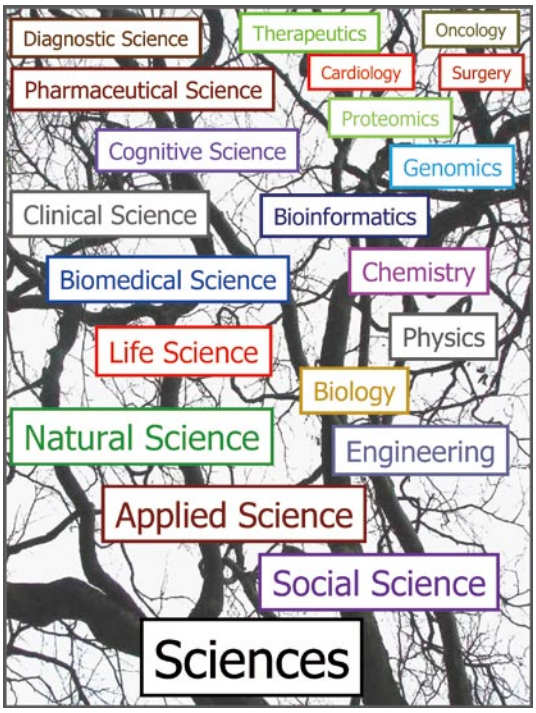


Figure 2 Representative components illustrate the methodological network and multidisciplinary relationship. Along the trunk of sciences, the development of modern life and biomedical sciences are fostered by the methodologies of other branching disciplines.

questions, expose unsolved problems and propose strategies on how to solve such problems; (5) Guidelines for Basic Research: to provide guidelines for basic research recommended by scientific communities; (6) Guidelines for Clinical Practice: to provide guidelines and consensuses for clinical diagnosis and treatment reached by international and national academic authorities; (7) Review: to systemically review progress and obstacles in the field, comment on the state of current research and make suggestions for future work; (8) Original Articles: to report innovative and original findings in basic and clinical medical research with emphasis on methodological aspects; (9) Brief Articles: To briefly report novel findings with improvement in basic and clinical medical research methodology; (10) Case Report: to report a rare, atypical or interesting case; (11) Letters to the Editor: to discuss and reply to the comments on the contributions published in the *WJM* or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: to introduce and comment on quality monographs of basic and clinical medical research methodology; and (13) Voices: to publicize methodology-related communications that have been rejected or impossible for publication elsewhere due to evident prejudice and/or unreasonable reasons. Similarly, your experiences of the proven mistreatment during the past grant applications can be narrated or documented in this corner. The corresponding responses and echoes from readers are also welcome here.

So, if you want to share any new methodologies, any

experiences on the application or improvement of such methodologies in biomedical research and any methodology-related academic issues with your peers, the *WJM* is a place you can feel at home!

REFERENCES

1 **Lander ES**. Initial impact of the sequencing of the human genome. *Nature* 2011; **470**: 187-197

2 **Monaghan P**. Telomeres and life histories: the long and the short of it. *Ann N Y Acad Sci* 2010; **1206**: 130-142

3 **Welch GR**, Clegg JS. From protoplasmic theory to cellular systems biology: a 150-year reflection. *Am J Physiol Cell Physiol* 2010; **298**: C1280-C1290

4 **Ni Y**, Wang H, Chen F, Li J, DeKeyzer F, Feng Y, Yu J, Bosmans H, Marchal G. Tumor models and specific contrast agents for small animal imaging in oncology. *Methods* 2009; **48**: 125-138

5 **Li J**, Sun Z, Zhang J, Shao H, Miranda Cona M, Wang H, Marysael T, Chen F, Prinsen K, Zhou L, Huang D, Nuyts J, Yu J, Meng B, Bormans G, Fang Z, de Witte P, Li Y, Verbruggen A, Wang X, Mortelmans L, Xu K, Marchal G, Ni Y. A dual-targeting anticancer approach: soil and seed principle. *Radiology* 2011; **260**: 799-807

6 **Ni Y**, Dymarkowski S, Chen F, Bogaert J, Marchal G. Occlusive myocardial infarction enhanced or not enhanced with necrosis-avid contrast agents at MR imaging. *Radiology* 2002; **225**: 603-605; author reply 605-606

7 **Ni Y**. Metalloporphyrins and functional analogues as MRI contrast agents. *Curr Med Imaging Rev* 2008; **4**: 96-112

8 **Ni Y**, Mulier S, Miao Y, Michel L, Marchal G. A review of the general aspects of radiofrequency ablation. *Abdom Imaging* 2005; **30**: 381-400

S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Methodology

Online Submissions: http://www.wjgnet.com/2222-0682office
wjm@wjgnet.com
doi:10.5662/wjm.v1.i1.4

World J Methodol 2011 September 26; 1(1): 4-11
ISSN 2222-0682 (online)

GUIDELINES CLINICAL PRACTICE

Improving psychotherapy research: The example of mindfulness based interventions

Alberto Chiesa

Alberto Chiesa, Institute of Psychiatry, University of Bologna, Viale Carlo Pepoli 5, 40123 Bologna, Italy
Author contributions: Chiesa A solely contributed to this paper.
Correspondence to: Alberto Chiesa, MD, Institute of Psychiatry, University of Bologna, Viale Carlo Pepoli 5, 40123 Bologna, Italy. albertopnl@yahoo.it
Telephone: +39-51-6584233 Fax: +39-51-521030
Received: July 27, 2011 Revised: September 6, 2011
Accepted: September 19, 2011
Published online: September 26, 2011

Abstract

The increasing number and sophistication of available psychotherapies suggests that a critical appraisal of the methodological issues of psychotherapy studies is highly needed. Several key questions regarding the efficacy of a given intervention, the understanding of whether positive effects observed following the delivery of a psychotherapeutic intervention are specifically attributable to the intervention itself or to other "non specific" factors, such as benefit expectations, therapist attention and support, and the possibility of improving psychotherapy research need an answer. This, in turn, could provide clinicians with more rigorous information about psychotherapy outcomes and could properly address several shortcomings that are frequently observed in current psychotherapy studies. Accordingly, in this editorial I will highlight some of the most important critical issues that a well designed psychotherapy study should take into account, including the need for appropriate control groups, appropriate randomization and blinding procedures, and the importance of performing appropriately powered studies that include a sufficiently long follow-up period. Finally, I will build on my expertise in the field of mindfulness based interventions, in particular mindfulness based stress reduction and mindfulness based cognitive therapy, to show how such issues have been and can be successfully implemented in the design of future psychotherapy studies.

Key words: Randomized controlled trials; Blinding; Non-specific factors; Mindfulness; Meditation

Peer reviewer: Robin Alexander Emsley, Professor, Department of Psychiatry, Faculty of Health Sciences, Stellenbosch University, PO Box 19063, Tygerberg Campus 7505, Cape Town, South Africa

Chiesa A. Improving psychotherapy research: The example of mindfulness based interventions. *World J Methodol* 2011; 1(1): 4-11 Available from: URL: http://www.wjgnet.com/2222-0682/full/v1/i1/4.htm DOI: http://dx.doi.org/10.5662/wjm.v1.i1.4

INTRODUCTION

How can we know that a psychotherapeutic intervention is efficacious? How can we ascertain that positive effects observed following the delivery of a psychotherapeutic intervention are specifically attributable to the intervention itself? And, most importantly, can psychotherapy research be improved and to what extent?

Such questions are just some of the more challenging and intriguing issues that researchers involved with the investigation of psychotherapeutic interventions have handled in the last decades and are still handling today. If one takes into account the large number of available psychotherapies as well as the difficulties inherent in any attempt to properly conduct a psychotherapy study, it becomes evident that consistent effort should be directed towards the improvement of the methodological quality of studies designed to investigate the efficacy of psychotherapeutic interventions. This, in turn, could provide clinicians with more rigorous information about psychotherapy outcomes and could properly address several shortcomings that are frequently observed in current psychotherapy studies.

Accordingly, in this editorial I will highlight some of

the most important critical issues that a well designed psychotherapy study should take into account and will build on my expertise into the field of mindfulness based interventions (MBIs) to show how such issues have been and can be successfully implemented in the design of future psychotherapy studies.

PSYCHOTHERAPY RESEARCH: WHAT SHOULD WE TAKE INTO ACCOUNT?

A thorough review of the large variety of methodological issues that could affect the results of a psychotherapy study is a huge matter that falls out with the aim and scope of this editorial. Rather, this paper aims to address some of the key issues that a psychotherapy study should take into account and suggests that the improvement of psychotherapy research is not only something that is largely needed but, more importantly, something that is feasible and should therefore be strongly encouraged.

The first question that a given psychotherapy study should address could be described as follows: how do we know that a specific intervention is efficacious for a given condition? A simple answer could be to deliver the intervention under investigation to a target population of subjects and to see if, by the end of the treatment period, some improvement, as measured with objective or subjective measures, can be observed. Although such an answer is somewhat intuitive and studies using an uncontrolled design have frequently been employed in psychotherapy studies, such a design does not allow control for important phenomena that could occur regardless of the administration of treatment. As Price and colleagues outlined in their seminal paper[1], the most common of such phenomena is the natural history of illness. Indeed, several conditions show a spontaneous improvement over time that can be unrelated to treatment. Furthermore, a second phenomenon that should be taken into account is the regression to the mean, a statistical phenomenon that assumes that individuals with extreme scores on any measure at one point probably will have less extreme scores, for purely statistical reasons, the next time they are tested.

How to deal with such issues? Two main approaches have usually been employed. The first one involves the comparison of the results of one's own study with those reported in scientific studies focusing on untreated samples of subjects prospectively followed for a given period of time. The second approach involves the inclusion of a waiting list control group that receives no treatment. Although an empirical investigation aimed at comparing these two approaches in the field of psychotherapy research is still lacking, it is reasonable to suggest that the second approach carries the advantage of reducing possible sources of variance that could derive from the qualitative comparison of different populations by randomizing individuals to the treatment under investigation or to the waiting list (see also below).

Even though we exclude that the benefits related to treatment are not simply due to the natural history of illness or to the regression to the mean, a more important effect remains to be considered: the placebo or the "non specific effect" of treatment[1]. Over the last decades, the conceptualization of the placebo effect has shifted from the impossibility of the inert content of a placebo agent to produce clinically significant benefits to the concept of a simulation of an active therapy within a psychosocial context that would empower the influence of placebo[2]. The nature and the accurate description of the non specific effects of a given intervention represent a significant challenge for researchers involved in psychotherapy studies. Indeed, as several authors have recently underscored[3-5], in psychotherapy studies, the "placebo" control condition should be ideally matched as closely as possible with the intervention under investigation with regard to such non specific factors as benefit expectations, therapist contact, therapist (and, in some cases, group) support and educational information while, at the same time, it should exclude the "active ingredient(s)" of the specific intervention under investigation. Accordingly, it appears evident that, because a waiting list does not elicit any benefit expectation nor involves any educational information and therapist or group support, trials comparing a psychotherapeutic intervention with a waiting list control group cannot distinguish between the specific and the non specific effects of treatment (e.g.[6]).

A third issue that should be carefully considered in psychotherapy studies regards the random assignment of subjects to the treatment under investigation or to the control condition. Empirical evidence consistently supports the role of randomization in bias reduction. It has been shown, for instance, that nonrandomized trials are more likely to show advantage of an innovation over a standard treatment[7]. Furthermore, randomization procedures should be appropriate. Indeed, as Schulz *et al*[8] have stressed, only a few randomization procedures can be considered as appropriate and it is not surprising that appropriate randomization is one of the five criteria outlined in the Jadad Scale, one of the most widely used scales used to assess the quality of controlled trials thus far, to decide whether the quality of a given study can be considered as high or low[9]. An example of an appropriate randomization procedure is simple randomization, which is analogous to repeated fair coin-tossing. Such a procedure, although it represents the most basic of sequence generation approaches, is considered as significantly more reliable than other approaches, irrespective of their complexity and sophistication. If such a procedure cannot be successfully implemented, a blocked randomization, a procedure that controls the probability of obtaining an allocation sequence with an undesirable sample size imbalance in the intervention, can likewise be employed[8]. On the other hand, other procedures such as alternated allocation of patients should be considered as inappropriate because they carry a high risk of allowing the investigator anticipate which is going to be the following assignment and therefore to introduce a methodological bias.

In line with this point, allocation concealment should

also be considered to ascertain that the methodological rigor of the randomization procedure is appropriately applied to a given study[10]. Indeed, without adequate allocation concealment, even random, unpredictable assignment sequences can be undermined. As an example, an analysis of 250 trials from 33 meta-analyses showed that randomized controlled trials in which treatment allocation was inadequately concealed, or in which concealment of allocation was unclear, yielded significantly larger estimates of treatment effects than those trials in which concealment was adequate[11]. As Schulz *et al*[10] outlined, many investigators involved with clinical trials can be tempted to decipher assignments, which, in turn, can subvert randomization. For some investigators implementing a trial, deciphering the allocation scheme might frequently become too great an intellectual challenge to resist. Therefore, methods that ensure appropriate allocation concealment should be implemented in future psychotherapy studies. One such example is the use of sealed envelopes numbered in advance, opened sequentially only after the participant's name and other details are written on the appropriate envelope[12] and possibly containing cardboard or aluminum foils placed inside the envelope aimed at inhibiting the detection of assignments *via* hot lights.

A fourth important issue that should be taken into account is blinding. The rich history of blinding in clinical trials spans a couple of centuries[13]. However, significant misunderstandings exist with regard to a correct definition of blinding and consistent effort has recently been given to more properly define different types of blinding[14]. In extreme sum, in a double-blind design, currently considered as the most appropriate blinding methodology, investigators and assessors (frequently the same persons) as well as participants all remain unaware of the intervention assignments throughout the trial. However, several types of studies such as surgical intervention studies and psychotherapy studies cannot be double-blinded because of the difficulty of keeping subjects unaware of the intervention they are assigned to. Nevertheless, even though double blinding can be difficult if not even impossible to use in psychotherapy research, a single blind design in which at least the investigator is blind as to whether a given subject is receiving the intervention under investigation or the control intervention can be employed to reduce the risk of an assessment bias. In line with this view, several reviews currently assign one point of the Jadad Scale[9] when single blinding is employed (e.g.[6,15]).

Even though an appropriate control group as well as appropriate randomization and blinding procedures are employed, a challenging issue for psychotherapy studies is to ascertain that the intervention is appropriately delivered. First of all, this implies that the intervention should be manualized. Otherwise there would be no comparison to which the delivered intervention can be contrasted. Furthermore, it is also important to be able to measure the degree to which the intervention, as described in its treatment manual, is actually being administered. In other words, it is important to rely on adherence measures that offer a way of quantifying how faithfully the intervention has been provided[16] and whether the treatment has been successfully manipulated. This is usually achieved by means of audiotape or videotape recordings of the sessions and the use of adequate adherence scales through which an external evaluator expert in the treatment under investigation evaluates the extent to which the delivered intervention differs from the intervention described in the manual[17]. Finally, therapist experience should be considered as well. Indeed, although such a variable could have only a small effect on psychotherapy outcomes (e.g.[18,19]), it could nonetheless provide important complementary information that parallel the more "technical" information of treatment adherence[5].

Even when the issues mentioned above are appropriately addressed, the results of a psychotherapy study may still have limited usefulness if the sample size is not sufficiently powered to detect differences between groups (in superiority studies) or to ascertain that the apparent lack of difference between the intervention under investigation and the established treatment used as a comparison is not simply due to the lack of statistical power (in non-inferiority studies)[20]. In both cases, the authors should rely, whenever it is possible, on an effect size estimate based on prior studies dealing with the same or similar interventions for the intended clinical condition. Furthermore, several issues including the notion that in the forthcoming study, effect sizes could tend to the lower extreme of improvement, that a certain proportion of patients is likely to drop out over the study period and that for still other patients some information may not be appropriate or available, should also be considered in the design of a methodologically sound psychotherapy study (e.g.[21]).

In addition to the points outlined above, several further methodological issues should be considered.

As an example, there is consensus that for superiority trials, the intent-to-treat population (ITT) should be considered as the primary analysis population because it tends to avoid the over-optimistic estimates of efficacy that results from a per-protocol (PP) population that excludes subjects that for various reasons have dropped out from the intervention[22]. However, the choice of the appropriate analysis population in non-inferiority studies is far less defined. Although relying on the ITT population could be considered as a conservative approach even in this case, a simple simulation study aimed at investigating the degree of anticonservatism of the ITT population and to quantify the influence of non-compliers on the conclusion of a non-inferiority study found that, in the presence of non-compliers, the test for non-inferiority gives higher type I error rates (false positive findings) that increase with the proportion of non-compliers, and the degree of anticonservatism of ITT is inversely related to the size of the treatment effect in the non-complier group[23]. Therefore some authors have put

forward that an hybrid ITT/PP analysis, which excludes non-compliant patients as in the PP analysis and properly addresses the impact of non-trivial missing data as in the maximum likelihood estimation-based ITT analysis, is a promising way of providing reliable non-inferiority tests (for a detailed description see[24]). Furthermore, the follow-up period should be consistent with that usually required to detect a significant effect of treatment on the target condition. In particular, the overall follow-up period should be based on existing literature focusing on a given psychotherapeutic intervention for a well specified clinical population and on the specific outcome under investigation (e.g. the reduction of acute depressive symptoms is supposed to require a shorter follow-up period in comparison with the prevention of future depression relapses). Finally, it is worth mentioning that authors other than the developers of the original psychotherapy program perform independent trials focusing on the efficacy of such interventions so as to provide evidence for treatment transportability and generalizability[25] and that large observational studies are performed in the community to ascertain intervention effectiveness. The distinction between efficacy and effectiveness is particularly important because, while efficacy measures how well a given intervention works in clinical trials, effectiveness relates to how well a treatment works in practice.

As we can see from this brief description, several issues should be considered in the design of a high quality psychotherapy study. In the next two sections I will briefly explore the concept of mindfulness and some of the main MBIs and will show how the methodological issues mentioned above have been successfully employed to improve current knowledge about such interventions.

MINDFULNESS BASED INTERVENTIONS

The word mindfulness derives from the Pali word *sati*, which can be found in early Buddhist scriptures such as the Abhidhamma[26], a classic scholastic compilation of Buddhist psychology and philosophy and, later, in the Vishuddimagga[27], a summary of the part of the Abhidhamma that deals with meditation. Because mindfulness concerns a clear awareness of one's inner and outer experience, including thoughts, sensations, emotions, actions or surroundings as they exist at any given moment, in the Buddhist classical literature it has often been termed as "bare" attention[28-30] or alternatively as "pure" or "lucid" awareness[28,31,32], emphasizing that mindfulness is supposed to reveal what is occurring, before or beyond conceptual and emotional classifications about what is or has taken place. This, in turn, is supposed to reduce suffering related to the concept of an individual ego and ultimately lead to psychological well-being and happiness[33].

The cultivation of mindfulness has been a key element of several Buddhist meditations including Vipassana meditation[34] and Zen meditation[35] for centuries. More recently, the development of mindfulness has also proven to be a fruitful topic within clinical psychology[4]. Although there is not complete consensus as to how the concept of mindfulness should be properly defined and classified so far[36-39], mindfulness is currently conceptualized in psychological terms as a systematic development of attention to the present moment with a non-judgmental awareness of the inner and/or outer experiences. Kabat-Zinn[40], the founder of one of the most popular MBIs, as an example, describes mindfulness as the process of "paying attention in a particular way, on purpose, in the present moment and non-judgmentally" or, alternatively, as "the awareness that emerges through paying attention on purpose, in the present moment and non-judgmentally to the unfolding of experience moment by moment"[41].

MBIs, which include, among others, Mindfulness-Based Stress Reduction (MBSR)[42,43] and Mindfulness-Based Cognitive Therapy (MBCT)[44], have become a very popular form of treatment in contemporary psychotherapy as a means to deal with a large variety of physical, psychological and stress related problems[6,45-49]. Of note, it is worth mentioning that clinical findings are also increasingly supported by a large amount of objective neuropsychological and neurobiological findings[50,51].

In sum, MBSR is a standardized group-based meditation program conceived in the late '70s from the effort to integrate Buddhist mindfulness meditation with contemporary Western clinical and psychological practice[43,52]. MBSR is mainly based on three different techniques including (1) "body scan" which involves a gradual sweeping of attention through the entire body from feet to head, focusing non-critically on any sensation or feeling in body regions and using periodic suggestions of breath awareness and relaxation; (2) "sitting meditation" which involves both mindful attention on the breath or on the rising and falling abdomen, as well as on other perceptions, and a state of non judgemental awareness of cognitions and of the stream of thoughts and distractions that continuously flow through the mind; and (3) "Hatha yoga" practice which includes breathing exercises, simple stretches and posture designed to strengthen and relax the musculoskeletal system[43]. The standard program consists of 8 wk sessions with a duration of 2 and a half hours each and homework for 45 min a day, 6 d a week[43,52].

On the other hand, MBCT is a manualized 8 wk skills-training group program[44] based upon the theoretical framework of information processing theories[53] and integrating aspects of cognitive behavioral therapy for major depression (MD)[54] with components of the MBSR program developed by Kabat-Zinn[43]. MBCT was originally designed to teach patients in remission from recurrent MD to become more aware of, and to relate differently to, their thoughts, feelings and bodily sensations. An example includes recognizing thoughts and feelings as passing events in the mind rather than necessarily accurate readouts of reality. The original program teaches skills that allow individuals to disengage from habitual, automatic dysfunctional cognitive routines as a way to

reduce future risk of relapses and recurrences of MD[44]. More recently, however, MBCT has also been successfully used for other clinical targets including, among others, the reduction of inter-episodic depression and anxiety levels in patients suffering from bipolar disorder[55,56] and the treatment of some anxiety disorders (e.g.[57-59]). In conclusion, MBIs can be described as psychological interventions whose purpose is to help patients achieve relief from such negative symptoms as chronic pain and depressive symptoms by targeting the extra baggage that is piled on to the symptoms in the form of, for example, negative thoughts and emotions by means of the development of an enhanced ability to cope with and/or relate differently to them.

MBIs AS AN EXAMPLE OF HOW PSYCHOTHERAPY RESEARCH MIGHT BE IMPROVED

As the field of mindfulness has grown exponentially in the last three decades in both quantity and complexity, it is well suited to show how the increasing sophistication of the methodological design can be successfully implemented in psychotherapy research and to highlight fruitful avenues for future research. Early studies focusing on the efficacy of MBSR for chronic pain patients mostly employed an uncontrolled design that did not distinguish between the specific effects of treatment, the non specific effects and the natural history of disease of such patients (e.g.[42,60]). Therefore, the only way observed findings could be critically evaluated was in a comparison between findings reported in the study and those usually observed in chronic pain patients under naturalist conditions. In the 1990s, the first studies appeared that compared MBSR with a waiting list control group to which subjects could be randomly (e.g.[61]) or non randomly assigned (e.g.[62]). Although the results were encouraging in that they suggested that subjects assigned to MBSR improved to a significantly higher extent than those assigned to the waiting list control group, such findings did not yet ascertain that benefits observed following MBSR could be specifically attributable to the interventions itself rather than to other non specific factors such as benefit expectations, group support, educational information and teacher's care[47].

It is worth noting, however, that in more recent times several studies have been published that used appropriate comparison groups. One such example is the study published by Grossman and colleagues[63] comparing MBSR with a comparison group designed to match the non specific effects of MBSR while excluding the claimed "active ingredient", i.e. mindfulness meditation practice. The control group employed by Grossman and colleagues included the presence of a trained, experienced group facilitator, participation in an 8 wk group setting of the same size and weekly format as the MBSR program, similar curriculum structure and equivalent amount of homework assignments, social support, relaxation training, gentle stretching exercises and weekly topical discussions. However, consistent emphasis was placed on not describing or training mindfulness skills to the control group. An even better design was subsequently employed by Zautra and colleagues[64]. The authors compared a MBI closely derived from MBSR with both an educational "non specific" control group and an active psychological control group (group cognitive behavioral therapy) in a sample of patients with rheumatoid arthritis. This design is particularly useful because, on the one hand it ascertains that both active treatments are significantly superior to the non specific comparison group and on the other hand, it investigates the existence of a possible specificity profile of active treatments that could be useful for future research. As an example, in the study by Zautra and colleagues[64], the authors found that mindfulness training was more efficacious for patients with rheumatoid arthritis and an history of MD while the cognitive behavioral intervention was more efficacious for patients with rheumatoid arthritis and without an history of MD.

With time, the improvement of randomization and blinding procedures has paralleled that of control groups employed in MBI research studies. Indeed, while the majority of early studies about MBIs employed an uncontrolled or a non randomized controlled design (e.g.[42,60,65], later studies have increasingly employed randomization, have properly described randomization procedures and have provided information about the appropriateness of allocation concealment[6]. A recent study investigating the efficacy of the adjunct of MBCT to treatment as usual (TAU) with TAU only for the prevention of MD relapses over a period of 1 year is a good example of the implementation of adequate randomization and blinding procedures to psychotherapy studies[66]. First of all, eligible subjects interested in MBCT were randomized to MBCT or to the waiting list control group using a stratified block randomization procedure. Stratification variables included site, number of previous depressive episodes and duration since remission from last episode. Secondly, they specified which strategy had been implemented to ensure adequate allocation concealment by stating that, after checking for inclusion and exclusion criteria and informed consent had been obtained, intervention was assigned to patients through sealed envelopes (Note, however, that information as to whether sealed envelopes contained cardboard or aluminum foils aimed at inhibiting detection of assignments was lacking).

Of note, the study by Bondolfi and colleagues[66], as well as many other ongoing (e.g.[21]) and recently published (e.g.[67]) studies, is also a good example of how sample size should be determined. Indeed, as the authors explained, sample size was estimated on the basis of previously reported differences of relapse rates between MBCT and waiting list control groups in MBCT studies. Additionally, an even better sample size estimate that has also taken into account the likelihood of drop outs has recently been described[68].

In the last decade, an increasing number of studies

has also successfully controlled treatment adherence. In particular, several recent MBCT studies have reported that sessions were videotaped, that adherence to the MBCT protocol was assessed by experienced and independent MBCT therapists with a specific adherence scale (i.e. the Mindfulness Based Cognitive Therapy Adherence Scale[69]) and that treatment adherence could be considered at least as acceptable (e.g.[66,67]). Furthermore, the majority of recent MBCT studies consistently reported therapist experience and adherence to homework (for a review see[6]).

Notably, increasing attention has recently been given to the appropriateness of employed statistical analyses[21,68] and appropriate follow-up periods are increasingly being considered (e.g.[21]), even in short term studies (e.g.[70]). Finally, although large observational studies allowing for a proper evaluation of the effectiveness of MBSR and MBCT in the community are still lacking thus far, it is encouraging that an increasing number of studies performed by authors other than the developers of such interventions have recently been published that allow for an appropriate understanding of treatment transportability and generalizability (e.g.[66,71]).

CONCLUSION

Although the lack of a quantitative approach does not unequivocally evaluate whether and to what extent more recent studies exploring the usefulness of MBIs interventions for a large variety of clinical conditions have used a higher methodological quality as compared with older studies, a qualitative evaluation of the short review of studies mentioned above suggests that, with time, researchers concerned with MBIs are giving increasing attention to the methodological quality of their studies. Such observation is noteworthy because it suggests that improving psychotherapy research is feasible and should therefore be encouraged. Furthermore, with the increasing availability of psychotherapeutic approaches, increasing emphasis should be given to the methodological quality of future studies so as to provide clinicians with more rigorous information about psychotherapy outcomes and more reliable data that allows for a better understanding of which treatment could be best employed for a specific population of patients.

Of note, this does not criticize all studies that do not employ the methodological approaches mentioned above. As Orme-Johnson[5] has recently pointed out, whereas good randomized controlled trials may be the method of choice for demonstrating clinical efficacy, they may not be appropriate or may be too expensive to answer many other kinds of research questions. As an example, early pilot studies of a new psychotherapeutic approach could employ an uncontrolled design. If positive results are found, randomized controls should be performed to ascertain that positive effects observed in early studies are not only attributable to non specific factors of the intervention and to determine treatment transportability and generalizability. Such a claim is in line with the principles of Onken *et al*[25] who underscore that the development of new approaches should involve different progressive stages that guide the process of treatment development in a manner informed by ever more complex and rigorous tests of the novel protocol.

In conclusion, as the field of psychotherapy research moves forward, it will be increasingly important to use more rigorous methodological approaches. MBIs offer a good example of how psychotherapy research can be successfully improved. If any progress is to be achieved, the observations mentioned above could provide a precious source of information for the improvement of future psychotherapy studies.

REFERENCES

1 **Price DD**, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol* 2008; **59**: 565-590
2 **Colloca L**, Benedetti F. Placebos and painkillers: is mind as real as matter? *Nat Rev Neurosci* 2005; **6**: 545-552
3 **Smits JA**, Hofmann SG. A meta-analytic review of the effects of psychotherapy control conditions for anxiety disorders. *Psychol Med* 2009; **39**: 229-239
4 **Chiesa A**, Serretti A. A systematic review of neurobiological and clinical features of mindfulness meditations. *Psychol Med* 2010; **40**: 1239-1252
5 **Orme-Johnson DW**. Commentary on the AHRQ report on research on meditation practices in health. *J Altern Complement Med* 2008; **14**: 1215-1221
6 **Chiesa A**, Serretti A. Mindfulness based cognitive therapy for psychiatric disorders: a systematic review and meta-analysis. *Psychiatry Res* 2011; **187**: 441-453
7 **Colditz GA**, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I: Medical. *Stat Med* 1989; **8**: 441-454
8 **Schulz KF**, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet* 2002; **359**: 515-519
9 **Jadad AR**, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1-12
10 **Schulz KF**, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet* 2002; **359**: 614-618
11 **Schulz KF**, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273**: 408-412
12 **Bulpitt C**. Randomised controlled clinical trials. Netherlands: Martinus Nijhoff, 1983
13 **Kaptchuk TJ**. Intentional ignorance: a history of blind assessment and placebo controls in medicine. *Bull Hist Med* 1998; **72**: 389-433
14 **Schulz KF**, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet* 2002; **359**: 696-700
15 **Coelho HF**, Canter PH, Ernst E. Mindfulness-based cognitive therapy: evaluating current evidence and informing future research. *J Consult Clin Psychol* 2007; **75**: 1000-1005
16 **Shaw BF**, Elkin I, Yamaguchi J, Olmsted M, Vallis TM, Dobson KS, Lowery A, Sotsky SM, Watkins JT, Imber SD. Therapist competence ratings in relation to clinical outcome in cognitive therapy of depression. *J Consult Clin Psychol* 1999; **67**: 837-846
17 **Waltz J**, Addis ME, Koerner K, Jacobson NS. Testing the in-

tegrity of a psychotherapy protocol: assessment of adherence and competence. *J Consult Clin Psychol* 1993; **61**: 620-630
18 **Stein DM**, Lambert MJ. On the relationship between therapist experience and psychotherapy outcome. *Clin Psychol Rev* 1984; **4**: 127-142
19 **Blatt SJ**, Sanislow CA, Zuroff DC, Pilkonis PA. Characteristics of effective therapists: further analyses of data from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Consult Clin Psychol* 1996; **64**: 1276-1284
20 **Tamayo-Sarver JH**, Albert JM, Tamayo-Sarver M, Cydulka RK. Advanced statistics: how to determine whether your intervention is different, at least as effective as, or equivalent: a basic introduction. *Acad Emerg Med* 2005; **12**: 536-542
21 **Kuyken W**, Byford S, Byng R, Dalgleish T, Lewis G, Taylor R, Watkins ER, Hayes R, Lanham P, Kessler D, Morant N, Evans A. Study protocol for a randomized controlled trial comparing mindfulness-based cognitive therapy with maintenance anti-depressant treatment in the prevention of depressive relapse/recurrence: the PREVENT trial. *Trials* 2010; **11**: 99
22 ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. 1998
23 **Garrett AD**. Therapeutic equivalence: fallacies and falsification. *Stat Med* 2003; **22**: 741-762
24 **Matilde Sanchez M**, Chen X. Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat. *Stat Med* 2006; **25**: 1169-1181
25 **Onken LS**, Blaine JD, Battjes R. Behavioral therapy research: a conceptualization of a process. In: Henggeler SW, Amentos R, editors. Innovative approaches for difficult-to-treat populations. Washington, DC: American Psychiatric Press, 1997: 477-485
26 **Kiyota M**. Mahayana Buddhist Meditation: Theory and Practice. Honolulu, University Press of Hawaii, 1978
27 **Buddhaghosa B**. Vissuddhimagga (The Path of Purification). Seattle: Shambala, 1976
28 **Gunaratana H**. Mindfulness in plain English. Boston: Wisdom Publications, 1993
29 **Thera N**. The heart of Buddhist meditation. London: Rider and Co., 1973
30 **Rahula WS**. What the Buddha taught. New York: Grove Press, 1974
31 **Das LS**. Awakening the Buddha within: Tibetan wisdom for the Western world. New York: Broadway Books, 1997
32 **Sogyal R**. The Tibetan book of living and dying. San Francisco, CA: Harper San Francisco, 1992
33 **Kang C**, Whittingham K. Mindfulness: a dialogue between buddhism and clinical psychology. *Mindfulness* 2010; **1**: 161-173
34 **Chiesa A**. Vipassana meditation: systematic review of current evidence. *J Altern Complement Med* 2010; **16**: 37-46
35 **Chiesa A**. Zen meditation: an integration of current evidence. *J Altern Complement Med* 2009; **15**: 585-592
36 **Chiesa A**, Malinowski P. Mindfulness-based approaches: are they all the same? *J Clin Psychol* 2011; **67**: 404-424
37 **Grossman P**. On measuring mindfulness in psychosomatic and psychological research. *J Psychosom Res* 2008; **64**: 405-408
38 **Baer RA**, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. *Assessment* 2006; **13**: 27-45
39 **Shapiro SL**, Carlson LE, Astin JA, Freedman B. Mechanisms of mindfulness. *J Clin Psychol* 2006; **62**: 373-386
40 **Kabat-Zinn J**. Wherever you go there you are: mindfulness meditations in every day life. New York: Hyperion, 1994
41 **Kabat-Zinn J**. Mindfulness-based interventions in context: past, present, and future. *Clin Psychol: Sci Pract* 2003; **10**: 144-156
42 **Kabat-Zinn J**. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen Hosp Psychiatry* 1982; **4**: 33-47
43 **Kabat-Zinn J**. Full catastrophe living: Using the wisdom of your body and mind to face stress, pain, and illness. New York: Dell Publishing, 1990
44 **Segal ZV**, Williams MG, Teasdale JD. Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse. New York: Guildford Press, 2002
45 **Grossman P**, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. *J Psychosom Res* 2004; **57**: 35-43
46 **Chiesa A**, Serretti A. Mindfulness-based stress reduction for stress management in healthy people: a review and meta-analysis. *J Altern Complement Med* 2009; **15**: 593-600
47 **Chiesa A**, Serretti A. Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *J Altern Complement Med* 2011; **17**: 83-93
48 **Ledesma D**, Kumano H. Mindfulness-based stress reduction and cancer: a meta-analysis. *Psychooncology* 2009; **18**: 571-579
49 **Hofmann SG**, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *J Consult Clin Psychol* 2010; **78**: 169-183
50 **Chiesa A**, Calati R, Serretti A. Does mindfulness training improve cognitive abilities? A systematic review of neuropsychological findings. *Clin Psychol Rev* 2011; **31**: 449-464
51 **Chiesa A**, Brambilla P, Serretti A. Neuro-imaging of mindfulness meditations: implications for clinical practice. *Epidemiol Psychiatr Sci* 2011; **20**: 205-210
52 **Kabat-Zinn J**. Mindfulness-based stress reduction (MBSR). *Construct Hum Sci* 2003; **8**: 73-107
53 **Teasdale JD**, Segal Z, Williams JM. How does cognitive therapy prevent depressive relapse and why should attentional control (mindfulness) training help? *Behav Res Ther* 1995; **33**: 25-39
54 **Beck AT**, Rush AJ, Shaw BF, Emery G. Cognitive therapy of depression. New York: Guilford Press, 1979
55 **Weber B**, Jermann F, Gex-Fabry M, Nallet A, Bondolfi G, Aubry JM. Mindfulness-based cognitive therapy for bipolar disorder: a feasibility trial. *Eur Psychiatry* 2010; **25**: 334-337
56 **Williams JM**, Alatiq Y, Crane C, Barnhofer T, Fennell MJ, Duggan DS, Hepburn S, Goodwin GM. Mindfulness-based Cognitive Therapy (MBCT) in bipolar disorder: preliminary evaluation of immediate effects on between-episode functioning. *J Affect Disord* 2008; **107**: 275-279
57 **Kim YW**, Lee SH, Choi TK, Suh SY, Kim B, Kim CM, Cho SJ, Kim MJ, Yook K, Ryu M, Song SK, Yook KH. Effectiveness of mindfulness-based cognitive therapy as an adjuvant to pharmacotherapy in patients with panic disorder or generalized anxiety disorder. *Depress Anxiety* 2009; **26**: 601-606
58 **Piet J**, Hougaard E, Hecksher MS, Rosenberg NK. A randomized pilot study of mindfulness-based cognitive therapy and group cognitive-behavioral therapy for young adults with social phobia. *Scand J Psychol* 2010; Epub ahead of print
59 **Evans S**, Ferrando S, Findler M, Stowell C, Smart C, Haglin D. Mindfulness-based cognitive therapy for generalized anxiety disorder. *J Anxiety Disord* 2008; **22**: 716-721
60 **Kabat-Zinn J**, Lipworth L, Burney R. The clinical use of mindfulness meditation for the self-regulation of chronic pain. *J Behav Med* 1985; **8**: 163-190
61 **Kabat-Zinn J**, Wheeler E, Light T, Skillings A, Scharf MJ, Cropley TG, Hosmer D, Bernhard JD. Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). *Psychosom Med* 1998; **60**: 625-632
62 **Goldenberg DL**, Kaplan KH, Nadeau MG, Brodeur C, Smith S, Schmid CH. A controlled study of a stress-reduction, cognitive-behavioral treatment program in fibromyalgia. *J Musculoskeletal Pain* 1994; **2**: 53-66
63 **Grossman P**, Tiefenthaler-Gilmer U, Raysz A, Kesper U.

Mindfulness training as an intervention for fibromyalgia: evidence of postintervention and 3-year follow-up benefits in well-being. *Psychother Psychosom* 2007; **76**: 226-233

64 **Zautra AJ**, Davis MC, Reich JW, Nicassario P, Tennen H, Finan P, Kratz A, Parrish B, Irwin MR. Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression. *J Consult Clin Psychol* 2008; **76**: 408-421

65 **Sagula D**, Rice KG. The effectiveness of mindfulness training on the grieving process and emotional well-being of chronic pain patients. *J Clin Psychol Med Settings* 2004; **11**: 333-342

66 **Bondolfi G**, Jermann F, der Linden MV, Gex-Fabry M, Bizzini L, Rouget BW, Myers-Arrazola L, Gonzalez C, Segal Z, Aubry JM, Bertschy G. Depression relapse prophylaxis with Mindfulness-Based Cognitive Therapy: replication and extension in the Swiss health care system. *J Affect Disord* 2010; **122**: 224-231

67 **Kuyken W**, Byford S, Taylor RS, Watkins E, Holden E, White K, Barrett B, Byng R, Evans A, Mullan E, Teasdale JD. Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. *J Consult Clin Psychol* 2008; **76**: 966-978

68 **Garland SN**, Carlson LE, Antle MC, Samuels C, Campbell T. I-CAN SLEEP: rationale and design of a non-inferiority RCT of Mindfulness-based Stress Reduction and Cognitive Behavioral Therapy for the treatment of Insomnia in CANcer survivors. *Contemp Clin Trials* 2011; **32**: 747-754

69 **Segal ZV**, Teasdale JD, Williams JM, Gemar MC. The mindfulness-based cognitive therapy adherence scale: inter-rater reliability, adherence to protocol and treatment distinctiveness. *Clin Psychol Psychother* 2002; **9**: 131-138

70 **Manicavasgar V**, Parker G, Perich T. Mindfulness-based cognitive therapy vs cognitive behaviour therapy as a treatment for non-melancholic depression. *J Affect Disord* 2011; **130**: 138-144

71 **Godfrin KA**, van Heeringen C. The effects of mindfulness-based cognitive therapy on recurrence of depressive episodes, mental health and quality of life: A randomized controlled study. *Behav Res Ther* 2010; **48**: 738-746

S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Methodology

Online Submissions: http://www.wjgnet.com/2222-0682office
wjm@wjgnet.com
doi:10.5662/wjm.v1.i1.12

World J Methodol 2011 September 26; 1(1): 12-14
ISSN 2222-0682 (online)

OBSERVATION

Challenges in estimating reproducibility of imaging modalities

Giovanni Di Leo

Giovanni Di Leo, Radiology Unit, IRCCS Policlinico San Donato, Piazza E. Malan, 20097 San Donato Milanese, Italy
Author contributions: Di Leo G solely contributed to this paper.
Correspondence to: Giovanni Di Leo, Assistant Professor, Radiology Unit, IRCCS Policlinico San Donato, Piazza E. Malan, 20097 San Donato Milanese, Italy. gianni.dileo77@gmail.com
Telephone: +39-2-52774468 Fax: +39-2-52774626
Received: August 12, 2011 Revised: September 5, 2011
Accepted: September 19, 2011
Published online: September 26, 2011

Peer reviewer: Domenico Rubello, MD, Professor, Head, Nuclear Medicine, PET Unit, S. Maria della Misericordia Hospital, Istituto Oncologico Veneto (IOV)-IRCCS, Viale Tre Martiri 140, 45100 Rovigo, Italy

Di Leo G. Challenges in estimating reproducibility of imaging modalities. *World J Methodol* 2011; 1(1): 12-14 Available from: URL: http://www.wjgnet.com/2222-0682/full/v1/i1/12.htm DOI: http://dx.doi.org/10.5662/wjm.v1.i1.12

Abstract

Estimating reproducibility is often wrongly thought of as basic science. Although it has a significant clinical relevance, its importance is underestimated. It was Alexander Pope in 1732 who was first to understand the value of reproducibility, with his famous comment "Who shall decide when doctors disagree?". Pope's question concerns the medical doctors' opinion on a patient's status, which from a statistical point of view may be considered a categorical variable. However, the same question may be posed for continuous quantitative variables. Reproducibility is complementary to variability: the larger the variability, the lower the reproducibility, and vice versa. Thus, we can think at them as interchangeable, even thought statistical methods have been developed for the estimation of variability. The question now is "Why do we need to know the reproducibility of measurements? ". The most important and simplest answer is that we need to know how reliable a measured value or a subjective judgment is before taking clinical decisions based on this measurement/judgment. Integrating this knowledge in clinical practice is a key aspect of evidence-based medicine.

Key words: Reproducibility; Intraobserver; Interobserver; Imaging

"Who shall decide when doctors disagree?" This question, raised by Alexander Pope in 1732, must have been a very common one in Pope's day, since medical practice at that time was based largely on tradition and opinion, not science. In the 21st century, medicine should be considered at least a combination of art and science. Consequently, careful clinical research should provide clear answers that stand the test of time and the scrutiny of additional investigations. This is the theory behind evidence-based, data-driven scientific medicine[1-3].

In scientific terms, when focused strictly on the evaluation of clinical variables, Pope's question challenges reproducibility, in particular interobserver reproducibility[4-8]. It relates to the common experience where two independent observers provide different results, with this disagreement implying a sort of uncertainty about the truth. From the patient's point of view, it may appear that his/her condition is not an objective one and that each clinician is allowed to have his/her own opinion. This may be very frustrating and cause the patient to lack trust in medicine.

In addition to interobserver reproducibility there is also intraobserver reproducibility, i.e. the ability of a single observer to provide the same opinion regarding a patient's condition if he/she is questioned again later. In fact, self-disagreements occur more frequently than might be expected, in particular if the question posed has more than two mutually exclusive answers (categorical variables).

An example of efforts to better clarify intra- and interobserver reproducibility is the BI-RADS score system for breast lesions[9]. Based mainly on the appearance at mammography, radiologists may apply one of the following scores: (0) Incomplete, when mammograms do not give the radiologist enough information to make a clear diagnosis; (1) Negative, when there is nothing to comment on; (2) Benign, in presence of a definite benign finding; (3) Probably benign, in presence of findings that have a high probability of being benign; (4) Suspicious abnormality, in presence of a lesion not characteristic of breast cancer, but with reasonable probability of being malignant; and (5) Highly suspicious of malignancy, in presence of a lesion that has a high probability of being malignant.

Because of their different experience in reading mammograms, two independent observers may apply two different scores to the same image (lack of interobserver reproducibility). On the other hand, the learning curve of an individual radiologist, may mean that he/she will apply a score to a single mammogram different to that applied during a previous reading (lack of intraobserver reproducibility).

Intra- and interobserver reproducibility not only apply to categorical and ordinal variables but also, and more strictly, to quantitative (continuous) variables. Examples include cardiac ventricle volumes, a vessel diameter, arterial blood pressure, and body temperature. From the observer's point of view, the numerical values observed for such variables are obtained by mean of "instruments", i.e. technical systems, based on a physical principle, that are sensitive to the quantity to be measured. Many of these instruments are now available as software algorithms implemented on computers used for imaging techniques.

Even if the use of a technical instrument may lead an observer the believe the measurement to be an objective process without uncertainty, we must remember that this process does not proceed by itself and that it needs the observer's intervention. This intervention may apply at any level and certainly impacts on the final observed value. For example, the measurement of a vessel diameter based on a magnetic resonance image needs the observer to place a ruler between two distant points (the vessel boundaries) and the repetition of this action rarely provides the same value as that previously obtained. Furthermore, an independent observer may perform this measurement by placing the ruler at another part of the vessel course, i.e. on another slice of the magnetic resonance scan. Therefore, as for categorical variables, the measurement of continuous variables also is characterized by intra- and interobserver variability.

Reproducibility and variability are two complementary concepts: the larger the variability, the lower the reproducibility, and vice versa. Thus, we may think of them as interchangeable, even though statistical techniques have been developed for estimating variability. Moreover, intra- and interobserver variability are only two of the possible sources of the total variability of a measurement obtained using imaging techniques. In general, if an examination on a patient is repeated after a treatment, the total variability associated with the measurements will consist of the following components: (1) The intraobserver variability of the radiologist who performed the measurement prior the treatment; (2) Intraobserver variability of the radiologist who performed the measurement after treatment; (3) The interobserver variability between those radiologists; (4) The interstudy variability, due to the repetition of the examination; (5) The inter-instrumentation variability, due to the possible use of two different machines; and (6) The biological variability, due to changes in the patient's health status during the time elapsed between the two examinations (the effect of treatment may also be a part of this variability).

Why do we need to know the variability of measurements of categorical and continuous variables? The most important and simplest answer is because we need to know the reliability of measured values before taking decisions based on those measurements! Recalling the previous example, if we observe a difference between the values measured before and after the treatment, can we establish that the patient's health status is changed, or is that difference within the overall variability? Of course, the only way to answer that question is to know the overall variability.

In theory, one way to estimate the measurement variability is to repeat a measurement many times, to calculate the mean value and the 95%-confidence interval. However, this approach has three important limitations. Firstly, it no longer holds if the measurements are taken by different observers, adding interobserver variability. Secondly, in clinical practice there is little or no time available for repeating the same measurement. Thirdly, although this allows estimation of the variability associated to a particular value, that variability cannot be applied to all possible values. Therefore, it is more practical to perform a preliminary analysis of at least intra- and interobserver variability.

The statistical techniques suitable for the estimation of the intra- and interobserver variability depend only on the type of the measured variables. Two main methods are available: Cohen k statistics for categorical variables[5] and Bland-Altman statistics for continuous variables[7,8]. Here, I will not go into the mathematical details of these methods (a complete description may be found in references[4]), but I would like to highlight the main difference between them. The Cohen k method provides a coefficient of agreement that lies within the range (-1, 1), where $k = 1$ indicates perfect agreement, $k = 0$ absolutely no agreement, and $k = -1$ the "perfect disagreement". Conversely, Bland-Altman analysis results in a value expressed with the same measurement units as the measured variable.

The estimation of the intra- and interobserver variability may be performed in parallel. In clinical settings, a suitable protocol would include two observers with different experience in the measurement under evalua-

tion. The less experienced observer should measure the variable of interest twice for each patient, with the more experienced observer making only one measurement per patient. The intraobserver variability may be estimated using the pairs of values obtained by the first observer, while the interobserver variability may be estimated using the first value of the first observer and the single value obtained by the second observer.

Let me conclude with an example taken from my own experience as an author. In 2008 we demonstrated that the interobserver variability in the measurement of the left ventricle ejection fraction on magnetic resonance imaging may be as large as 17%, in absolute units[10]! This means that if an observer obtains a value of, for example, 50% for a patient's ejection fraction, a second observer may obtain a value of between 33% to 67% for the same patient. Considering such variability, I can only smile when I see continuous variables expressed to two or three decimals places.

REFERENCES

1 **Sardanelli F**, Hunink MG, Gilbert FJ, Di Leo G, Krestin GP. Evidence-based radiology: why and how? *Eur Radiol* 2010; **20**: 1-15

2 **Malone DE**. Evidence-based practice in radiology: an introduction to the series. *Radiology* 2007; **242**: 12-14

3 **Sackett DL**, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; **312**: 71-72

4 **Sardanelli F**, Di Leo G. Biostatistics for radiologists. Milan: Springer, 2009

5 **Cohen J**. A coefficient of agreement for nominal scales. *Educ Psychol Meas* 1960; **20**: 37-46

6 **Di Leo G**, Di Terlizzi F, Flor N, Morganti A, Sardanelli F. Measurement of renal volume using respiratory-gated MRI in subjects without known kidney disease: Intraobserver, interobserver, and interstudy reproducibility. *Eur J Radiol* 2010; Epub ahead of print

7 **Bland JM**, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999; **8**: 135-160

8 **Bland JM**, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307-310

9 **American College of Radiology**. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas. Reston, VA: American College of Radiology, 2003

10 **Sardanelli F**, Quarenghi M, Di Leo G, Boccaccini L, Schiavi A. Segmentation of cardiac cine MR images of left and right ventricles: interactive semiautomated methods and manual contouring by two readers with different education and experience. *J Magn Reson Imaging* 2008; **27**: 785-792

S- Editor Wang JL **L- Editor** Hughes D **E- Editor** Zheng XM

World Journal of Methodology

Online Submissions: http://www.wjgnet.com/2222-0682office
wjm@wjgnet.com
doi:10.5662/wjm.v1.i1.15

World J Methodol 2011 September 26; 1(1): 15-21
ISSN 2222-0682 (online)

REVIEW

Risk of fracture and pneumonia from acid suppressive drugs

Chun-Sick Eom, Sang-Soo Lee

Chun-Sick Eom, Department of Family Medicine, Institute for Skeletal Aging, Hallym University-Sacred Heart Hospital, Kangwondo 200-704, South Korea
Sang-Soo Lee, Institute for Skeletal Aging and Orthopedic Surgery, Infectious Disease Medical Research Center, Hallym University-Sacred Heart Hospital, Kangwondo 200-704, South Korea
Author contributions: Eom CS and Lee SS contributed equally to this paper.
Supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (2011-000-6208 and 2011-001-4792)
Correspondence to: Sang-Soo Lee, MD, PhD, Professor, Director, Institute for Skeletal Aging and Orthopedic Surgery, Infectious Disease Medical Research Center, Hallym University-Sacred Heart Hospital, 153 Gyodong, Chunchonsi, Kangwondo 200-704, South Korea. totalhip@hallym.ac.kr
Telephone: +82-33-2405197 Fax: +82-33-2520177
Received: August 12, 2011 Revised: September 8, 2011
Accepted: September 19, 2011
Published online: September 26, 2011

Abstract

A recently published systematic review and meta-analysis, incorporating all relevant studies on the association of acid suppressive medications and pneumonia identified up to August 2009, revealed that for every 200 patients, treated with acid suppressive medication, one will develop pneumonia. They showed the overall risk of pneumonia was higher among people using proton pump inhibitors (PPIs) [adjusted odds ratio (OR) = 1.27, 95% CI: 1.11-1.46, I^2 = 90.5%] and Histamine-2 receptor antagonists (H_2RAs) (adjusted OR = 1.22, 95% CI: 1.09-1.36, I^2 = 0.0%). In the randomized controlled trials, use of H_2RAs was associated with an elevated risk of hospital-acquired pneumonia (relative risk 1.22, 95% CI: 1.01-1.48, I^2 = 30.6%). Another meta-analysis of 11 studies published between 1997 and 2011 found that PPIs, which reduce stomach acid production, were associated with increased risk of fracture. The pooled OR for fracture was 1.29 (95% CI: 1.18-1.41) with use of PPIs and 1.10 (95% CI: 0.99-1.23) with use of H_2RAs, when compared with non-use of the respective medications. Long-term use of PPIs increased the risk of any fracture (adjusted OR = 1.30, 95% CI: 1.15-1.48) and of hip fracture risk (adjusted OR = 1.34, 95% CI: 1.09-1.66), whereas long-term H_2RA use was not significantly associated with fracture risk. Clinicians should carefully consider when deciding to prescribe acid-suppressive drugs, especially for patients who are already at risk for pneumonia and fracture. Since it is unnecessary to achieve an achlorhydric state in order to resolve symptoms, we recommend using the only minimum effective dose of drug required to achieve the desired therapeutic goals.

Key words: Acid-suppressive drugs; Pneumonia; Fracture

Peer reviewer: Hung-Jen Liu, DVM, PhD, Professor, Institute of Molecular Biology, National Chung Hsing University, 250, Kuo Kuang RD, Taichung 402, Taiwan, China

Eom CS, Lee SS. Risk of fracture and pneumonia from acid suppressive drugs. *World J Methodol* 2011; 1(1): 15-21 Available from: URL: http://www.wjgnet.com/2222-0682/full/v1/i1/15.htm DOI: http://dx.doi.org/10.5662/wjm.v1.i1.15

INTRODUCTION

Recently, the medical literature has paid considerable attention to unrecognized adverse effects of commonly used medications and their potential public health impact[1,2]. Acid-suppressive drugs (ASDs), represent the second leading category of medication worldwide, with sales totalling US$26.9 billion in 2005[3]. Experts have generally viewed proton pump inhibitors (PPIs) as safe[4]. However, potential complications such as gastrointestinal neoplasia, malabsorption of nutrients and increased susceptibility to infection and fracture have caused concern[5].

Of special interest is the possibility that ASDs could increase susceptibility to respiratory infections because these drugs increase gastric pH, thus allowing bacterial colonization[6,7]. Several previous studies have shown that treatment with ASDs might be associated with an increased risk of respiratory tract infections[8] and community-acquired pneumonia in adults[6,7] and children[9]. Given the widespread use of PPIs and Histamine-2 receptor antagonists (H_2RAs), clarification of the potential impact of acid-suppressive therapy on the risk of pneumonia is of great importance to public health[10].

Some findings have raised the possibility that PPIs may prevent osteoporosis and fractures. Several *in vitro* and animal studies have suggested that PPIs may decrease bone resorption by inhibiting osteoclastic vacuolar hydrogen potassium adenosine triphosphatase (H+/K+ ATPase) activity[11-15]. Osteoclasts possess proton pumps, which are used during the excretion of H+ ions for bone resorption. Osteoclast-selective PPIs may therefore be used as antiresorptive agents[16] with the potential of preventing fractures[17-20]. Administration of a selective inhibitor of the osteoclastic vacuolar H+/K+ ATPase prevents bone loss in ovariectomized rats, an animal model representative of postmenopausal osteoporosis[19]. However, as bone resorption is necessary for the development of normal bone microstructure, one may speculate that PPI-induced blockade of the osteoclast-associated vacuolar proton pump may actually increase fracture risk[21].

USE OF ACID-SUPPRESSIVE DRUGS AND RISK OF PNEUMONIA

A recently published systematic review and meta-analysis, which incorporated all relevant studies on the association of acid suppressive medications and pneumonia that could be identified to August 2009, showed that of every 200 inpatients treated with acid suppressive medication one will develop pneumonia. From a total of 2377 articles identified in the initial search for observational studies, the authors reviewed 60 abstracts and 18 full articles, including 8 of these articles in their final analysis. They identified 8513 randomized controlled trials, and reviewed 914 abstracts and 35 full articles, including 23 of articles and 2 bibliographies of relevant articles in the study. In summary, they included five case-control studies[6,7,10,22,23], three cohort studies[3,24,25], and 23 randomized controlled trials[26-48] in the final analysis.

Main pooled analyses

Meta-analyses on observational studies with the two types of ASD showed significant positive associations between use of PPI and risk of pneumonia [adjusted odds ratio (OR) = 1.27, 95% CI: 1.11-1.46, I^2 = 90.5%] and between use of H_2RA and risk of pneumonia (adjusted OR = 1.22, 95% CI: 1.09-1.36, I^2 = 0.0%). Meta-analysis of randomized controlled trials examining risk of hospital-acquired pneumonia in association with use of H_2RA s confirmed the findings of the observational studies (relative risk: 1.22, 95% CI: 1.01-1.48, I^2 = 30.6%).

Subgroup meta-analyses

In subgroup analyses by type of pneumonia, a significant positive association was observed between use of PPIs and community- acquired pneumonia (adjusted OR = 1.34, 95% CI: 1.14-1.57, I^2 = 93.6%) and between use of H_2RAs and hospital-acquired pneumonia (adjusted OR = 1.24, 95% CI: 1.05-1.47, I^2 = 0.0%). Subgroup analyses by dose indicated a dose-response relationship. A higher dose of PPIs was more strongly associated with pneumonia (adjusted OR = 1.52, 95% CI: 1.31-1.76, I^2 = 27.5%) than the usual dose (adjusted OR = 1.37, 95% CI: 1.08-1.74, I^2 = 86.5%).

Subgroup analyses by duration of exposure showed that the strength of the association between use of PPIs and risk of pneumonia decreased with longer duration of therapy before the index date (date of diagnosis of pneumonia). There were significant positive associations between risk of pneumonia and use of PPIs within 7 d before the index date (adjusted OR = 3.95, 95% CI: 2.86-5.45, I^2 = 0.0%), within 30 d before the index date (adjusted OR = 1.61, 95% CI: 1.46-1.78, I^2 = 30.6%) and from 30 to 180 d before the index date (adjusted OR = 1.36, 95% CI: 1.05- 1.78, I^2 = 84.3%).

The risk of pneumonia was greater with the use of H_2RAs within 7 d before the index date (adjusted OR = 5.21, 95% CI: 4.00-6.80, I^2 not available). This risk also appeared greater with the use of these drugs within 30 d before the index date (adjusted OR = 1.49, 95% CI: 0.82-2.72, I^2 = 80.4%) and from 30 to 180 d (adjusted OR = 1.21, 95% CI: 0.94-1.56, I^2 = 27.6%), although these associations were not statistically significant.

Subgroup analyses of the 23 randomized controlled trials by comparators showed a significant positive association between use of H_2RAs and risk of pneumonia in studies that employed sucralfate as a control (relative risk: 1.33, 95% CI: 1.04-1.69, I^2 = 24.7%). Placebo-controlled studies also indicated an overall increase in the risk of pneumonia with these drugs, but this increase was not statistically significant (relative risk: 1.09, 95% CI: 0.80-1.48, I^2 = 37.9%).

The authors conducted subgroup meta-analyses of the observational studies and randomized controlled trials according to methodological quality. Among the observational studies, they observed a significant positive association for both high-quality studies (adjusted OR = 1.29, 95% CI: 1.17-1.42, I^2 = 0.0%) and low-quality studies (adjusted OR = 1.15, 95% CI: 1.00-1.32, I^2 = 82.1%). Among the randomized controlled trials, the risk of pneumonia appeared greater in low-quality studies (relative risk: 1.35, 95% CI: 1.10-1.67, I^2 = 12.5%), whereas there was no effect among the high-quality studies (relative risk: 0.96, 95% CI: 0.65-1.43, I^2 = 47.0%).

Discussion

Several lines of evidence point to the biological plausi-

bility of these observations. Firstly, ASDs may increase the risk of pneumonia by inhibiting the secretion of gastric acid, thus allowing bacterial overgrowth and colonization in the upper alimentary tract with subsequent translocation to the lungs by aspiration[6,7,49]. Secondly, H+/ K+ ATPase is present not only in the parietal cells of the stomach, but also in the respiratory tract[50,51]. It is conceivable that use of a PPI could alter the pH of the seromucinous secretions by inhibiting this enzyme, thereby encouraging bacterial growth in the respiratory tract, which could in turn lead to increased risk of pneumonia[5]. Thirdly, *in vitro* studies have shown that ASDs may impair the function of neutrophils and the activity of natural killer cells[52-58].

Interestingly, the most striking increase in the risk of pneumonia in association with PPIs was observed in the first week of use. The risk of pneumonia associated with use of PPIs was attenuated, but still significant, between 30 and 180 d. Recipients of H2RAs between 30 and 180 d before the index date appeared to have an increased risk of pneumonia, although the association was not statistically significant. These findings might reflect tolerance[5]. Tolerance to H2RAs generally develops within 2 wk with repeated administration, resulting in a decline in acid suppression[59]. Another reason may be that those who are more susceptible to pneumonia become ill with this disease soon after starting ASDs, leaving fewer susceptible individuals among those using these drugs for longer periods. That is, patients who remain on the drug are those who can tolerate it, whereas those who are susceptible select themselves out of the population at risk. This depletion of susceptibility effect has been considered in other pharmacoepidemiologic studies of adverse events[60].

USE OF ACID-SUPPRESSIVE DRUGS AND RISK OF FRACTURE

A recently published meta-analysis found possible evidence linking PPI use to an increased risk of fracture, but no association between H2RA use and fracture risk. The widespread use of PPIs means that the potential risk of fracture is of great importance to public health. The authors excluded 170 duplicate articles and an additional 1621 articles that did not meet the selection criteria. They reviewed the full texts of the remaining 18 articles, eventually excluding 7 of them. The remaining 11 studies were included in the final analysis[61-67].

Main pooled analyses

The overall use of PPIs was associated with a significantly increased risk of any fracture in a random-effects model meta-analysis of 4 case-control studies, 3 nested case-control studies, and 3 cohort studies (adjusted OR = 1.29, 95% CI: 1.18-1.41, I^2 = 69.8%). However, use of H2RAs was not associated with an increased fracture risk (adjusted OR = 1.10, 95% CI: 0.99-1.23, I^2 = 86.3%).

Subgroup meta-analyses

A positive association between the use of PPIs and fracture risk was observed in all types, but a positive association between the use of H2RAs and fracture risk was found only when nested case-control studies were combined (adjusted OR = 1.20, 95% CI: 1.13-1.28, I^2 = 0.0%) or when cohort studies were combined (adjusted OR = 1.08, 95% CI: 1.02-1.13, I^2 = 0.0%). In contrast, no significant association was observed in case-control studies (adjusted OR = 1.11, 95% CI: 0.81-1.51, I^2 = 85.6%).

Grouping of studies according to methodological quality showed a significantly increased fracture risk with PPI use in both high-quality studies (adjusted OR = 1.32, 95% CI: 1.18- 1.47, I^2 = 63.7%) and low-quality studies (adjusted OR = 1.25, 95% CI 1.06- 1.48, I^2 = 78.7%). There was also a significant positive association between H2RA use and fracture risk in high-quality studies (adjusted OR = 1.13, 95% CI: 1.05-1.21, I^2 = 40.3%) but not in low-quality ones (adjusted = OR 1.09, 95% CI: 0.87-1.38, I^2 = 90.6%).

Grouping studies by the number of patients showed marginally no association between PPI use and fracture risk (adjusted OR = 1.16, 95% CI: 0.98-1.38, I^2 = 66.5%), but no significant association between H2RA use and fracture risk (adjusted OR = 1.11, 95% CI: 0.81- 1.51, I^2 = 85.6%).

When studies were grouped by fracture outcome, the authors found a significant positive association between PPI use and hip fracture risk (adjusted OR = 1.31, 95% CI: 1.11-1.54, I^2 = 88.4%) and vertebral fracture risk (adjusted OR = 1.56, 95% CI: 1.31-1.85, I^2 = 6.3%), whereas there was no significant association between PPI use and the risk of other fractures, or between H2RA use and risk hip or any other fracture.

In subgroup meta-analyses by duration of use, long-term use of PPIs increased the risk of any fracture (adjusted OR = 1.30, 95% CI: 1.15-1.48) and the risk of hip fracture (adjusted OR = 1.34, 95% CI: 1.09- 1.66). There was no association between long-term use of H2RAs and either of these outcomes.

Grouping studies by dose, a significantly increased risk of hip fracture was observed for both high-dose use of PPIs (adjusted OR = 1.53, 95% CI: 1.18-1.97) and usual-dose use of PPIs (adjusted OR = 1.42, 95% CI: 1.31-1.53). In contrast, there was no association with hip fracture for either high-dose or usual-dose use of H2RAs.

Subgroup analyses by sex showed no significant association between PPI or H2RA use and hip fracture risk in men, or with hip fracture or vertebral fracture risk in women.

Discussion

In this meta-analysis of observational studies, the authors found that the use of PPIs was associated with a moderate increase in the risk of fracture compared with nonuse of PPIs, whereas no significant association was observed between H2RA use and this risk. Similarly, long-term PPI

use and any dose of PPIs increased the risk of fracture in a meta-analysis of all the studies reporting duration of use and dose, whereas for H2RAs neither long-term use and nor use of any dose was significantly associated with fracture risk.

No significant association was found between use of H2RAs, which are less potent acid inhibitors than PPIs, and fracture risk. On average, H2RAs block only 70% of gastric acid production, whereas PPIs suppress acid production by up to 98%[68-70]. More prolonged exposure to H2RAs may be necessary to observe similar effects on fracture risk, although long-term use of these agents was not found to increase risk. These results suggest that H2RAs and PPIs may have differing effects on bone metabolism.

Some studies suggest that H2RAs may have antiresorptive properties[71,72] and even increase bone mineral density, which could decrease fracture risk[66]. Cimetidine also has been shown to prevent osteoclast differentiation induced by histamine[73,74]. Because of the possible mixed effects of H2RAs on bone health, data regarding long-term use of these drugs and fracture risk[63,64,66,67] or bone mineral density[75] have been inconsistent.

In contrast, PPIs have been shown to inhibit gastric proton pumps at physiological concentrations, whereas the inhibition of osteoclast and other tissue H+/K+ ATPase activity, such as osteoclast proton pumps, is much less pronounced[76]. It was, however, noted that the use of H2RAs was associated with a mild increase in fracture risk in studies having high-quality methodology (NOS score > 7) and in studies adjusting for at least 5 variables, but not in studies having low-quality methodology and adjusting for fewer than 5 variables. Further research in this area is needed.

Interestingly, the subgroup meta-analyses by the number of adjustment variables showed a significantly increased risk of fracture for both PPI and H2RA use when the data were adjusted for at least 5 variables. The results for H2RAs conflict with those of Vestergaard *et al*[66], who reported a statistically significant protective effect with use of these drugs for any fracture and for hip fracture. The positive association they found between H2RA use and fracture risk in studies with a high level of statistical adjustment may also be consistent with the marginal association they observed in high-quality studies (NOS score > 7).

Several potential mechanisms by which PPI therapy may lead to fractures have been identified. Firstly, the small intestine's ability to absorb ingested calcium salts depends on pH[77,78]. Calcium solubility is believed to be important for its absorption[79], and an acidic environment in the gastrointestinal tract facilitates the release of ionized calcium from insoluble calcium salts[80]. Secondly, impaired calcium absorption might lead to compensatory secondary hyperparathyroidism, which may increase the rate of osteoclastic bone resorption. Thirdly, PPIs may interfere with the resorptive activity of osteoclasts. Without osteoclast activity, old bone cannot be replaced, predisposing patients to fractures[21,67]. However, further research is required to determine the precise effect of long-term use of PPIs on bone mineral metabolism[65]. Finally, gastric parietal cells appear to have a potent endocrine role in secreting estrogens[81,82]. Atrophy of the gastric mucosa, observed in patients infected with CagA-positive *Helicobacter pylori*[83], reduces the number of gastric parietal cells and may decrease local production of estrogens. Estrogens produced in the stomach directly induce expression and production of ghrelin[84,85], which appears to increase bone formation by osteoblasts[86].

CONCLUSION

Clinicians should carefully consider any decision to prescribe ASDs, especially for patients who are already at risk for pneumonia[87] and fracture[88-90]. Since it is unnecessary to achieve an achlorhydric state in order to resolve symptoms, we recommend using only the minimum effective dose of the drug required to achieve desired therapeutic goals.

REFERENCES

1 **Eom CS**, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ* 2011; **183**: 310-319
2 **Eom CS**, Park SM, Myung SK, Yun JM, Ahn JS. Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies. *Ann Fam Med* 2011; **9**: 257-267
3 **Roughead EE**, Ramsay EN, Pratt NL, Ryan P, Gilbert AL. Proton-pump inhibitors and the risk of antibiotic use and hospitalisation for pneumonia. *Med J Aust* 2009; **190**: 114-116
4 **Vanderhoff BT**, Tahboub RM. Proton pump inhibitors: an update. *Am Fam Physician* 2002; **66**: 273-280
5 **Savarino V**, Di Mario F, Scarpignato C. Proton pump inhibitors in GORD An overview of their pharmacology, efficacy and safety. *Pharmacol Res* 2009; **59**: 135-153
6 **Gulmez SE**, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med* 2007; **167**: 950-955
7 **Laheij RJ**, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; **292**: 1955-1960
8 **Laheij RJ**, Van Ijzendoorn MC, Janssen MJ, Jansen JB. Gastric acid-suppressive therapy and community-acquired respiratory infections. *Aliment Pharmacol Ther* 2003; **18**: 847-851
9 **Canani RB**, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, Passariello A, Manguso F, Morelli L, Guarino A. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006; **117**: e817-e820
10 **Sarkar M**, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. *Ann Intern Med* 2008; **149**: 391-398
11 **Sahara T**, Itoh K, Debari K, Sasaki T. Specific biological functions of vacuolar-type H(+)-ATPase and lysosomal cysteine proteinase, cathepsin K, in osteoclasts. *Anat Rec A Discov Mol Cell Evol Biol* 2003; **270**: 152-161
12 **Sasaki T**. Recent advances in the ultrastructural assessment of osteoclastic resorptive functions. *Microsc Res Tech* 1996; **33**: 182-191

13 **Shibata T**, Amano H, Yamada S, Ohya K. Mechanisms of proton transport in isolated rat osteoclasts attached to bone. *J Med Dent Sci* 2000; **47**: 177-185
14 **Tuukkanen J**, Väänänen HK. Omeprazole, a specific inhibitor of H+-K+-ATPase, inhibits bone resorption in vitro. *Calcif Tissue Int* 1986; **38**: 123-125
15 **Zaidi M**. Modularity of osteoclast behaviour and "mode-specific" inhibition of osteoclast function. *Biosci Rep* 1990; **10**: 547-556
16 **Gagliardi S**, Nadler G, Consolandi E, Parini C, Morvan M, Legave MN, Belfiore P, Zocchetti A, Clarke GD, James I, Nambi P, Gowen M, Farina C. 5-(5,6-Dichloro-2-indolyl)-2-methoxy-2,4-pentadienamides: novel and selective inhibitors of the vacuolar H+-ATPase of osteoclasts with bone antiresorptive activity. *J Med Chem* 1998; **41**: 1568-1573
17 **Rzeszutek K**, Sarraf F, Davies JE. Proton pump inhibitors control osteoclastic resorption of calcium phosphate implants and stimulate increased local reparative bone growth. *J Craniofac Surg* 2003; **14**: 301-307
18 **Sundquist K**, Lakkakorpi P, Wallmark B, Väänänen K. Inhibition of osteoclast proton transport by bafilomycin A1 abolishes bone resorption. *Biochem Biophys Res Commun* 1990; **168**: 309-313
19 **Visentin L**, Dodds RA, Valente M, Misiano P, Bradbeer JN, Oneta S, Liang X, Gowen M, Farina C. A selective inhibitor of the osteoclastic V-H(+)-ATPase prevents bone loss in both thyroparathyroidectomized and ovariectomized rats. *J Clin Invest* 2000; **106**: 309-318
20 **Xu J**, Feng HT, Wang C, Yip KH, Pavlos N, Papadimitriou JM, Wood D, Zheng MH. Effects of Bafilomycin A1: an inhibitor of vacuolar H (+)-ATPases on endocytosis and apoptosis in RAW cells and RAW cell-derived osteoclasts. *J Cell Biochem* 2003; **88**: 1256-1264
21 **Mizunashi K**, Furukawa Y, Katano K, Abe K. Effect of omeprazole, an inhibitor of H+,K(+)-ATPase, on bone resorption in humans. *Calcif Tissue Int* 1993; **53**: 21-25
22 **Marciniak C**, Korutz AW, Lin E, Roth E, Welty L, Lovell L. Examination of selected clinical factors and medication use as risk factors for pneumonia during stroke rehabilitation: a case-control study. *Am J Phys Med Rehabil* 2009; **88**: 30-38
23 **Myles PR**, Hubbard RB, McKeever TM, Pogson Z, Smith CJ, Gibson JE. Risk of community-acquired pneumonia and the use of statins, ace inhibitors and gastric acid suppressants: a population-based case-control study. *Pharmacoepidemiol Drug Saf* 2009; **18**: 269-275
24 **Beaulieu M**, Williamson D, Sirois C, Lachaine J. Do proton-pump inhibitors increase the risk for nosocomial pneumonia in a medical intensive care unit? *J Crit Care* 2008; **23**: 513-518
25 **Herzig SJ**, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 2009; **301**: 2120-2128
26 **Apte NM**, Karnad DR, Medhekar TP, Tilve GH, Morye S, Bhave GG. Gastric colonization and pneumonia in intubated critically ill patients receiving stress ulcer prophylaxis: a randomized, controlled trial. *Crit Care Med* 1992; **20**: 590-593
27 **Ben-Menachem T**, Fogel R, Patel RV, Touchette M, Zarowitz BJ, Hadzijahic N, Divine G, Verter J, Bresalier RS. Prophylaxis for stress-related gastric hemorrhage in the medical intensive care unit. A randomized, controlled, single-blind study. *Ann Intern Med* 1994; **121**: 568-575
28 **Cheadle WG**, Vitale GC, Mackie CR, Cuschieri A. Prophylactic postoperative nasogastric decompression. A prospective study of its requirement and the influence of cimetidine in 200 patients. *Ann Surg* 1985; **202**: 361-366
29 **Cloud ML**, Offen W. Continuous infusions of nizatidine are safe and effective in the treatment of intensive care unit patients at risk for stress gastritis. The Nizatidine Intensive Care Unit Study Group. *Scand J Gastroenterol Suppl* 1994; **206**: 29-34
30 **Cook D**, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, Peters S, Rutledge F, Griffith L, McLellan A, Wood G, Kirby A. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med* 1998; **338**: 791-797
31 **Driks MR**, Craven DE, Celli BR, Manning M, Burke RA, Garvin GM, Kunches LM, Farber HW, Wedel SA, McCabe WR. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. The role of gastric colonization. *N Engl J Med* 1987; **317**: 1376-1382
32 **Eddleston JM**, Vohra A, Scott P, Tooth JA, Pearson RC, McCloy RF, Morton AK, Doran BH. A comparison of the frequency of stress ulceration and secondary pneumonia in sucralfate- or ranitidine-treated intensive care unit patients. *Crit Care Med* 1991; **19**: 1491-1496
33 **Hanisch EW**, Encke A, Naujoks F, Windolf J. A randomized, double-blind trial for stress ulcer prophylaxis shows no evidence of increased pneumonia. *Am J Surg* 1998; **176**: 453-457
34 **Kantorova I**, Svoboda P, Scheer P, Doubek J, Rehorkova D, Bosakova H, Ochmann J. Stress ulcer prophylaxis in critically ill patients: a randomized controlled trial. *Hepatogastroenterology* 2004; **51**: 757-761
35 **Laggner AN**, Lenz K, Base W, Druml W, Schneeweiss B, Grimm G. Prevention of upper gastrointestinal bleeding in long-term ventilated patients. Sucralfate versus ranitidine. *Am J Med* 1989; **86**: 81-84
36 **Maier RV**, Mitchell D, Gentilello L. Optimal therapy for stress gastritis. *Ann Surg* 1994; **220**: 353-360; discussion 360-363
37 **Martin LF**, Booth FV, Karlstadt RG, Silverstein JH, Jacobs DM, Hampsey J, Bowman SC, D'Ambrosio CA, Rockhold FW. Continuous intravenous cimetidine decreases stress-related upper gastrointestinal hemorrhage without promoting pneumonia. *Crit Care Med* 1993; **21**: 19-30
38 **Metz CA**, Livingston DH, Smith JS, Larson GM, Wilson TH. Impact of multiple risk factors and ranitidine prophylaxis on the development of stress-related upper gastrointestinal bleeding: a prospective, multicenter, double-blind, randomized trial. The Ranitidine Head Injury Study Group. *Crit Care Med* 1993; **21**: 1844-1849
39 **Misra UK**, Kalita J, Pandey S, Mandal SK, Srivastava M. A randomized placebo controlled trial of ranitidine versus sucralfate in patients with spontaneous intracerebral hemorrhage for prevention of gastric hemorrhage. *J Neurol Sci* 2005; **239**: 5-10
40 **Moesgaard F**, Jensen LS, Christiansen PM, Thorlacius-Ussing O, Nielsen KT, Rasmussen NR, Bardram L, Nielsen HJ. The effect of ranitidine on postoperative infectious complications following emergency colorectal surgery: a randomized, placebo-controlled, double-blind trial. *Inflamm Res* 1998; **47**: 12-17
41 **Mustafa NA**, Aktürk G, Ozen I, Köksal I, Erciyes N, Solak M. Acute stress bleeding prophylaxis with sucralfate versus ranitidine and incidence of secondary pneumonia in intensive care unit patients. *Intensive Care Med* 1995; **21**: 287
42 **O'Keefe GE**, Gentilello LM, Maier RV. Incidence of infectious complications associated with the use of histamine2-receptor antagonists in critically ill trauma patients. *Ann Surg* 1998; **227**: 120-125
43 **Pickworth KK**, Falcone RE, Hoogeboom JE, Santanello SA. Occurrence of nosocomial pneumonia in mechanically ventilated trauma patients: a comparison of sucralfate and ranitidine. *Crit Care Med* 1993; **21**: 1856-1862
44 **Prod'hom G**, Leuenberger P, Koerfer J, Blum A, Chiolero R, Schaller MD, Perret C, Spinnler O, Blondel J, Siegrist H, Saghafi L, Blanc D, Francioli P. Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine,

or sucralfate as prophylaxis for stress ulcer. A randomized controlled trial. *Ann Intern Med* 1994; **120**: 653-662
45 **Reusser P**, Zimmerli W, Scheidegger D, Marbet GA, Buser M, Gyr K. Role of gastric colonization in nosocomial infections and endotoxemia: a prospective study in neurosurgical patients on mechanical ventilation. *J Infect Dis* 1989; **160**: 414-421
46 **Ryan P**, Dawson J, Teres D, Celoria G, Navab F. Nosocomial pneumonia during stress ulcer prophylaxis with cimetidine and sucralfate. *Arch Surg* 1993; **128**: 1353-1357
47 **Thomason MH**, Payseur ES, Hakenewerth AM, Norton HJ, Mehta B, Reeves TR, Moore-Swartz MW, Robbins PI. Nosocomial pneumonia in ventilated trauma patients during stress ulcer prophylaxis with sucralfate, antacid, and ranitidine. *J Trauma* 1996; **41**: 503-508
48 **Yildizdas D**, Yapicioglu H, Yilmaz HL. Occurrence of ventilator-associated pneumonia in mechanically ventilated pediatric intensive care patients during stress ulcer prophylaxis with sucralfate, ranitidine, and omeprazole. *J Crit Care* 2002; **17**: 240-245
49 **Nealis TB**, Howden CW. Is there a dark side to long-term proton pump inhibitor therapy? *Am J Ther* 2008; **15**: 536-542
50 **Altman KW**, Waltonen JD, Hammer ND, Radosevich JA, Haines GK. Proton pump (H+/K+-ATPase) expression in human laryngeal seromucinous glands. *Otolaryngol Head Neck Surg* 2005; **133**: 718-724
51 **Altman KW**, Waltonen JD, Tarjan G, Radosevich JA, Haines GK. Human lung mucous glands manifest evidence of the H+/K+-ATPase proton pump. *Ann Otol Rhinol Laryngol* 2007; **116**: 229-234
52 **Aybay C**, Imir T, Okur H. The effect of omeprazole on human natural killer cell activity. *Gen Pharmacol* 1995; **26**: 1413-1418
53 **Capodicasa E**, De Bellis F, Pelli MA. Effect of lansoprazole on human leukocyte function. *Immunopharmacol Immunotoxicol* 1999; **21**: 357-377
54 **Mikawa K**, Akamatsu H, Nishina K, Shiga M, Maekawa N, Obara H, Niwa Y. The effects of cimetidine, ranitidine, and famotidine on human neutrophil functions. *Anesth Analg* 1999; **89**: 218-224
55 **Noble DW**. Proton pump inhibitors and stress ulcer prophylaxis: pause for thought? *Crit Care Med* 2002; **30**: 1175-1176
56 **Scaringi L**, Cornacchione P, Fettucciari K, Rosati E, Rossi R, Marconi P, Capodicasa E. Activity inhibition of cytolytic lymphocytes by omeprazole. *Scand J Immunol* 1996; **44**: 204-214
57 **Yoshida N**, Yoshikawa T, Tanaka Y, Fujita N, Kassai K, Naito Y, Kondo M. A new mechanism for anti-inflammatory actions of proton pump inhibitors--inhibitory effects on neutrophil-endothelial cell interactions. *Aliment Pharmacol Ther* 2000; **14** Suppl 1: 74-81
58 **Zedtwitz-Liebenstein K**, Wenisch C, Patruta S, Parschalk B, Daxböck F, Graninger W. Omeprazole treatment diminishes intra- and extracellular neutrophil reactive oxygen production and bactericidal activity. *Crit Care Med* 2002; **30**: 1118-1122
59 **Wilder-Smith CH**, Merki HS. Tolerance during dosing with H2-receptor antagonists. An overview. *Scand J Gastroenterol Suppl* 1992; **193**: 14-19
60 **Moride Y**, Abenhaim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. *J Clin Epidemiol* 1994; **47**: 731-737
61 **Chiu HF**, Huang YW, Chang CC, Yang CY. Use of proton pump inhibitors increased the risk of hip fracture: a population-based case-control study. *Pharmacoepidemiol Drug Saf* 2010; **19**: 1131-1136
62 **Corley DA**, Kubo A, Zhao W, Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. *Gastroenterology* 2010; **139**: 93-101
63 **Grisso JA**, Kelsey JL, O'Brien LA, Miles CG, Sidney S, Maislin G, LaPann K, Moritz D, Peters B. Risk factors for hip fracture in men. Hip Fracture Study Group. *Am J Epidemiol* 1997; **145**: 786-793
64 **Kaye JA**, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. *Pharmacotherapy* 2008; **28**: 951-959
65 **Targownik LE**, Lix LM, Metge CJ, Prior HJ, Leung S, Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ* 2008; **179**: 319-326
66 **Vestergaard P**, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. *Calcif Tissue Int* 2006; **79**: 76-83
67 **Yang YX**, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; **296**: 2947-2953
68 **Colin-Jones DG**. The role and limitations of H2-receptor antagonists in the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1995; **9** Suppl 1: 9-14
69 **Olbe L**, Cederberg C, Lind T, Olausson M. Effect of omeprazole on gastric acid secretion and plasma gastrin in man. *Scand J Gastroenterol Suppl* 1989; **166**: 27-32; discussion 41-42
70 **Schuler A**. Risks versus benefits of long-term proton pump inhibitor therapy in the elderly. *Geriatr Nurs* 2007; **28**: 225-229
71 **Lesclous P**, Guez D, Baroukh B, Vignery A, Saffar JL. Histamine participates in the early phase of trabecular bone loss in ovariectomized rats. *Bone* 2004; **34**: 91-99
72 **Lesclous P**, Guez D, Saffar JL. Short-term prevention of osteoclastic resorption and osteopenia in ovariectomized rats treated with the H(2) receptor antagonist cimetidine. *Bone* 2002; **30**: 131-136
73 **Dobigny C**, Saffar JL. H1 and H2 histamine receptors modulate osteoclastic resorption by different pathways: evidence obtained by using receptor antagonists in a rat synchronized resorption model. *J Cell Physiol* 1997; **173**: 10-18
74 **Jacobs NA**, Trew DR. Occlusion of the central retinal artery and ocular neovascularisation: an indirect association? *Eye* (Lond) 1992; **6** (Pt 6): 599-602
75 **Adachi Y**, Shiota E, Matsumata T, Iso Y, Yoh R, Kitano S. Bone mineral density in patients taking H2-receptor antagonist. *Calcif Tissue Int* 1998; **62**: 283-285
76 **Mattsson JP**, Väänänen K, Wallmark B, Lorentzon P. Omeprazole and bafilomycin, two proton pump inhibitors: differentiation of their effects on gastric, kidney and bone H(+)-translocating ATPases. *Biochim Biophys Acta* 1991; **1065**: 261-268
77 **Bo-Linn GW**, Davis GR, Buddrus DJ, Morawski SG, Santa Ana C, Fordtran JS. An evaluation of the importance of gastric acid secretion in the absorption of dietary calcium. *J Clin Invest* 1984; **73**: 640-647
78 **Shangraw RF**. Factors to consider in the selection of a calcium supplement. *Public Health Rep* 1989; **104** Suppl: 46-50
79 **Nordin BE**. Calcium and osteoporosis. *Nutrition* 1997; **13**: 664-686
80 **Wood RJ**, Serfaty-Lacrosniere C. Gastric acidity, atrophic gastritis, and calcium absorption. *Nutr Rev* 1992; **50**: 33-40
81 **Campbell-Thompson M**, Reyher KK, Wilkinson LB. Immunolocalization of estrogen receptor alpha and beta in gastric epithelium and enteric neurons. *J Endocrinol* 2001; **171**: 65-73
82 **Zhang Y**, Lai WP, Wu CF, Favus MJ, Leung PC, Wong MS. Ovariectomy worsens secondary hyperparathyroidism in mature rats during low-Ca diet. *Am J Physiol Endocrinol Metab* 2007; **292**: E723-E731
83 **Sozzi M**, Valentini M, Figura N, De Paoli P, Tedeschi RM, Gloghini A, Serraino D, Poletti M, Carbone A. Atrophic gastritis and intestinal metaplasia in Helicobacter pylori infection: the role of CagA status. *Am J Gastroenterol* 1998; **93**: 375-379

84 **Matsubara M**, Sakata I, Wada R, Yamazaki M, Inoue K, Sakai T. Estrogen modulates ghrelin expression in the female rat stomach. *Peptides* 2004; **25**: 289-297
85 **Sakata I**, Tanaka T, Yamazaki M, Tanizaki T, Zheng Z, Sakai T. Gastric estrogen directly induces ghrelin expression and production in the rat stomach. *J Endocrinol* 2006; **190**: 749-757
86 **Fukushima N**, Hanada R, Teranishi H, Fukue Y, Tachibana T, Ishikawa H, Takeda S, Takeuchi Y, Fukumoto S, Kangawa K, Nagata K, Kojima M. Ghrelin directly regulates bone formation. *J Bone Miner Res* 2005; **20**: 790-798
87 **Brandt D**. Acid suppression and pneumonia. *Am J Nurs* 2005; **105**: 21
88 **Gullberg B**, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int* 1997; **7**: 407-413
89 **Kanis JA**. The incidence of hip fracture in Europe. *Osteoporos Int* 1993; **3** Suppl 1: 10-15
90 **O'Connell MB**, Madden DM, Murray AM, Heaney RP, Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. *Am J Med* 2005; **118**: 778-781

S- Editor Wang JL **L- Editor** Hughes D **E- Editor** Zheng XM

World Journal of Methodology

Online Submissions: http://www.wjgnet.com/2222-0682office
wjm@wjgnet.com
doi:10.5662/wjm.v1.i1.22

World J Methodol 2011 September 26; 1(1): 22-26
ISSN 2222-0682 (online)

ORIGINAL ARTICLE

Electrodermal mapping: A new technology

Gerhard Litscher, Lu Wang, Xin-Yan Gao, Ingrid Gaischek

Gerhard Litscher, Lu Wang, Xin-Yan Gao, Ingrid Gaischek, TCM Research Center Graz and Research Unit of Biomedical Engineering in Anesthesia and Intensive Care Medicine, Medical University of Graz, 8036 Graz, Austria
Xin-Yan Gao, Department of Physiology, Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing 100700, China
Author contributions: Litscher G and Wang L designed the study; Litscher G performed data acquisition; Wang L, Gao XY and Gaischek I participated in data analysis and interpretation; Litscher G and Wang L drafted the manuscript; Gao XY and Litscher I revised the manuscript critically for intellectual content; all authors read and approved the final version of the manuscript.
Correspondence to: Gerhard Litscher, Professor, MSc, PhD, MDsc, TCM Research Center GrazResearch Unit of Biomedical Engineering in Anesthesia and Intensive Care Medicine, Medical University of Graz, Auenbruggerplatz 29, 8036 Graz, Austria. gerhard.litscher@medunigraz.at
Telephone: +43-316-38513907 Fax: +43-316-38513908
Received: May 17, 2011 Revised: September 5, 2011
Accepted: September 19, 2011
Published online: September 26, 2011

Abstract

AIM: To provide the first objective data to show that the electrical conditions of an acupuncture point and a non acupuncture point are different.

METHODS: A newly developed multi-channel skin resistance measuring system is used to characterize the variability in electrical resistance measurements in and around an acupoint, a non-acupoint and a scar. The system measures the electrical skin resistance at 48 points, both absolutely and continuously. The study was performed at the Medical University of Graz in 10 male volunteers, aged between 20 and 30 years and of euro-caucasian descent. With software developed along with the hardware, both a high-resolution measurement and a graphical presentation of possible changes in electrical resistance in the region of interest are possible.

RESULTS: Using the new electrodermal mapping system, differences in skin resistance of an acupoint, a non-acupoint and around a scar could be observed. The values varied within a range of up to 100-500 kOhm. Thermography measurements for control reasons in the same spot did not show these changes.

CONCLUSION: Electrodermal mapping is an innovative method for highly precise skin resistance measurements.

Key words: Electrodermal mapping; Acupuncture point; Scar; Complementary medicine; Electrical skin resistance

Peer reviewer: Catherine E Ulbricht, PharmD, Chief Editor, Natural Standard Research Collaboration, One Davis Square, Somerville, MA 02144, United States

Litscher G, Wang L, Gao XY, Gaischek I. Electrodermal mapping: A new technology. *World J Methodol* 2011; 1(1): 22-26 Available from: URL: http://www.wjgnet.com/2222-0682/full/v1/i1/22.htm DOI: http://dx.doi.org/10.5662/wjm.v1.i1.22

INTRODUCTION

The discipline of biomedical engineering has emerged as an integrating medium for two dynamic professions, medicine and engineering. In this process, biomedical engineers have become actively involved in the design, development and utilization of devices and new techniques[1].

The Research Unit of Biomedical Engineering in Anesthesia and Intensive Care Medicine at the Medical University of Graz (http://litscher.info) has been dealing with the development and implementation of new instruments, especially in the field of high-tech acupuncture research for more than 14 years[2-12].

Acupuncture has been used for medical treatment for thousands of years. A large number of empirical data is available but the technical quantification of effects was

not possible until now. Using electro-acupuncture, needle or laser needle stimulation and modern biomedical techniques, it was possible to quantify changes in biological activities caused by acupuncture[2-12]. In the middle of the 20th century, researchers found lower skin resistance of acupuncture points compared to non acupuncture sites. Impedance measuring devices were developed[13-23] in order to locate the acupuncture points precisely and guarantee the success of the therapy. But a few years later, new measurements were made that disproved this discovery by potential confounders.

In this context, electrical characterization of acupuncture points is a real challenge[13]. The numerous complicating factors, like electrode-tissue interface, electrode material, contact medium, electrode geometry, electrode arrangements, *etc.*, involved in electrodermal readings present a daunting challenge for anyone intent on studying the electrical characteristics ascribed to the acupuncture point[13].

In order to approach the issue of electrical characterization of acupuncture points scientifically, basic research is absolutely necessary because at the moment there are many open questions. It is not clear if the electrical skin resistance at and around an acupuncture point is higher, lower or equal to a non acupuncture point. The same questions arise concerning scars on the human body. In numerous publications acupuncture points are described as having distinct electrical properties[13]. Therefore, comprehensive, high-precision measurement of skin resistance in the area of an acupoint or a scar plays an important role, especially since there is currently no reliable data on the subject. This is also very important because it is a commonly held opinion that acupuncture structures (acupuncture points and meridians) are special conduits for electrical signals. It has to be mentioned here that this opinion has always been viewed sceptically by the scientific community in general.

Within the present editorial, the first measurements of newly developed equipment for electrodermal mapping[14] which allows precise measurements of skin resistance are presented. In a previous manuscript from our research team, a short technical description of the system and two measurement examples during acupuncture needle insertion and needle stimulation as well as during violet laser application can be found[14]. In that publication[14], information concerning other devices in the area of acupuncture research can be found.

MATERIALS AND METHODS

The study was performed at the Medical University of Graz in 10 male volunteers, aged between 20 and 30 years (mean age ± SD: 24.6 ± 2.5 years) and of eurocaucasian descent[15,16]. The aim of this study was to take measurements of the skin resistance of acupuncture points compared to a non acupuncture point.

The basis for the "electrodermal mapping system" was laid with the development and initial testing of a multichannel skin resistance measuring system.

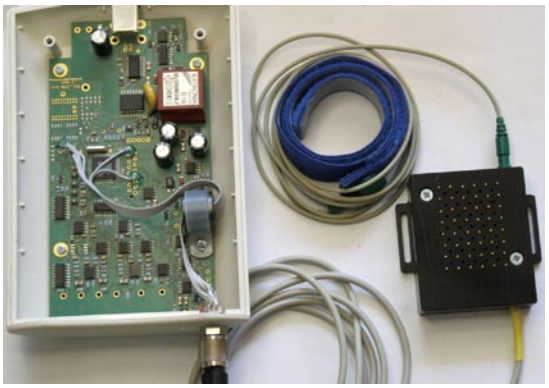


Figure 1 Measurement system for electrodermal mapping (modified from[14,15]).

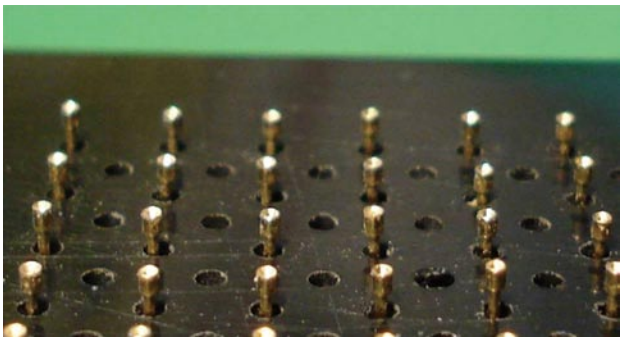


Figure 2 Part of the electrode arrays of the sensor for electrodermal mapping.

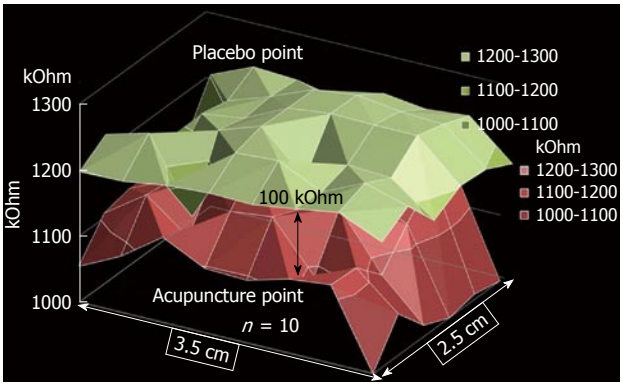


Figure 3 Graphical analysis of 48 channels of electrodermal skin impedance (average values of *n* = 10 persons) at an acupuncture point (below) and a non-acupuncture point (placebo point; above). Note the mean difference between the two surrounding areas is about 100 kOhm. Modified from[16].

The new Grazer ElectroDermal Impedance measurement System (GEDIS)[15,16] has been used. It is an 8 × 6 electrode array with spring-mounted electrodes.

GEDIS, the new system (Figure 1), was developed to register the skin resistance over a period ranging from seconds to hours. The signals of 48 channels are detected simultaneously using a multiplexer. The electrodes have a diameter of 0.9 mm (Figure 2) and consist of a gold-plated beryllium-copper alloy. While it is not possible to measure the constant pressure of the spring-mounted

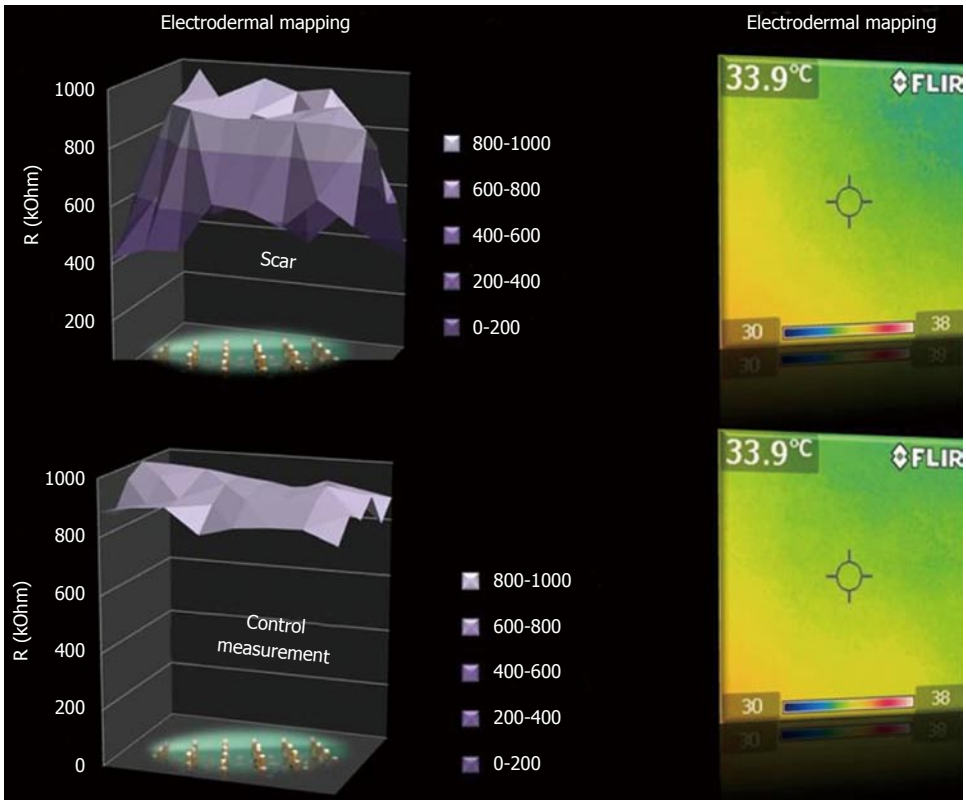


Figure 4 Three-dimensional presentation of the electrodermal activity at and around a scar (top) and a control area (bottom) (left) and corresponding thermal images of the same areas (right). Modified from[17].

electrodes during online monitoring, the contact pressure of an electrode is estimated to be about 0.5 to 1 N[14,15]. The measurement current was 1.46 μA.

The point Kŏngzuì (Lu6) and a placebo-point on the same level of the acupoint but located on the ulnar side of the heart meridian were used. These points were located by an experienced acupuncture practitioner. At these points, the measurement system was easy to apply. The results of acupuncture points and placebo points were then compared.

In addition, thermal imaging was performed of the areas surrounding the scar. These were taken with a Flir i5 (Flir Systems Inc., Portland, USA) infrared camera. These pictures were taken to exclude a difference in the surface of the body temperature at the location of the scar and the surrounding tissue.

RESULTS

Figure 3 shows the results of the first study with the system[16]. The results of the electrical characterization (skin resistance) of the areas surrounding the acupuncture point and the placebo point were compared. The measurements of skin resistance at the acupuncture point showed lower impedance values than those taken from the placebo point on the same arm (Figure 3). A significant ($P < 0.01$; ANOVA on ranks) difference of the values was found. Measured values on the acupuncture point were significantly lower (by 106 kOhm; mean values placebo point: 1218 kOhm, mean values acupuncture point 1112 kOhm)[16].

The changes of skin resistance at the appendectomy scar (20 years old) can be seen in Figure 4 (top left). The three-dimensional presentation clearly shows the increased resistance values around the scar, ranging from 800-1000 kOhm. In comparison, the impedance of the surrounding tissue is markedly lower. A control measurement of intact tissue located lateral to the incision is shown in Figure 4, bottom left. The resistance values within the control measurement area are more uniform than those of the region of interest (skin incision). In addition to the results of the electrodermal mapping, Figure 4 shows thermographic images on the right. In contrast to the impedance measurements, the two thermal images show absolutely no difference[17].

DISCUSSION

Because of the controversially discussed results of existing studies in acupuncture research[14,18-23], a new multichannel skin impedance measurement system was developed at the Research Center for Traditional Chinese Medicine at the Medical University of Graz. This system was designed to supply objective data for the first time, taking into consideration the previously existing technical limitations[14].

Many non-scientific contributions report that scars show altered electrical skin resistance and this difference can be detected with one-channel measurements. It is

concluded that these altered conditions of the electrical activity indicate an interference field, which could then be "erased" using simple injection techniques with a few drops of local anesthetics. It is claimed that this would require only one or two sessions. However, to our knowledge there are no evidence-based publications available on this topic.

We found, for example, that skin resistance within a very small area can differ by up to 500 kOhm. These alterations cannot be detected by any other method currently (e.g. thermography).

Thus, "electrodermal mapping" is a method which allows a highly precise electrical characterization of acupoints, non-acupoints and scars for the first time. Further studies are needed to show whether "electrodermal mapping" may contribute to clarification of important questions concerning the existence and possible structure of the tissue of acupuncture points and/or meridians in complementary medicine.

ACKNOWLEDGMENTS

The author wants to thank Mr. Gebhard Raich for the innovative electronic development work. The study was performed within the project "Bioengineering and clinical assessment of high-tech acupuncture - A Sino-Austrian research pilot study" (BMG, BMWF, Eurasia-Pacific Uninet).

COMMENTS

Background

Although acupuncture has been used as a medical treatment for thousands of years, there are still many open questions concerning this ancient method. For example, it is not clear if the electrical skin resistance at and around an acupuncture point is higher, lower or equal to a non acupuncture point. The same questions arise concerning scars on the human body. This is very important because it is a commonly held (though scientifically still controversially discussed) opinion that acupuncture structures (acupuncture points and meridians) are special conduits for electrical signals. In the mid-20th century, researchers found lower skin resistance of acupuncture points compared to non acupuncture sites. Impedance measuring devices were developed in order to locate the acupuncture points precisely and guarantee the success of the therapy. But a few years later, new measurements seemed to disprove this discovery as several potential confounders were found. To date, no scientific consensus on the electrical properties of acupuncture points *vs* non-acupuncture points has been achieved.

Research frontiers

In numerous publications acupuncture points are described as having distinct electrical properties. Therefore, comprehensive, high-precision measurement of skin resistance in the area of an acupoint or a scar plays an important role, especially since there is currently no reliable data on the subject.

Innovations and breakthroughs

Because of the controversially discussed results of existing studies in acupuncture research, a new multichannel skin impedance measurement system ("GEDIS") was developed at the Research Center for Traditional Chinese Medicine at the Medical University of Graz. GEDIS was designed to supply objective data for the first time, taking into consideration the previously existing technical limitations. We found, for example, that skin resistance within a very small area can differ by up to 500 kOhm. These alterations cannot be detected currently by any other method (e.g. thermography).

Applications

"Electrodermal mapping" using the GEDIS system is a method which allows a highly precise electrical characterization of acupoints, non-acupoints and scars for the first time. However, further studies are needed to show whether electrodermal mapping may contribute to a clarification of important questions concerning the existence and possible structure of the tissue of acupuncture points and/or meridians in complementary medicine.

Terminology

Electrodermal mapping: a (mainly) graphical presentation of electrical skin resistance measured simultaneously and continuously in 48 sites, thus covering an area of about 2.5 cm x 3.5 cm. (Electrical) skin resistance/impedance: Human skin has electrical properties; one of them is its electrical resistance/impedance. The electrical resistance of the skin measures its opposition to the passage of an electric current. Electrical impedance extends the concept of resistance to alternating current circuits, describing not only the relative amplitudes of the voltage and current, but also the relative phases. When the circuit is driven with direct current, there is no distinction between impedance and resistance.

Peer review

This paper provided the first objective data to show that the electrical conditions of an acupuncture point and a non acupuncture point are different. This paper may be interesting for the readers.

REFERENCES

1 **Bronzino JD**. The biomedical engineering handbook. Boca Raton: CRC Press Inc., 1995
2 **Litscher G**. Ten Years Evidence-based High-Tech Acupuncture--A Short Review of Peripherally Measured Effects. *Evid Based Complement Alternat Med* 2009; **6**: 153-158
3 **Litscher G**. Ten Years Evidence-based High-Tech Acupuncture-A Short Review of Centrally Measured Effects (Part II). *Evid Based Complement Alternat Med* 2009; **6**: 305-314
4 **Litscher G**. Ten Years Evidence-based High-Tech Acupuncture Part 3: A Short Review of Animal Experiments. *Evid Based Complement Alternat Med* 2010; **7**: 151-155
5 **Litscher G**. Bioengineering assessment of acupuncture, part 1: thermography. *Crit Rev Biomed Eng* 2006; **34**: 1-22
6 **Litscher G**. Bioengineering assessment of acupuncture, part 2: monitoring of microcirculation. *Crit Rev Biomed Eng* 2006; **34**: 273-294
7 **Litscher G**. Bioengineering assessment of acupuncture, part 3: ultrasound. *Crit Rev Biomed Eng* 2006; **34**: 295-326
8 **Litscher G**. Bioengineering assessment of acupuncture, part 4: functional magnetic resonance imaging. *Crit Rev Biomed Eng* 2006; **34**: 327-345
9 **Litscher G**. Bioengineering assessment of acupuncture, part 5: cerebral near-infrared spectroscopy. *Crit Rev Biomed Eng* 2006; **34**: 439-457
10 **Litscher G**. Bioengineering assessment of acupuncture, Part 6: monitoring--neurophysiology. *Crit Rev Biomed Eng* 2007; **35**: 1-36
11 **Litscher G**. Bioengineering assessment of acupuncture, part 7: heart rate variability. *Crit Rev Biomed Eng* 2007; **35**: 183-195
12 **Litscher G**. Bioengineering assessment of acupuncture, part 8: innovative moxibustion. *Crit Rev Biomed Eng* 2010; **38**: 117-126
13 **Ahn AC**, Martinsen OG. Electrical characterization of acupuncture points: technical issues and challenges. *J Altern Complement Med* 2007; **13**: 817-824
14 **Litscher G**, Wang L. Biomedical engineering meets acupuncture--development of a miniaturized 48-channel skin impedance measurement system for needle and laser acupuncture. *Biomed Eng Online* 2010; **9**: 78
15 **Litscher G**. Akupunkturgrundlagenforschung: Grazer ElektroDermales ImpedanzmessSystem (GEDIS) - Entwicklung und Erprobung eines innovativen miniaturisierten 48-Kanal-Hautwiderstandsmessgerätes für Nadel- und Laserakupunktur. *Schmerz Akupunktur* 2010; **4**: 118-120
16 **Litscher G**, Niemtzow RC, Wang L, Gao X, Urak CH. Electrodermal mapping of an acupuncture point and a non-acupuncture point. *J Altern Complement Med* 2011; **17**: 781-782

17 **Litscher G**. Electrodermal mapping - A highly precise skin interface analysis to objectify potentially interfering cicatrices [in German]. *Schmerz Akupunktur* 2011; **2**: 69–72
18 **Colbert AP**, Larsen A, Chamberlin S, Decker C, Schiffke HC, Gregory WL, Thong T. A multichannel system for continuous measurements of skin resistance and capacitance at acupuncture points. *J Acupunct Meridian Stud* 2009; **2**: 259-268
19 **Cho SH**, Chun SI. The basal electrical skin resistance of acupuncture points in normal subjects. *Yonsei Med J* 1994; **35**: 464-474
20 **Becker RO**, Reichmanis M, Marino AA, Spadaro JA. Electrophysiological correlates of acupuncture points and meridians. *Psychoenergetic Syst* 1976; **1**: 105-112
21 **Kramer S**, Zaps D, Wiegele B, Irnich D. Changes in electrical skin resistance at gallbladder 34 (GB34). *J Acupunct Meridian Stud* 2008; **1**: 91-96
22 **Ahn AC**, Colbert AP, Anderson BJ, Martinsen ØG, Hammerschlag R, Cina S, Wayne PM, Langevin HM. Electrical properties of acupuncture points and meridians: a systematic review. *Dt Ztschr f Akup* 2008; **51**: 48-49
23 **Ahn AC**, Colbert AP, Anderson BJ, Martinsen OG, Hammerschlag R, Cina S, Wayne PM, Langevin HM. Electrical properties of acupuncture points and meridians: a systematic review. *Bioelectromagnetics* 2008; **29**: 245-256

S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Methodology

Online Submissions: http://www.wjgnet.com/2222-0682office
wjm@wjgnet.com
www.wjgnet.com

World J Methodol 2011 September 26; 1(1): I
ISSN 2222-0682 (online)

Acknowledgments to reviewers of *World Journal of Methodology*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Methodology*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

Richard W Bohannon, EdD, DPT, Professor, Kinesiology, University of Connecticut, 358 Mansfield Road, Storrs, CT 06269, United States

Sang-Soo Lee, MD, PhD, Professor, Head of Orthopedic Surgery, Chief Planning Officer, Institute for Skeletal Aging and Orthopedic Surgery, Chunchon Sacred Heart Hospital-Hallym University, 153 Gyodong, Chunchonsi, Kangwondo 200-704, South Korea

Wen-Hsiung Chan, PhD, Professor, Department of Bioscience Technology, Chung Yuan Christian University, No. 200, Chung Pei Road, Chung Li 32023, Taiwan, China

András Komócsi, MD, PhD, Heart Centre, University of Pécs, 13. Ifjuság, Pécs H-7621, Hungary

Rodolfo G Wuilloud, PhD, Analytical Chemistry Research and Development Group, LISAMEN – CCT – CONICET – Mendoza, Av. Ruiz Leal S/N Parque General San Martín, M 5502 IRA Mendoza, Argentina

Mariana de Andrea Hacker, PhD, Laboratory of Leprosy, Oswaldo Cruz Foundation, Avenida Brasil 4365 –Manguinhos, Rio de Janeiro 21040360, Brazil

Richard WJ Neufeld, PhD, Professor, Department of Psychology, University of Western Ontario, Westminster Hall, London, Ontario N6B 2K3, Canada

William CS Cho, PhD, FHKIMLS, Chartered Scientist (UK), FHKSMDS, FIBMS (UK), Consultant of Registered Chinese Medicine Practitioner Association, Department of Clinical Oncology, Queen Elizabeth Hospital, Room 1305, 13/F, Block R, 30 Gascoigne Road, Kowloon, Hong Kong, China

Hong-Xiang Sun, PhD, Associate Professor, College of Animal Sciences, Zhejiang University, Yuhangtang Road 866, Hangzhou 310053, Zhejiang Province, China

Marijeta Kralj, PhD, Senior Scientist, Head of Laboratory of Experimental Therapy, Division of Molecular Medicine, Rudjer Boskovic Institute, Zagreb 10000, Croatia

Qing Wu, MD, ScD, Assistant Professor of Biostatistics, College of Medicine, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259, United States

Peter J Quesenberry, MD, Division of Hematology, Oncology, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903, United States

Thomas TH Wan, PhD, MHS, Professor and Associate Dean for Research, College of Health and Public Affairs, PO Box 163680, Orlando, FL 32826-3680, United States

World Journal of Methodology

Online Submissions: http://www.wjgnet.com/2222-0682office
wjm@wjgnet.com
www.wjgnet.com

World J Methodol 2011 September 26; 1(1): I
ISSN 2222-0682 (online)

Events Calendar 2011

January 14-15, 2011
AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011,
Loews Miami Beach Hotel, Miami, FL, United States

January 27, 2011
Symposium of the Swiss Society of Pharmacology and Toxicology, Advances in Pharmacology-Psychopharmacology,
Bern, Switzerland

January 29-February 2, 2011
LabAutomation2011,
Palm Springs, CA, United States

February 5-6
Washington Neuroradiology Review
Arlington, VA, United States

February 17-18
2nd National Conference Diagnostic and Interventional Radiology 2011
London, United Kingdom

February 28-29
MIAD 2011 - 2nd International Workshop on Medical Image Analysis and Description for Diagnosis System
Rome, Italy

March 6-9
World Congress Thoracic Imaging - IV
Bonita Springs, FL, United States

March 21-23
World Congress on Biotechnology
Hyderabad, India

March 22-24, 2011
11th South East Asian Western Pacific Regional Meeting of Pharmacologists in conjunction with the 84th Annual Meeting of the Japanese Pharmacological Society,
Yokohama, Japan

March 26, 2011
Stem Cell Agency Governance Subcommittee Meeting, Crowne Plaza SFO, 1177 Airport Blvd,
Burlingame, CA, United States

March 27-31, 2011
SBS 17th Annual Conference and Exhibition, Orlando, FL,
United States

April 3-8
43rd International Diagnostic Course Davos on Diagnostic Imaging and Interventional Techniques
Davos, Switzerland

April 6-8
Faraday Discussion 150: Frontiers in Spectroscopy,
Basel, United States

April 28-May 1
74th Annual Scientific Meeting of the Canadian Association of Radiologists CAR,
Montreal, Canada

May 1-6
46th EUCHEM Conference on Stereochemistry,
Brunnen, United States

June 4-8
58th Annual Meeting of the Society of Nuclear Medicine,
San Antonio, TX, United States

June 17-19
ASCI 2011 - 5th Congress of Asian Society of Cardiovascular Imaging,
Hong Kong, China

July 11-13
Ubiquitin Conference
Philadelphia, United States

July 18-20
2nd International Congress on Analytical Proteomics
Ourense, Spain

August 3-4
From beads on a string to the pearls of regulation: the structure and dynamics of chromatin,
Cambridge, United Kingdom

September 10-14, 2011
ICE 2011-International Congress of Endoscopy,
Los Angeles Convention Center,
1201 South Figueroa Street
Los Angeles, CA 90015, United States

October 02-06, 2011
12th International Congress of Therapeutic Drug Monitoring & Clinical Toxicology,
Stuttgart, Germany

October 12-14
International Conference Vipimage 2011 - Computational Vision and Medical Image Processing
Algarve, Portugal

November 11-12, 2011
Falk Symposium 180, IBD 2011: Progress and Future for Lifelong Management,
1-12-33 Akasaka, Minato-ku, Tokyo 107-0052, Japan

November 15-19
EANM 2011 - Annual Congress of the European Association of Nuclear Medicine,
Birmingham, United Kingdom

December 04-07, 2011
Perth 2011 joint Meeting between the Australian Physiological Society, the Australian Society of Clinical and Experimental Pharmacologists and the High Blood Pressure Research Council of Australia, Perth Convention Centre, Perth. WA, Australia

World Journal of Methodology

Online Submissions: http://www.wjgnet.com/2222-0682office
wjm@wjgnet.com
www.wjgnet.com

World J Methodol 2011 September 26; 1(1): I-V
ISSN 2222-0682 (online)

GENERAL INFORMATION

World Journal of Methodology (*World J Methodol*, *WJM*, online ISSN 2222-0682, DOI: 10.5662) is a bimonthly peer-reviewed, online, open-access (OA), journal supported by an editorial board consisting of 238 experts in methodology from 41 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJM* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJM* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJM* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

WJM aims to rapidly report the most recent results in medical diagnostics, therapeutic techniques and equipment, clinical medical research, clinical and experimental techniques and methodology. It provides a platform to facilitate the integration of clinical medicine and experimental techniques and methodology to help clinicians improve diagnostic accuracy and therapeutic efficacy. The journal publishes original articles and reviews on the following topics: (1) Clinical medical techniques, including but not limited to those for pharmaceutical medicine, laboratory medicine, radioactive medicine, medical imaging, nuclear medicine, physical therapy, pathology, surgery, disinfection, nutritional therapy, transfusion and medical equipment; (2) Clinical medical research on etiology, epidemiology, pathogenesis, morphology and function, signs and symptoms, clinical trials, and evidence-based medicine; and (3) Laboratory methodology, including but not limited to techniques in DNA/RNA sequencing, preparation and transformation of competent cells, PCR, protein biochemistry, cell biology, genetics and epigenetics, immunology, microbiology, animal models of human pathologies, bioinformatics, and laboratory equipment manipulation and control.

Columns

The columns in the issues of *WJM* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide Guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in basic and clinical medical research methodology; (9) Brief Articles: To briefly report the novel and innovative findings in basic and clinical medical research methodology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJM*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of basic and clinical medical research methodology; (13) Guidelines: To introduce Consensuses and Guidelines reached by international and national academic authorities worldwide on the research basic and clinical medical research methodology; and (14) Voices: to publicize methodology-related communications that have been rejected or impossible for publication elsewhere due to evident prejudice and/or unreasonable reasons. Similarly, your experiences of the proven mistreatment during the past grant applications can be narrated or documented in this corner. The corresponding responses and echoes from readers are also welcome here.

Name of journal
World Journal of Methodology

ISSN
ISSN 2222-0682 (online)

Frequency
Bimonthly

Indexed and Abstracted in
Digital Object Identifier.

Published by
Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statistical review is performed after peer review. We invite an expert in Biomedical Statistics from to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJM* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should conform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/2222-0682office. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/2222-0682/g_info_20100722180909.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjm@wjgnet.com, or by telephone: +86-10-85381892. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by ICMJE, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Essen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g. Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-85381892 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJM*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/2222-0682/g_info_20100725072755.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/2222-0682/g_info_20100725073806.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing

Editorial: http://www.wjgnet.com/2222-0682/g_info_20100725071851.htm

Frontier: http://www.wjgnet.com/2222-0682/g_info_20100725071932.htm

Topic highlight: http://www.wjgnet.com/2222-0682/g_info_20100725072121.htm

Observation: http://www.wjgnet.com/2222-0682/g_info_20100725072232.htm

Guidelines for basic research: http://www.wjgnet.com/2222-0682/g_info_20100725072344.htm

Guidelines for clinical practice: http://www.wjgnet.com/2222-0682/g_info_20100725072543.htm

Review: http://www.wjgnet.com/2222-0682/g_info_20100725072656.htm

Original articles: http://www.wjgnet.com/2222-0682/g_info_20100725072755.htm

Brief articles: http://www.wjgnet.com/2222-0682/g_info_20100725072920.htm

Case report: http://www.wjgnet.com/2222-0682/g_info_20100725073015.htm

Letters to the editor: http://www.wjgnet.com/2222-0682/g_info_20100725073136.htm

Book reviews: http://www.wjgnet.com/2222-0682/g_info_20100725073214.htm

Guidelines: http://www.wjgnet.com/2222-0682/g_info_20100725073300.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of *WJM*. The revised version including manuscript and high-resolution image figures (if any) should be copied on a floppy or compact disk. The author should send the revised manuscript, along with printed high-resolution color or black and white photos, copyright transfer letter, and responses to the reviewers by courier (such as EMS/DHL).

Editorial Office

World Journal of Methodology
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjm@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893

Language evaluation

The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form

Please download a Copyright assignment form from http://www.wjgnet.com/2222-0682/g_info_20100725073726.htm.

Responses to reviewers

Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/2222-0682/g_info_20100725073445.htm.

Proof of financial support

For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript

WJM will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases

Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee

WJM is an international, peer-reviewed, OA, online journal. Articles published by this journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. Authors of accepted case report must pay a publication fee. The related standards are as follows. Publication fee: 1300 USD per article; Reprints fee: 350 USD per 100 reprints, including postage cost. Editorial, topic highlights, original articles, book reviews and letters to the editor are published free of charge.