The implementation of mindfulness in healthcare systems: a theoretical analysis

M.M.P. Demarzo, Ph.D., M.D. a, A. Cebolla, Ph.D. b, c, J. Garcia-Campayo, M.D., Ph.D. d,*

a Department of Preventive Medicine, “Mente Aberta” — Brazilian Center for Mindfulness and Health Promotion, Universidade Federal de São Paulo, São Paulo, Brazil
b Department of Basic and Clinical Psychology and Psychobiology, Universitat Jaume I, Castellón, Spain
c CIBEROBN Fisiopathology of Obesity and Nutrition, ISCIII, Santiago de Compostela, Spain
d Department of Psychiatry, Miguel Servet University Hospital and University of Zaragoza, REDAPP, Instituto Aragonés de Ciencias de la Salud, Zaragoza, Spain

A R T I C L E  I N F O

Article history:
Received 26 July 2014
Revised 12 November 2014
Accepted 26 November 2014

Keywords:
Mindfulness
Primary Care
Healthcare systems
Implementation
Stepped-care model

A B S T R A C T

Objective: Evidence regarding the efficacy of mindfulness-based interventions (MBIs) is increasing exponentially; however, there are still challenges to their integration in healthcare systems. Our goal is to provide a conceptual framework that addresses these challenges in order to bring about scholarly dialog and support health managers and practitioners with the implementation of MBIs in healthcare.

Method: This is an opiniative narrative review based on theoretical and empirical data that address key issues in the implementation of mindfulness in healthcare systems, such as the training of professionals, funding and costs of interventions, cost effectiveness and innovative delivery models.

Results: We show that even in the United Kingdom, where mindfulness has a high level of implementation, there is a high variability in the access to MBIs. In addition, we discuss innovative approaches based on “complex interventions,” “stepped-care” and “low intensity–high volume” concepts that may prove fruitful in the development and implementation of MBIs in national healthcare systems, particularly in Primary Care.

Conclusion: In order to better understand barriers and opportunities for mindfulness implementation in healthcare systems, it is necessary to be aware that MBIs are “complex interventions,” which require innovative approaches and delivery models to implement these interventions in a cost-effective and accessible way.

1. Introduction

One of the main challenges faced by all types of psychotherapies, including mindfulness-based interventions (MBIs), is the conversion of studies on their efficacy, developed under controlled conditions, to routine clinical practice within national healthcare systems. It has now been more than three decades since MBIs were proposed to improve symptoms of chronic pain, depression and anxiety symptoms among patients and the general population, and exponential evidence-based data have built a scientific foundation for the use of these interventions in healthcare [1]. However, no healthcare system seems to offer suitable and equitable access for MBIs to patients and the general population who could benefit from these interventions. In this opiniative narrative review article [2], we provide a conceptual framework for the implementation of MBIs in healthcare systems based on available theoretical and empirical data that address key issues such as the training of professionals, funding and costs of interventions, cost effectiveness and innovative delivery models. We discuss innovative approaches based on “complex interventions,” “stepped-care” and “low intensity–high volume” concepts that may prove fruitful in the evolution and implementation of MBIs in national healthcare systems, particularly in Primary Care (PC). This conceptual framework may bring about scholarly dialog [2] and support health managers and practitioners with the implementation of MBIs and other types of psychosocial interventions in healthcare systems.

2. Implementing mindfulness in the healthcare system: the case of United Kingdom

Although mindfulness interventions designed for clinical settings were originally developed in the United States (US), and currently there is a widespread interest for them in many countries (mainly in mindfulness-based stress reduction — MBSR — the original program designed by Jon Kabat-Zinn in 1979 at the University of Massachusetts), the United Kingdom (UK) is apparently the most developed country in terms of the formal implementation of MBIs in an integrated national healthcare system [3–5], which involves institutional support in terms of funding and the training of human resources. In the UK, mindfulness-based cognitive therapy (MBCT), applied to patients with a history of major depression who are at risk of relapse, is recommended in clinical guidelines and its implementation in the health system is a priority [3,4]. Despite this recommendation, only a small portion of mental health services in the UK systematically offer MBIs for depression [3,4]. According to Crane and Kuyken [4], who recently evaluated the process of MBCT implementation in the UK, many factors may be considered
for the correct development and success of this type of intervention. One of the main components involves developing a strategic plan for implementing MBIs in services at national, regional and local levels [4]. The existence of a strategic plan is associated with an increased supply of MBIs, greater support for professionals interested in undertaking training and offering these services, better and more appropriate referrals to mindfulness groups, a better understanding of what mindfulness is and how it benefits patients, the existence of appropriate locations for organizing mindfulness groups and adequate administrative support within healthcare systems [4].

Another fundamental element of this implementation is that of testing these interventions first for professionals, which decreases resistance to and prejudice toward the interventions [4], and thus a considerable number of health services also offer mindfulness training for employees [4]. Other relevant topics raised for the study of Crane and Kuyken [4] are as follows: the majority (60%) of professionals who may refer patients to mindfulness groups do not have sufficient knowledge on MBIs; the existence of an expert within the service increases the chances of success; many centers (62%) do not have spaces suitable for group activities; there is a lack of an administrative structure needed to facilitate mindfulness classes (72%); there is enormous competition with other routine service; there is a lack of resources for training and supervising professionals to teach classes; collaboration between primary care services and universities increases the success of implementation, as does the existence of one or more project leaders who may implement MBIs in services [4].

3. PC: the gateway for mindfulness in healthcare systems

PC is the main gateway for patients in a healthcare system and is essential for the proper prevention and management of chronic mental illnesses [6]. The characteristics of PC—equitable access; services close to people’s residence; continuous, lifelong, person-centered care; focus on preventive actions and people’s health needs—may enhance the accessibility of and adherence (motivation and compliance) to MBIs.

However, there are barriers to the implementation of mindfulness in PC services that must be identified. A key point is that PC professionals have a full schedule of appointments and activities, and it is important that time be set aside to enable these professionals to deliver MBIs as part of a strategic implementation plan. Additionally, there are several actions that may be performed, such as the development of online MBIs, which take less time to implement. There are reports of some experiences with such actions that have yielded interesting results [7]. Another possible strategy would be to simplify interventions, such as by including theoretical aspects and simple mindfulness exercises in health promotion groups that already exist within PC services (for example, physical activity or dietary re-education groups). A final strategy would be to create suitable spaces inside health centers in which to hold mindfulness groups.

Table 1

<table>
<thead>
<tr>
<th>Dimensions of MBIs that define them as “complex interventions”</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. They involve a large number of components and interactions between the different components, both practical (different techniques and mindfulness exercises) and theoretical (different theoretical contents depending on the focus or population of interest).</td>
</tr>
<tr>
<td>2. They involve complex changes in conduct and behavior (acceptance, psychological flexibility, compassion) on behalf of participants and professionals.</td>
</tr>
<tr>
<td>3. They require coordinated efforts (strategic plan) for implementation among people at various levels of services, including both professionals and managers.</td>
</tr>
<tr>
<td>4. They include many different types of potential variables (organic, psychological, use of services, etc.) to evaluate results.</td>
</tr>
<tr>
<td>5. They allow great variability in the intervention models (mindfulness-based stress reduction, mindfulness-based cognitive therapy, short programs, etc.).</td>
</tr>
</tbody>
</table>

4. MBIs are “complex interventions” in healthcare systems

Complex interventions are defined as those comprising several interrelated components. These present a challenge for researchers and managers of health services. The challenges involved in the evaluation of these interventions include the following: difficulties in standardizing designs and modes of application for various existing programs; the influence of ethnocultural and political contexts; organizational, logistical and political difficulties in evaluating an intervention in health services [8,9].

MBIs may be defined as “complex interventions,” as they present all of the dimensions (Table 1) of this type of intervention [8,9]. This characteristic implies that the development and evaluation of MBIs in healthcare systems are also complex, and researchers and healthcare managers interested in implementing MBIs in health services must consider this complexity (Tables 2 and 3) [8,9]. The key question to be clarified by researchers, managers and developers of “best practice” policies for mindfulness in health systems is: are MBIs effective and cost-effective in health systems?

Another point concerns how information on results from investigation, evaluations, clinical guidelines and “best practice” guides for MBIs are delivered to opinion makers, professionals, managers, patients and the general population [8,9]. Among scientific publications, there should also be a standard orientation that addresses the characteristics of complex interventions and their evaluations, such as describing in detail the content, the mode of application and the barriers identified in studies on implementation in healthcare systems [10–13].

5. Professional qualifications to teach and deliver MBIs

There are three key aspects to ensuring the quality of professional MBI training: (a) the content, method and process of development and training; (b) training standards; and (c) the definition of skills needed to teach mindfulness groups and/or train other instructors [14].

At present, there are still no accepted international standards or professional qualifications with regard to MBI training [5]. However, professional training guidelines for teaching MBIs and training new mindfulness instructors already exist, with the most prominent being those developed by Jon Kabat-Zinn’s Center for Mindfulness [5] and the UK Network for Mindfulness-Based Teachers [5]. These two guidelines differ

1. There is a need for an appropriate theoretical model that allows for understanding of how the intervention can cause changes in people’s health and/or in the use of services and that identifies the weak points in the causal chain to strengthen them.

2. If the case of mindfulness, such a model implies a complex network of knowledge in medical, psychological and social areas, as well as in the evaluation of health services and policies.

3. A lack of results does not necessarily mean that interventions are not effective; rather, there may be failures or barriers in the implementation process (absence of or noncompliance with the strategic plan, nonadherence to practices or programs, etc.). Therefore, evaluations of the process are very important in implementing MBIs.

4. Variability in individual results may be due to the characteristics of healthcare systems. Therefore, an adequate sample size and the use of appropriate methodological designs (cluster samples, for example) are key to decreasing the influence of such factors. It is best to use a range of variables and indicators for processes and results (physiological, psychological, clinical, use of services, etc.) rather than focusing on a few indicators.

5. The requirement of strict compliance with intervention protocols may not be appropriate, as interventions may work more effectively if the ability to adapt to local conditions and healthcare systems exists.
Table 3
Theoretical framework for the development and assessment of MBI implementation in healthcare systems, based on the model for “complex interventions” [6,9]

For the development and/or assessment of feasible formats of MBIs for application and implementation in different healthcare systems and contexts, the following general steps should be followed:

1. Before the large-scale implementation or assessment of an MBI, it should be designed up until an “optimal” point or until there is a good expectation that it will be effective. To do so, one may rely on an already existing systematic review or develop one, if necessary. From then on, one must think about the implementation process for MBIs, asking the following questions: “Will it be feasible to use this intervention in healthcare services?” “Who will benefit?” and “What are the barriers and facilitators?”

2. A second step would be to clarify the theoretical model underlying MBIs – i.e., what the expected changes with the intervention are and what the mechanisms driving these changes are. This information could be obtained from already existing data. Alternatively, if necessary, new research could be implemented through, for example, qualitative studies with target professionals and patients of the intervention.

3. A step in conjunction with number 2, even before implementation on a large scale, would be to model the intervention in real conditions – i.e., to model MBIs on target services, obtaining key information about the design, viability and assessment of the intervention.

4. Once the “optimal” design and intervention viability are defined, the pilot study would be conducted, where the acceptability of MBIs among patients, professionals and managers would be tested; the recruitment and retention (adherence) rate would be estimated for participants; and the magnitude of the effect and an appropriate sample would be calculated for large-scale studies. Including qualitative methods with the quantitative methods is key to understanding the barriers and facilitators of the implementation process (“process evaluation”). In addition, an initial economic evaluation will be developed here, which will give complementary information on the effect size of the intervention and its viability in a specific healthcare system context.

5. The next step would be the large-scale experimental evaluation of MBIs or testing them in experimentally controlled conditions in several centers and services and using appropriate methods for this through “pragmatic” studies.

6. The final step would be the long-term monitoring of the effects of MBIs on patients, professionals and the healthcare system. This step, although difficult to implement and manage, would be key for the effective implementation of the MBIs, as it would provide information that is difficult to obtain in controlled experimental studies, such as unexpected or adverse effects of interventions or context barriers that were not identified in experimental studies.

in some regard, but both claim that the instructor’s personal practice is key for teaching mindfulness and teaching new instructors. Training should last the minimum amount of time needed to enable practitioners to develop stable personal practices and absorb key concepts related to MBIs, with more training needed for those who wish to teach other instructors.

Regarding the type of professionals who typically teach mindfulness groups, specifically in relation to MBCT, the study by Crane and Cuyken [4] found that it is most common for psychologists to administer them (in 83% of services). The authors also found occupational therapists (58%), social workers (44%) and nurses specializing in psychiatry (55% of services) administering these groups. Other professionals who teach groups, if less frequently, are cognitive behavioral therapists, dieticians, family therapists, psychiatrists and physiotherapists [4]. Moreover, the type of professional background required depends on the target of target patient or population. It is well established that mindfulness teachers should only work with certain patients or certain health conditions if they have been professionally trained to work with them, or if they are part of a larger team prepared to manage those conditions. This is a fundamental issue to ensure that patients with more severe problems will not be guided by teachers or teams who are not experienced to deal with or recognize these problems.

Specific professional skills are also important as criteria for determining when individuals are able to begin teaching MBIs. According to Crane et al. [14], in addition to recommended training qualifications to manage certain types of patients, instructors should integrate the following skills: knowing and complying with the content of the mindfulness programs in which they are trained; having relational skills; knowing how to direct mindfulness practices; appropriately approaching fundamental theoretical themes and participants’ demands during courses; and, most importantly, incorporating mindfulness qualities into their daily lives and during the courses. Importantly, these skills are developed throughout life and, thus, may be classified in stages, from someone being “not competent” in teaching MBIs to someone being at an “advanced” level [14].

6. Funding, costs and number of instructors

The issue of financing MBIs is also key to implementing them in national healthcare systems. In the case of the UK, as already mentioned, MBIs are supported by governmental clinical guidelines [4].

In universal healthcare systems, MBIs should be part of interventions that are formally recommended by the system to allow funding, including payment for groups and professionals’ hours of labor. To save on long-term costs in countries where there is a relevant role for health insurance companies, insurers could choose to pay for participation in MBIs or suggest copayments, discounts or awards for policyholders who wish to join mindfulness groups [5].

To encourage the implementation of mindfulness in services, the national health system could offer awards to professionals who choose to train and teach mindfulness, as well as for universities that invest in offering training for these professionals [5]. In addition to benefiting patients, this initiative would also be useful for professionals and managers, as the effects of MBIs are well known to prevent burnout and its consequences, such as absences and frequent changes in service professionals [5].

An important issue for managers implementing MBIs in healthcare systems concerns the prediction of the necessary number of professionals who will teach mindfulness groups and knowing the costs involved. A Canadian study [15], based on epidemiological data of MBCT programs, has made a conjecture for patients with major depression with more than three previous relapses (estimated at 4.2% of that population) and has arrived at the conclusion that 2 MBCT professionals are needed for every 200,000 people in the community.

Although there are no studies on the subject, if the programs are general such as MBSR, reaching diverse patient populations (with anxiety, depression, chronic pain, etc.) and people or professionals with high-stress symptoms, a greater number of instructors will be needed. Based on the calculation by Patten et al. [15], considering a hypothetically conservative prevalence of these conditions at approximately 30% of the general population and an acceptable rate of mindfulness of 20%, the need for MBI instructors would be approximately 12 for every 200,000 people, or 1 for every 15,000 people.

Another author [16] has speculatively estimated that the cost of providing an MBI group is 2.25 euro (3 US dollars) per hour per patient. Therefore, a group of eight 2-h sessions with 15 participants would cost approximately 540 euro. This estimate does not include extra costs, such as room rental, materials (pillow, mattresses, blankets, prints, CDs with audiovisual guides) or professional training, which may cost up to 3500 euro per person.

An equally important point is the issue of support groups for maintaining mindfulness practices for people who have participated in groups for 8 weeks or similar. These groups appear to be essential for adhering to the practices learned and for maintaining long-term benefits [16].

7. Cost effectiveness of MBIs

Appropriate cost effectiveness is essential in order for MBIs to be accepted and implemented in healthcare systems. Studies on the cost effectiveness of MBIs are still scarce, but the results of some of the existing studies are encouraging. For example, in 2002, Roth and Stanley [17] showed that an 8-week MBSR group at a primary care center in the US decreased the number of visits to the health center for chronic illnesses among the patients who attended the group, suggesting that MBIs may be effective and cost-effective. Recently, similar results
regarding health service utilization were observed in a large population-based study conducted in Canada by Kurdyak and colleagues [18]. Based on a controlled retrospective cohort of 10,663 patients receiving MBCT, they observed that, among high utilizers (4851 patients), there was a significant reduction in nonmental health service utilization when comparing MBCT recipients to a control group (number needed to treat was two for a reduction in one nonmental health visit).

Moreover, in 2008, Kuyken et al. [19] studied the prevention of relapse in patients with recurrent depression. The authors observed that the patients who attended an MBCT group, compared to patients who took antidepressants (usual treatment), showed a lower rate of relapse (47% vs. 60%), took less medication, showed fewer residual depression systems and had a better score on quality of life questionnaires. No differences in annual costs were found between the two groups [19].

Furthermore, van Ravesteijn et al. [20,21] studied the effect of MBCT on somatizers (patients with persistent unexplained physical symptoms) in a sample of primary care patients. The authors observed that although there was no difference in overall health within this sample compared to patients who followed standard treatments, mindfulness improved psychological functioning without increasing costs. In addition, patients in the MBCT group attended hospital services less and community mental health services more, thereby decreasing long-term costs involved in caring for these patients [20].

8. “Stepped-care” and “low intensity–high volume”: key concepts for the large-scale implementation of mindfulness

When we discuss the implementation of MBIs in healthcare systems, we consider high-volume interventions. A large-scale strategic implementation plan for mindfulness may benefit from concepts such as “stepped-care” and “low intensity–high volume” interventions [22–24], thereby making the models of these types of MBIs more flexible and increasing access to MBIs.

The “stepped-care” intervention model is based on the notion that there is a gap between population demand for these therapies and the ability of services to offer them. In other words, there is an access barrier to therapies, mainly related to the lack of professional skills needed to provide them [22–24]. A useful strategy would be the “stepped-care” model, which consists of offering the same interventions (trying to keep the same theoretical models and practices normally offered) in increasing levels (steps) of intensity, according to the needs of patients, and maximizing healthcare system resources. That is, a person with a low-level access to systems is offered a low-intensity intervention, often based on self-care (with or without professional supervision). This, thereby, reserves the most classic intensive models of therapies, using highly specialized professionals, for the most acute patients.

The “stepped-care” model may be applied and assessed during the implementation of MBIs in healthcare systems, integrating different types of MBIs with a continuous progressive focus of intensity and complexity. To develop this idea in a more didactic manner, we will use the concepts involved in the offering of “physical activity” (PA) and different types of “physical exercise” (PE) as health interventions in an analogy to the different types of intensities of MBIs (Table 4). The promotion model for PA/PE appears to be similar to that for MBIs, as both interventions require practical experience and behavioral changes for participants.

In general, the promotion of PA (defined as any body movement that creates increased energy expenditure) follows a “low intensity–high volume” model; i.e., PA focuses on low-intensity interventions based on a “more active lifestyle” through, for example, educational campaigns that promote walking, climbing stairs and active cycling for transportation. The same idea also guides the “stepped-care” model, which understands that a modest clinical effect of an intervention applied on a large scale may cause more health benefits for a population than a high-impact intervention whose application is restricted to a very small number of patients [24].

The equivalent of promoting PA to MBIs would be promoting a more “mindful” lifestyle. Doing so entails brief mindfulness interventions in which lifestyles are taught based on full attention to routine activities or promoting “informal practice” on a large scale. This practice could be taught in short introductory groups (2 h on average), where basic mindfulness concepts and some simple practices could be taught, such as the “raisin exercise” and “3 min of mindfulness practice.” In addition, introductory courses could be offered remotely (by computer or mobile applications). Preliminary evidence on the impact of brief mindfulness interventions on health already exists [25–27], and it is feasible to speculate that such initiatives could have a considerable impact on the population’s perceived stress levels, quality of life and well-being, preventing future cases of anxiety or depression [28].

Table 4
Theoretical model of “stepped-care” and “low intensity–high volume” applied to MBIs and comparative analogy with concepts of “physical activity” and “exercise”

<table>
<thead>
<tr>
<th>Type of MBI</th>
<th>Analogy with PA/exercise</th>
<th>Form of teaching</th>
<th>People/patients potentially benefited</th>
<th>Goal</th>
<th>Instruction or training</th>
<th>Profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBCT (specific contents)</td>
<td>PE (specific context)</td>
<td>“Classic” (8 sessions)/adapted with help of ICT</td>
<td>Patients with more complex clinical conditions</td>
<td>Complementary treatment</td>
<td>“Classic”</td>
<td>Professionals trained in the specific context/collaborative care between skilled professionals and primary care General health practitioners</td>
</tr>
<tr>
<td>MBRT (general)</td>
<td>PE (general)</td>
<td>“Classic” (8 sessions)/adapted with help of ICT</td>
<td>General population/primary care patients</td>
<td>Health promotion/complementary treatment</td>
<td>“Classic”</td>
<td>General health practitioners (including community health officials)</td>
</tr>
<tr>
<td>Informal practice/Promotion of “mindful” lifestyle</td>
<td>PA/Promotion of active lifestyle</td>
<td>In-person introductory workshops (2 h on average)/self-guided remote practices supported by ICT</td>
<td>General population</td>
<td>Health promotion (improved quality of life and well-being)</td>
<td>Reduced (to be determined)</td>
<td>General health professionals</td>
</tr>
</tbody>
</table>

MBRT - Mindfulness-based Stress Reduction; MBCT - Mindfulness-based Cognitive Therapy; MBI - Mindfulness-based Interventions; ICT - information and communication technology; PE - physical exercise; PA - physical activity.
Representing the equivalent of PE in the context of mindfulness are MBIs, such as MBSR, MBCT and their derivatives, which require professionals trained in protocol and have specific indications for certain types of patients. In this sense, the indications of MBSR are more general, as it is recommended for healthy populations as a tool for health promotion. This characteristic implies that a large number of professionals should be trained to provide them. In addition, these types of MBIs may benefit from information and communication technology (ICT).

Based on the analogy presented here, a theoretical model may be constructed for implementing mindfulness in healthcare services in a “stepped-care” format associated with the “low intensity–high volume” strategy (Table 4). In this case, introductory mindfulness groups could be offered on a large scale and, following a model with increasing intensity and complexity (in steps), could offer classic models of MBIs, such as MBSR and MBCT, in the most advanced group.

This is a theoretical and speculative model; therefore, the same principles applied to all therapies should be followed: quality, safety, patient acceptability, clinical effectiveness, cost effectiveness and efficiency (understood here as having clinical results at least equal to other intervention models, but with lower costs) [22–24].

9. Conclusion and agenda for future studies

In evidence-based terms, different MBIs may have distinct approaches and barriers in order to be implemented in highly diverse healthcare systems worldwide, and thus many questions regarding the implementation of mindfulness interventions in health systems remain unanswered. A good theoretical framework for researchers and managers is to follow a progressive development and assessment model for MBIs, based on the approach for “complex interventions” (see Table 3) [8,9]. This general framework facilitates addressing the unresolved research questions of MBIs, specifically those related to its implementation in healthcare systems [4,5,24], which generally are as follows:

1. Are MBIs interventions that may be used alone in certain clinical conditions (such as anxiety or depression) or are they always employed as a complement to standard treatments?

2. Are they cost-effective compared to other existing therapies, such as pharmacological or classic cognitive behavioral therapies?

3. Are they acceptable for patients, professionals and managers from different countries, ethnic groups and healthcare systems?

4. Could the offer of MBIs in PC enhance accessibility, motivation, adherence to and compliance with these interventions?

5. Could mindfulness interventions benefit from a “stepped-care” model in healthcare systems?

In conclusion, MBIs are promising and feasible interventions in healthcare systems, and their implementation worldwide may be benefited by innovative approaches based on “complex interventions,” “stepped-care” and “low intensity–high volume” concepts, especially in PC.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

M.M.P. and J.G.C. presented the initial concept, drafted the first version and organized subsequent versions until the final format of the manuscript. All authors contributed to the development and improvement of the manuscript until its final version.

Acknowledgments

M.M.P.D. is grateful to the National Council for Scientific and Technological Development – Brazilian National Council for Research and Technological Development — for a postdoctoral fellowship under supervision of Professor Javier García-Campayo (“Science without Borders Program”). The authors thank Rebecca S. Crane, Centre for Mindfulness Research and Practice, Dean Street Building, Bangor University, LL571UT, UK, for the revision of previous drafts of this paper, as well as Mari Cruz Pérez-Yus, Instituto Aragónes de Ciencias de la Salud, Zaragoza, Spain, for her technical support.

CIBEROBN is an initiate of the ISCIII.

References


