

Integrative medicine review

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ABSTRACT

Integrative Medicine is a growing branch of medicine which integrates the best aspects of conventional (allopathic) and complementary and alternative medicines. This kind of medicine recognizes that the mechanistic, fragmentary and linear view of science, i.e. reductionism, has many limitations, particularly in biological and medical sciences. Moreover, Integrative Medicine provides a particular care to each patient, orienting its practices towards healing and emphasizing the therapeutic relationship. Its principles harmonize with the proposals of Systemic Biology which acknowledges the complexity, integrality and holistic nature of living beings. Based on the aforementioned postulates integrate our Five-Spheres Model for patient care.

Keywords: Integrative medicine, system medicine, system biology.

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INTRODUCTION

Over the past two centuries the predominant scientific paradigm has been “reductionism” (Ahn et al., 2006). This paradigm assumes that complex problems are solvable by dividing them into smaller fractions and finding the linear mechanism that controls their behavior (Rivas et al., 2017; Ahn et al., 2006). Reductive strategies have been used to understand biological systems, which made possible the development of many technological advances (Wolkenhauer and Green, 2013) and have prevailed mainly in some branches of medicine, such as pharmacology (Fardet and Rock, 2015). However, this approach is beginning to reach its limits (Fardet and Rock, 2015; Ahn et al., 2006). For instance, in some cases, technological and/or pharmaceutical advances are related to high costs in the health care system (Rakel, 2012). For example, in the United States, it was estimated that 252 billion of dollars were spent on drugs in 2006. This fact by itself proves how expensive and unsustainable this system can be (Mukau, 2009).

Reductionism pervades the medical sciences and affects the way diseases are diagnosed, treated and prevented (Loscalzo and Barabasi, 2011; Ahn et al., 2006). For instance, contemporary views on disease are based on a simple correlation between clinical syndromes and pathological analysis (Loscalzo and Laszlo, 2011). As a result, disease is defined in relation to the main organ in which manifesting the symptoms. Although quite useful, classifying diseases in this way vastly overgeneralizes pathophenotypes and usually overlooks susceptibility states or preclinical manifestations (Loscalzo and Barabasi, 2011). Likewise, each symptom is regarded as a mechanical failure and its treatment only requires the correction of specific parameters of the damaged mechanism (Ahn et al., 2006). This type of approaches to disease cannot be used to individualize its diagnosis or therapy (Loscalzo and Barabasi, 2011). For example, Sickle Cell Disease, a simple genetically determined disease, shows complex manifestations depend on diverse factors such as the

presence of disease-modifying genes (e.g., hemoglobin F) and/or environmental influences (e.g., hypoxia) (Loscalzo and Barabasi, 2011). A reductionist approach would fail to treat such manifestations. For this and other reasons many physicians and researchers have been given the task of searching for new treatment strategies.

Some treatment strategies have shown several advantages, for example strategies where diverse types of medicines are integrated to help patient engagement and compliance to self-care, reduced reliance on pharmacotherapy and enhanced symptom control (Katz and Ali, 2009). Particularly in the treatment of heart failure, the combination of Traditional Chinese Medicine with allopathic medicine has shown several advantages such as multi-target treatment; dialectical logic; personalized therapy; and reduction of side effects (Zhang, 2015). This and other treatment strategies have impact in the Health Care System principally to preventive level where help to health promotion; to prevent the inception of disease, treatment of presymptoms, control and progression of the disease (Katz and Ali, 2009). Moreover, researchers observed that this kind of models have the potential to reduce the burden of chronic disease, lower the cost of healthcare, and offer a sustainable health financial paradigm (Herman et al., 2014). Due to its shortcomings, many researchers and physicians consider this type of medicine important and they have been searching for new ways of this kind of treatment, named as Integrative Medicine (IM).

INTEGRATIVE MEDICINE

Integrative Medicine has different definitions: Madsen et al. in 2017 indicate that it is a current health care paradigm which promotes a “whole person” approach to health through a coordinated use of appropriate therapies originating from inside and outside of conventional medicine (Madsen et al., 2017). Among its principles this branch of medicine consider health is more than the absence of disease (broad definition of health), the exploration of a wide-ranging spectrum of therapeutics and beliefs (inclusivity), coordination of all the parts involve in healing process and patient-centered care (Ko and Schiffman, 2013). The recent inclusion of IM in the pediatric field has allowed to recognize others of its basic principles as prevention, contextually-centered, importance of communication between health professionals and families, evidence-informed that show the safety-effectivity of the treatment plan and ecological sustainability (Esparham et al., 2018).

The IM is oriented towards a kind healing elements that takes the body, mind and spirit of the person into account; encompasses all aspects of lifestyle; named as optimal healing and wellness, and emphasizes the therapeutic relationship (Thornton, 2013; Rayner et al., 2011). Other element of IM is to use less invasive, toxic

and cheaper methods to treat diseases (Rakel, 2012). In different countries, this type of medicine includes traditional medicines too (Robinson, 2015), for instance Traditional Mexican Medicine, due to its efficacy, effectiveness, efficiency in different diseases, like diabetes (Laguna-Hernández et al., 2017), diarrhea and dysentery (Calzada et al., 2017), among others. As a case in point, a study shows that *Justicia spicigera* Schltdl. (Acanthaceae), a traditional Mexican medicine plant, affects the proliferation of cancer cells culture (LNCaP) (Fernández-Pomares et al., In press). As a result of the foregoing, Integrative Medicine is exploring integration strategies for diverse health systems (Robinson, 2015).

Other relevant element in IM also tries to integrate healing practices and whole medical systems informed by evidence (Thornton, 2013) from the Complementary and Alternative Medicines (CAM) into the patient's usual treatment (Rakel, 2012). Actually, there are already clinical practice guidelines in which the scientific evidence is question or evaluate about the effectivity on its use in Integrative therapies as supportive care in some diseases (Greenlee et al., 2014). The screening, or grade of recommendation, of this therapies is: A, high certainty of net benefit, B, moderate certainty of net benefit, C, less moderate certainty of net benefit, D, moderate or high certainty than the modality has no net benefit, and GPP, evidence insufficient to assess the benefits (Cho et al., 2018). For example, meditation has shown grade A for stress reduction and mood improvement during radiation therapy in breast cancer patients (Greenlee et al. 2014). On the other hand, lifestyle changes, such as diet and physical activity modification, had grade B for cardiovascular disease with previous existing cardiovascular risk factors and the same grade for behavioral counseling for overweightness (Kushner and Mechanick, 2015).

Thanks to scientific evidence of its effectiveness in different diseases the IM and the CAMs are widely used in different countries. To cite an instance, a research showed that in United States 62% of adults used one type of CAM (Barnes et al., 2002). In Mexico, a study pointed out that 64% of patients with hematological diseases have used some sort of CAM (Jaime-Pérez et al. 2012). Another research revealed that in the Pediatric Hospital of the National West Medical Center at the Mexican Social Security Institute from Guadalajara, Mexico, 83% of the researchers and the 69.2% of the physicians have used CAMs (Gómez Martínez et al., 2016). Due to the growing use of this medical facilities among people, health dependencies, like the Medicine Institute from the United States, have developed strategies to understand how CAMs could become a conventional medical practice (Rakel, 2012). This is the main reason why such interest in research and development of Integrative Medicine (Rakel, 2012) has grown; for example, in United States, in 2012, there were already 29 hospitals making use of Integrative Medicine

(Horrigan et al., 2012).

Integrative Medicine has implemented some important elements, like Patient-Centered Care, which refers to treatment recommendations and decision making taking into account the patient's preferences and beliefs (Maizes et al., 2009). Another element is empathy in the clinical relationship or therapeutic partnerships construction (Thornton, 2013), which is built upon listening and trusting without judgment and delivered not through paternalistic prescribing but through artful questioning that allows patients to find their own inner motivation to change (Rakel, 2012). This influences in the role of the patient in their healing process emphasized the importance of the patient's "taking control" over their health decisions (Willis and Rayner, 2013), the patient empowerment element (Thornton, 2013), always accompanied by the health professional. The decision making could be complemented with a transdisciplinary approach that increases the chances of achieving information synergies, thereby allowing us to frame better questions, gather more comprehensive data, and existing information to guide health decisions (Ciesielski et al., 2017). Along this perspective, Integrative Medicine's idea of continuity in health care is an important element as well: when a patient continuously visits a specific practitioner and the latter always has the necessary information about their health process, among other matters (Thornton, 2013; Maizes et al., 2009). This continuity could encourage patients to become more open towards the practitioner regarding emotional and mental causes of their disease (Maizes et al., 2009). Evidence points out that this way of treatment brings good results. For example, it has been reported in a patient with non-small cell lung cancer treated integrating acupuncture and allopathic treatment showed an improvement in his cough, as well as his anxiety (Raz et al., 2017).

SYSTEM MEDICINE

The integrative approach to medicine emerged in a socio-cultural context defined by changing patterns of illness, changing roles in the health care sector and its practice is often defined as contrary to the most heavily criticized traits of the "biomedical model" (Willis and Rayner, 2013). Integrative Medicine deals with the "whole person" where dynamic interactions are manifested along with all health and disease components through the integration of multiple networks and connectivity (Federoff and Gostin, 2009). From this point of view, the biological complexity of a whole system, not found within its individual parts, can be perceived (Taw, 2015), which also allows to observe what Del Bufalo (Del Bufalo et al., 2014) acknowledges as the Complex Phenotype of biological systems.

The issue of biological complexity multi-levelness

applied to health processes is addressed by System Medicine (Wolkenhauer and Green, 2013). Here, some authors described the Complex Phenotype as not merely a sum of the typical phenotypes that are linked to every single possible competitor in the same individual pathology, but as the result of the integration and interaction of all the components that characterize the "person" (Del Bufalo et al., 2014). Also, it is considered that a patient presenting similar clinical manifestations may have different underlying disease manifestations, showing disease heterogeneity (Gustafsson et al., 2014). In this manner, the disease is described as a non-linear dynamical phenomenon that requires time-resolved monitoring of biological key parameters (Wolkenhauer et al., 2013). For this reason, System Medicine included information stemming from molecular, cellular, physiological and clinical domains (Del Bufalo et al., 2014). Thus clinical decisions are based on a diagnostic model consisting of a multi-layered pattern recognition of multiple data inputs linked to scientific reasoning about causality (Gustafsson et al., 2014). In summary, System Medicine could contribute to the integration of clinical and non-clinical data and of the expertise from a wide range of disciplines (Wolkenhauer et al., 2013), as well as Integrative Medicine.

SYSTEM BIOLOGY

The foundation of Systems Medicine comes from System Biology, this strand of biology deals with the complexity inherent of the biological systems. Bertalanffy's proposed that biological systems comply with general organizational characteristics (Cordon, 2013; Kitano, 2007), such as steady state, equifinality, energy conservation, among others (Bertalanffy, 1950). Steady state refers to a time-independent state where the system remains constant, despite the permanent flow of matter and energy with the environment, and their associated reactions are irreversible (Bertalanffy, 1950). The equifinality is the ability of biological systems to reach a final state from different initial conditions and in different ways (Bertalanffy, 1950). Bertalanffy proposed that in the cell an effective work balance exists where the conservation of energy allows the maintenance of this steady state (Bertalanffy, 1950). In fact, this proposition has been reinforced by studies about thermodynamics of open systems from different researchers, like Mae Wan Ho (Ho and Ulanowicz, 2005).

Another important characteristic of biological systems in System Biology is robustness (Ahn et al., 2006), which is defined as a property that allows a system to maintain its functions despite external and internal perturbations (Kitano, 2004). Another innovative principle related to this strand of biology is dynamic stability which can take many forms, including homeostatic, bistable, oscillatory or chaotic (Ahn et al., 2006). These and other principles

of Systemic Biology have shown that diseases require a deep understanding of the underlying cells functions and that a disease is a non-linear dynamical phenomenon (Wolkenhauer et al., 2013). Researchers, like Andrew C. Ahn, suggest that in order to understand the former and other principles of systemic biology an integrative approach is necessary, where scientists from different areas cooperate (Ahn et al., 2006). In synthesis, System Thinking helps us to understand the complexity of the disease. In the case of Malaria, for example, this notion helps us to take into account both environmental and ecological changes as well as human behaviors (Xia et al., 2017). As a result of the foregoing and other reasons, it is proposed that the effectiveness of disease interventions depends on the efficacy of resource allocation, compliance with target host populations and responsive feedback of environmental modifications (Xia et al., 2017).

Thereupon, Integrative Medicine is a branch of medicine that takes care of the whole person, including physical, emotional, spiritual and mental levels (Rakel, 2012). System Medicine is the application of the notions of biological complexity, at the molecular, cellular and organismic level, to the pathological processes (Wolkenhauer et al., 2013). Also, System Biology is responsible for the research of the organizational principles of the system level (Kitano, 2007). These outlooks form part of System-Integrative Medicine, whereby our research team wants to show how biological complexity is related to the wholeness of human beings and how it affects their diseases.

FIVE-SPHERES MODEL

Some researchers, specially from the transdisciplinary approach, explained how the development of a structured intervention is necessary in combining the knowledge from different disciplines (John et al., 2017) and models. For example, in 2017, John and his collaborators structured a complex health intervention that helped to increased self-awareness, autonomy of the self, physical level of self-understanding, self-regulation of the emotions and self-monitoring in adolescents (John et al., 2017). Here we integrate the principles and elements of IM of some of its models, like Rakel (2012) and John et al. (2017) models, and take that we for integrate a complexly structured model that includes five principal spheres or areas: human context, physical, emotional, mental and spiritual human aspects (Figure 1).

Human context

Many contextual factors influence human health: family, community, sociocultural context, environmental conditions, among others. One of these factors is family

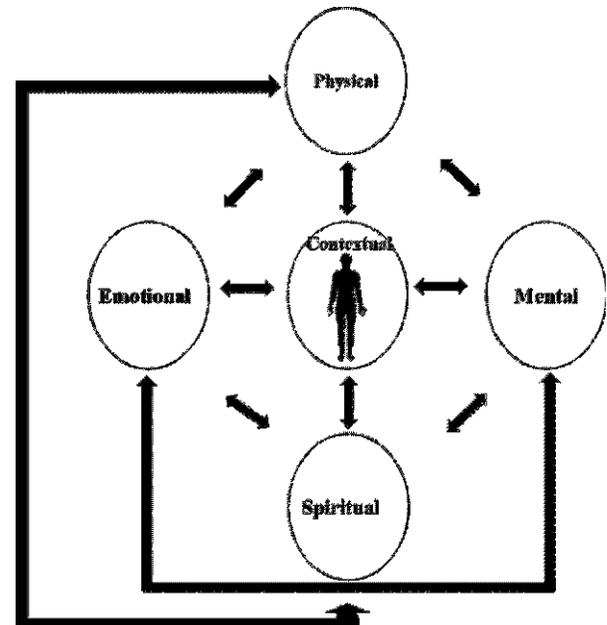


Figure 1. Schematic representation of Five-Spheres Model. In this model we can observe the dynamic interdependency between the principal components of human been.

interaction which is known to be associated with health because family can promote healthful eating, physical activity behaviors and prevent child obesity (Lindsay et al., 2015). Some works show that community-based participation and taking into account cultural context could effectively organize and facilitate large, health-promoting partnerships, involving multiple and diverse communities (Johnson-Shelton et al. 2015). Other contextual factor includes environmental conditions (e.g., electromagnetic fields). In this case it was reported that a 50 Hz-sinusoidal electromagnetic field influences cell autophagy in Chinese hamster lungs (Shen et al., 2016).

Social factors are another contextual aspect that could influence the initiation and maintenance of behavioral changes associated with physical health (Hughes and Gove, 1981). Another very important contextual factor associated with health is the therapeutic relationship (Maizes et al., 2009). A significant issue in this regard is communication. The main goals of current doctor-patient communication involve having a good interpersonal relationship, facilitating exchange of information, and including patients in the decision making (Ha and Longnecker, 2010; Feudtner, 2007). For example, studies on colon cancer patients point out that those who trusted their oncologists presented significant changes in physical functioning (Ernstmann et al., 2017). Owing to this rationale, our research team, like others around the world, has taken into consideration the importance of generating a respectful dialogue between health professional and patient, where the skills of both are used

collaboratively.

Physical sphere

The model of Integrative Medicine proposes that exercise, breathing, detoxification and nutrition can be used as a treatment at the physical-human level. Exercises, like Taichi, Yoga and Qigong, may improve functionality and health, since the nervous system affects the endocrine and immune systems while performing these mind-body exercises (Wang et al., 2017). For example, Sun and coworkers, in a study with 32 patients with type 2 diabetes, showed that one 60 min session per week of Qigong plus the additional practice of this discipline for 30 min during 12 weeks, resulted in a significant reduction in fasting glucose levels and it demonstrated trends toward the improvement of insulin resistance (Sun et al., 2010). Another study with 22 individuals shows that after 3 months of Qigong practice, mental and physical fatigue decreased while spirituality and psychological scores in QoL test improved (Li et al., 2015). On the other hand, it was observed that deep breathing decreases pain, improves the motion of extremities (Lee, 2015) and controls hypertension (Cernes and Zimlichman, 2017).

Detoxification is recommended because we are exposed to the abuse of several recreational and medical drugs, occupational and environmental chemicals, among other intoxicating elements (Klein and Kiat, 2015). Studies indicated that detoxification could be associated with the regulation of blood pressure, improvement in psychological aspects and a decrease in cholesterol levels (Schnare et al, 1982). Another study in diabetics showed that food could have different proprieties and physiological effects depending on their preparation (Granfeldt et al., 1991). In addition, another research showed observational evidence: individuals with a high intake of fruits and vegetables rich in betacarotene had lower incidences of lung cancer, in contrast to people who took a beta-carotene supplement instead (Omenn et al., 1996). All these results emphasize that, in order to possess a complete understanding of nutritional facts, parts cannot be separated from their whole (Wongvibulsin et al., 2012).

The foregoing, along with other reasons, suggests that exercise and nutrition belong to some of the elements that directly treat the physical component in the Five-Spheres Model of Integrative Medicine. Certainly, these means of treatment can and should be supplemented integrally with elements of allopathic medicine and other CAM's (Rakel, 2012).

Emotional sphere

Emotional states can be related to some psychological disorders like alexithymia, which is characterized by

deficits in the processing of emotional stimuli. In cases of individuals with high, medium and low levels of alexithymia, it was registered that this condition affects their pleasantness sensation response to odors (Cecchetto and Rumiati, 2017). Also, emotions seem to affect people at their organic level; for example, in a research with healthy individuals exposed to a stimulus of disgust, a tachygastric response in the stomach was observed, as well as activity in their right anterior insula, and a reduction in parasympathetically mediated influences on the heart (Harrison et al., 2010). At a neurological level there are evidences indicating that a deficit in their dopaminergic system existed in 94 patients who consumed methamphetamines. Such deficit related to problems with emotion regulation, possibly contributing to personal and interpersonal behavioral problems (Okita et al., 2016).

Emotions are linked to the endocrine system, and one example of these links is cortisol, which has been associated with an attenuated negative emotional arousal in response to acute stress, and together with previous pharmacological studies, these data seem to support the hypothesis of mood-buffering effects of cortisol (Het et al., 2012). On the other hand, stress, an emotional state, has been linked to the activity of some immune cell. For instance, in 2000 Delahanty and his collaborators, reported that in some individuals, a stressful stimulus increased NK cell activity (Delahanty et al., 2000). Moreover, other studies point out that positive emotions were associated with lower circulating levels of inflammation markers, like IL-6, C reactive protein and fibrinogen in 175 adults. These findings highlight the role that daily positive emotions play in biological health (Ong et al., 2017).

These evidences suggest that emotions are a human area that affects at psychological, neurological, endocrinological and immunological levels; thus reinforcing the notion from many researchers about the existence of a neuroendocrine regulation of the immune system, as shown by the recent advances in the knowledge of the psychoneuroendocrine-immunology (PNEI) (Lissoni et al., 2017). For example, it is known that melatonin, a hormone produced by the pineal gland, could regulate and be regulated by IL-2 and TNF- α (Lissoni, 1999).

Thanks to these and other evidences, our research team considers emotional states have been like an 'attractor' (from a systems theory perspective) of pathological processes in Integrative Medicine. Hence our team uses some non-invasive therapies that regulate emotions, such as art therapy (Haeyen et al., 2017) and ecotherapy (Kjøs, 2011).

Mental sphere

This fourth sphere in our model of Integrative Medicine is related to our way of thinking, rationalizing and their

relationship to health. For instance, some studies indicated that the mental representations of illness for patients with breast cancer influence their quality of life (Kovács et al., 2017). Mindfulness is a tool to change these kinds of thoughts. This technique involves attending relevant aspects of experience in a nonjudgmental manner (Ludwig and Kabat-Zinn, 2008), helping patients to improve some pathologies. In 2017, Ruskin and his collaborators registered that adolescents who participated in an eight-week mindfulness group improved their acceptance of reality by allowing them to notice their thoughts and emotions, enabling them to learn new strategies for pain management (Ruskin et al., 2017).

Another tool for the treatment of the mental aspect in human being proposed by several authors is the development of the so-called critical thinking. Critical thinking is linked to solving and finding better explanations by making sense of information using creative, intuitive, logical and analytical processes, mainly by both health professionals (Tyreman, 2000) and patients. Likewise, treatment of the mental aspect of human being has been related to an improvement in serotonin level related markers, cortisol (Maron and Nutt, 2017) and IL-6 (Martinac et al., 2017). Thanks to the mentioned evidences this element is included in our treatment of the Mental Sphere in our model of Integrative Medicine through the use of the mindfulness meditation techniques.

Spiritual sphere

The fifth and final sphere, the Spiritual element, is regarded as an important and central theme in healthcare (Steinhorn et al., 2017). Spirituality involves a connection to something greater than oneself. It is an individual's experience and relationship to a fundamental, non-material aspect of the universe that may be referred in many ways: God, Higher Power, the Force, Mystery and the Transcendence and the way whereby an individual finds meaning and relates it to life (Mohandas, 2008). In 2017, Griffiths and his collaborators showed a spiritual practice could be associated with positive changes in psychological functioning, in trait measures of pro-social attitudes and behaviors like, interpersonal closeness, gratitude, life meaning/purpose, forgiveness, death transcendence, daily spiritual experiences, religious faith and coping, and community observer ratings (Griffiths et al., 2017).

In some cases, spiritual factors can influence decision-making: as a case in point, the parents of a child with a fatal metabolic condition had a realization through a shamanic healing process that allowed them to permit the discontinuation of artificial life support of their son (Steinhorn et al., 2017). Similarly, some places are related to spiritual healing; these places are associated

with witnesses and/or interpretations of healing events such as miracles or shared experiences of gradual improvement in health after attendance these sites (Perriam, 2015). To point another instance, a research indicated that the relationship between environment and the physical and mental well-being could be linked to "spiritual awareness" as a result of embodied and emotional practice in particular places (Muirhead, 2012). Ceremonies of some cultures use rhythm and dance to create a spiritual experience. By way of illustration, a modified African Ngoma Healing ceremony was related to an improvement in depression, anxiety, emotional well-being and social functioning in eleven women (Vineset et al., 2017). Also spiritual activity could be related to changes in levels of dopamine (Kjaer et al., 2002), cortisol, aldosterone, dehydroepiandrosterone sulfate, 5-hydroxyindoleacetic acid (5-HIAA) (Walton et al., 1995), and IFN- γ (Gopal et al., 2011).

Thereupon, based on these and other evidences, through the treatment of the spiritual element in this Integrative Medicine Model our research team intends to regulate different organic components at the same time. Additionally, like Steinhorn and his collaborator in their 2017 study mentioned, we believe that Integrative Medicine can augment care for patients by supporting the human spirit within their frail bodies to which we are entrusted. For that purpose, our team uses different spiritual practices that we know could improve the spiritual element, like meditation (Mohandas, 2008) and other body-mind practices (Li et al., 2015). Thus we propose a treatment strategy based on the systemic principles of complexity of human beings.

CONCLUSION

Integrative Medicine, as well as other areas of science, arises from the need to cover the gaps of the reductionist-mechanistic paradigm of science applied mainly in pathological processes. This branch of medicine tries to integrate the knowledge of both allopathic medicine and alternative and complementary medicines (Rakel, 2012). The complexity of human beings is approached from the notions of Systemic Medicine where a pathology is considered to be the result of a network where all the components that characterize the person integrate and interact (Del Bufalo et al., 2014). These approaches come from Systemic Biology where different fundamental principles of living beings organization are evidenced, such as robustness, dynamic stability and non-linear dynamics (Ahn et al., 2006).

One of the important contributions of this review that impact in IM is to highlight the importance of integrate transdisciplinary the knowledge of different strands of biological science like integrative medicine, system medicine and system biology in healthcare process. By taking all this knowledge our research team proposes the

Five-Spheres Model of Integrative Medicine so as to influence, through non-invasive therapies, based on evidence, different organic components, such as the psychological, neurological, endocrine and immune aspects and at the same time, we deal with the health practitioner-patient relationship and the physical, emotional, mental and spiritual spheres of the person. So we showed clearly a complex strategy of integrative treatment where we delimit markedly an integral, recursive and synergic treatment of each one of the aspects of the wholeness of the human being.

Finally, we want to clarify that our proposed model represents only a choice for an integrative treatment of different pathologies that, like other options, needs different studies to prove clinically its efficacy and pertinence.

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