

Biomedical science limitations and flaws: why not choose wisely?

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Abstract Biomedical science is experiencing a reassessment of its practices of healthcare management where more appropriate cost-benefit profiles are being combined with improvements in knowledge, effectiveness, and safety of diagnostic/therapeutic procedures to drive the advances in medicine. This review aims to assess: (a) possible biases of the scientific literature and research, (b) the clinical value and the cost-effectiveness of the principal medical practices and (c) the possible contribution of integrative and translational medicine.

Literature shows that current medical research has cognitive (mostly industry-induced) biases that negatively impact clinical practice: the ever-increasing use of drugs and technologies, united with a certain inattention to the basic mechanisms of pathophysiology are paving the

way of reductionism in medical practice. A critical view of innovations in medicine, together with a sound understanding and application of the scientific method, would improve the effectiveness, safety and sustainability of therapies.

Translational and integrative medicine can contribute to develop a new patient-centered approach. Conversely, reductionism, eminence/reimbursement-based medical decisions, lack of patient education, industry-influenced science, and limited awareness from physicians may compromise the efficacy, safety, appropriateness, and cost-effectiveness of diagnostic and therapeutic processes.

Keywords integrative medicine, choosing wisely, pharmacoeconomics, overuse, bias

1. Background

Biomedical science deals with the sum of all psychobiological changes that affect the individual over the course of life. Aging is characterized by lifelong negative effects on performance, functional reserves and psychophysical homeodynamic adaptation to internal and external/environmental changes¹.

Epigenetics studies the heritable phenotype changes that do not involve alterations in the genome, while investigating the changes that affect gene activity and expression; the relative effects on human health may

basically result from external (nutritional, lifestyle, psychosocial and environmental) factors². A more comprehensive view of this phenomenon is slowly paving the way towards a functional approach that looks at the root causes of the signs and the symptoms of a given disease, moving away from reductionism.

In view of the fundamental role played by this interaction between human psychobiology and the outer stimuli, biomedical science is focusing on the individual resilience as a major factor in health and disease³.

1.a) socio-economic issues

Importantly, the social costs of the current biomedical therapeutic approaches have recently become less sustainable; furthermore, an exponential increase in the prevalence of several chronic degenerative diseases (CDD), such as cancer, neurodegeneration, cardiovascular and cerebral atherosclerosis, obesity, diabetes and autoimmune diseases, has been documented in the general population and particularly in the elderly. Similarly, the recent COVID-19 pandemic has highlighted the negative prognostic value of these CDD when patients get infected⁴.

Consequently, health systems suffer problems of sustainability due to this cumulative and overwhelming burden which has led to a dramatic increase in patient disability and an overall consumption of health resources.

This narrative review aims to provide a range of data, information, and reflections on some scientific and socio-economic issues related to advances in biomedical science and to biases and flaws in medical research and clinical practice.

Today, 2 to 2.5 billion people worldwide are overweight or obese; in the US alone, it is estimated that 50% of the population could suffer from obesity by 2030, resulting in a \$549.5 billion increase in spending compared to the cost of obesity in 2010⁵.

Similarly, the European commission estimated a 21% increase in new cancer cases by 2040 in Europe, compared to 2020⁶; even more worrying data were provided in 2010 by the American heart association which predicted that by 2030 40.5% of the US population would have some form of cardiovascular diseases, with a triple direct medical cost (from \$273 to \$818 billion) compared to 2010⁷.

Neglecting these vitally important health issues may lead to several complex biomedical and socio-economic problems in the near future, which invariably also affect the vascular disciplines⁵.

1.b) Integrative medicine, Epigenetics and Pharmacoeconomics

Notwithstanding the relevant pharmacological/technological advances, the maximum length of human life and the so-called healthspan have not increased, while the average lifespan has increased significantly over the past century.

Human diseases were shown to depend on chromosomal inheritance for about 25%⁸, whereas the remaining 75% of pathological processes depend mainly on epigenetics; thus, the individual's experiences and decisions regarding own environment, nutrition, lifestyle and psychosocial conditions determine the cellular metabolic pathways through epigenetic mechanisms.

In addition to conventional pharmacological and technological support, many complementary interventions (based on proper lifestyle, diet, stress management) have been validated and recognized as fundamental pillars in an integrative treatment of aging processes and of CDD.

Table I summarizes the integrative medicine interventions that were shown to be of help in CDD management

Unfortunately, daily medical practice often shows a reductionist approach solely based on the treatment of symptoms and signs, thereby neglecting basic pathophysiological mechanisms which are fundamental in the disease.

Given the fact that science is a constantly changing base of knowledge base⁹, it would be desirable for the medical community to take into account the impermanent and limited nature of scientific progress and adopt a more balanced view of any innovative step in diagnostic/therapeutic methodologies.

Real progress in medicine occurs when an improvement in the efficacy and safety of diagnostic/therapeutic procedures meets with a reasonable (possibly better) cost-benefit profile¹⁰.

Pharmacoeconomics, which is the branch of health that evaluates the effectiveness and costs of medical interventions, mainly drugs and technologies¹¹, is pushing medical research and practice to develop more comprehensive diagnostic and therapeutic pathways which include cost-effectiveness profiles.

Apart from the obvious positive impact of pharmacoeconomics on the scientific community, several institutions can benefit from this cultural approach and develop appropriate healthcare strategies¹². COVID-19 and the current economic challenges that are introducing socio-economic constraints worldwide, provide further motivation to reflect on the need to improve the cost-effectiveness of healthcare.

2. Literature analysis

It is known that the best medical practice today relies on evidence-based medicine (EBM), but this process of constant revision of scientific knowledge has moments of transition where various pathophysiological, diagnostic and

therapeutic proposals do not meet the full consensus of the scientific community. One of the causes of this is that the interplay of prejudices and other biasing factors affect EBM-derived decisional processes.

2.a) Critical Issues of Medical Literature

In 2005 J. Ioannidis published what is currently considered the most provocative (and useful) article in the revision of the scientific evidence entitled "Why Most Published Research Findings are False"¹³, in which he listed a number of prejudices and controversies, which have compromised scientific research and publications. Further research has shown how several biases interfere with scientific and clinical research¹⁴⁻¹⁵, and how these biases, whether cognitive or otherwise, can inhibit the critical thinking of doctors and researchers, leading them to take wrong clinical decisions.

There are different reasons why biases manifest and the most common is probably subsidies. In fact, economic and logistical support from the industry is seen as essential to complete extremely expensive and complex research and therefore, over the past few decades, we had a multitude of industry-supported scientific studies that somehow overwhelmed the independent studies.

Interestingly, only a few of these industry-sponsored proposals has been confirmed to be valid in terms of cost-benefit improvement¹⁶.

In addition, several issues have been raised about unpublished industry-funded studies because of their negative results¹⁷ and about retracted studies after their publication due to scientific misconduct (72%) and errors (28%)¹⁸. Finally, some discrepancies have been highlighted between the results of independent studies and the results published in industry-sponsored studies¹⁹.

Goldacre reported about the penetrating effect of corporate marketing strategies on medical practice²⁰. In fact, the role of industries in medicine has been long debated and a case for tackling corruption in global health care has recently been raised in some significant publications²¹⁻²³, demonstrating the need for more attention to some specific aspects of medical advances, as reported above.

2.b) Reductionism in Medical Practice

Nowadays, in the curricula of medical training the study of basic pathophysiology of most diseases is poorly represented, whereas systematic treatment of symptoms and signs of the diseases is promoted. Similarly, in today's biomedical education, the detrimental role of improper diet, lifestyle, environmental factors and chronic stress are underemphasized.

While there is an inherent risk of reductionism for the current medical approach²⁴, we are witnessing a dramatic global increase of many CDDs that is likely to push healthcare systems into collapse.

In addition to the shortcomings of health professionals that we just described and to the lack of critical assessment of the medium/long-term results, also the attitude of patients towards medical care and caregivers

may represent an obstacle. Thus, the typical unwillingness of patients who are eager to follow fashionable novelties in healthcare or to delegate own health to medications, technology, and ultimately to caregivers, can hinder a more comprehensive management of chronic diseases.

The development of modern civilization has definitely affected environment, nutrition, lifestyle and stress tolerance, which are the cornerstones of human health/disease processes^{25,26}. At the same time, human diets have shifted from beneficial natural foods interspersed with periods of compulsory fasting to easily procured processed foods, as well as from good to bad (e.g. trans) fats, and from lower to higher proportions of (mostly refined) carbohydrates. Finally, sedentarism is becoming increasingly widespread among newer generations.

Table I
Integrative medicine interventions

Adequate physical activity
Caloric restriction/quality nutrition (reduced intake of carbohydrates and of hydrogenated and processed fats, above all)/intermittent fasting
Intake of nutraceuticals (including compounds, such as polyphenols) with beneficial metabolic-epigenetic features
Regulation of the psychoneuroendocrineimmunology (PNEI) system by means of interventions such as breathing, meditation/mindfulness, sleep regulation, and psychotherapy
Microbiota/microbiome regulation through targeted probiotics, prebiotics and nutrition
Activation of hormesis pathways, which favor the improvement of the individual's psychophysical resilience through low dose exposure to biophysical/biochemical stimuli: a) thermal stressors b) fasting c) physical exercise d) chemical stressors (e.g. polyphenols).
So-called "mitochondrial" therapy to improve biogenesis and proper function of mitochondria and an adequate mitophagy

Profit-driven industries nowadays dictate the quality and quantity of daily food intake by providing wrong nutritional models: the media and industries tend to disseminate outright harmful dietary habits (e.g., brain-rewarding sugar intake) creating addictions. Unfortunately, these stimuli encounter little criticism from healthcare professionals and from population in general.

"Diabesity", the widespread condition which includes type 2 diabetes, obesity, and dysmetabolism is one of the best examples of a relevant clinical problem that dramatically affects the course of all CDD and namely of cardiovascular diseases^{5,27,28}. When assessing biomedical literature, the presence of eminence-based medicine is a risk that has been raised by a few authors²⁹ who highlight the financial, geographical, and cultural reasons for it: in fact, EBM is often overflowing with publications written by authors that are deemed "important" by the community.

Another important factor is that the diagnostic and therapeutic pathways can vary significantly across countries or continents, not just due to cultural factors but also due to the organizational structure of the national-public/private/insurance-based healthcare systems: medical treatments and diagnostics are often accepted based on whether and how they are reimbursed by health insurance companies (intuitively: procedures with higher reimbursements are more easily accepted).

Medicine generally should rely on the results of scientific research to devise appropriate health care strategies. Of great concern, though, is the fact that in 2013 a reliable review of the randomized controlled trials of 3000 treatments currently in use³⁰ highlighted the following: 11%

of the reviewed therapies were rated beneficial, 24% were rated likely beneficial, 7% a compromise between benefit and harm, 5% unlikely beneficial, and 3% ineffective or harmful. The remaining 50% were classified as unknown in terms of effectiveness because they were not supported by randomized controlled trials.

A very recent well-documented and extensively-referenced article³¹ examined 2428 Cochrane reviews and the authors found that only of 5.6% of the 1,567 eligible interventions had high-quality evidence which supports their provision. Conversely, there was a statistically evidence for harm in 8.1% of the 127 assessed Cochrane-validated interventions.

In line with these disappointing findings, the overuse of medical services is well recognized around the world³², and a movement towards wiser selection of diagnostic tests and therapies (the so-called "choosing wisely" movement) is spreading valuable ideas^{33,34}. Aside from the potential harm to patients resulting from overdiagnosis and overtreatment which make medical errors the third leading cause of death among patients³⁵, overuse contributes significantly to overall healthcare spending worldwide. In the United States, approximately \$270 billion was spent on medical overuse in 2013³² and in a few countries, healthcare spending poses the greatest threat to financial balance, which will deteriorate as populations age.

A recent UK-based review documented that hospital admissions in for adverse drug reactions passed from 6.5% in 2004 to 18.4% in 2021, which may cost more than £2 billion per year³⁶. Similarly, a 2019 JAMA article³⁷ highlighted that the estimated yearly cost of waste in the US

health care system ranged from \$760 billion to \$935 billion (about 25% of total health care spending).

In order to reduce the expenses and the risk of potential harm to patients, the U.S. Department of Health and Human Services Office of Inspector General focused on one single month (October 2018) to assess the potential adverse events rate during hospitalization for Medicare patients. The authors found that 25% of the hospitalized patients experienced some harm from medical care, which would have been prevented in 43% of the cases providing a better care, as to a specific physician-based review³⁸.

Overall, it was repeatedly highlighted that the resolution of the problem of overuse^{32,39} could reduce the employment of low-value diagnostics and therapeutic interventions, and induce beneficial ethical and socio-economic changes in society.

In the assessment of the major factors which may negatively impact health care, specific attention should be given also to the attitude of patients, health professionals, industries and politicians.

2.c) EBM and a Patient-Centred Approach

Regrettably, a series of issues have been raised regarding the currently available models for primary, preventive medicine worldwide; in fact, a few relevant obstacles have been identified in the achievement of an efficient primary care system: the lack of equity in the access to the primary health care, the frequently episodic fruition of the primary care system and finally the presence of a mixed health system (public and private) which contributes to inequities in access and health outcomes⁴¹. Recently, a few authors have proposed a different approach to the patient's care: to combine EBM with the physician's elaboration that comes from a comprehensive assessment of the patient⁴². Such change would account for the fact that science can be fallible, biased, and subject to controversy. In fact, EBM only provides standard recommendations based on the available scientific evidence, and since the concept of standardization is inherently opposite to "patient-centrism", medical practice should try to mediate between these two ends transforming itself into "a transitive relationship between a truth of reason and a truth of fact, hence among evidence, doctor and patient"⁴². Thus, the "statistical regularity" of medical evidence cannot assume that constant findings are irrefutable truths, especially given the infinite peculiarities of patients. Such change would mitigate the fact that science can be fallible, biased, and subject to controversy.

It's a well-known fact that patients prefer pills and technology over changes in their lifestyle, diet, environmental and psychosocial conditions. This trend in patients is mirrored by physicians who tend to prescribe drugs and use technology in healthcare systems instead of pursuing patient education, because that process is often tedious and doesn't bring immediate results, especially for chronic diseases.

In view of the fact that patients have basically delegated their own health care to doctors and to the technological or pharmaceutical industries, it would be desirable to have a more proactive attitude from patients and health professionals, so to improve the outcomes of the therapies in terms of costs and social organization.

Primary health care may undoubtedly play a major role in terms of the prevention of chronic diseases (especially of non-communicable type), and in reducing the costs for the single individuals and the society, also improving patients' quality of life⁴⁰.

Leucht and coll.⁴³ assessed through a meta-analysis the efficacy of a few common medications and they generally found that differences larger than one standard deviation between the drug (e.g. pump inhibitors, oxycodone, antidepressants, paracetamol) and placebo groups are uncommon. The authors also documented that most studies use surrogate outcomes like diastolic blood pressure or fasting plasma glucose, and not patient-centred outcomes such as pain, mortality or adverse events, to demonstrate efficacy and safety of a given medication (e.g. statin, proton pump inhibitors, anti-diabetic and anti-hypertensive drugs). Moreover, many of the investigated meta-analyses were found to have a low methodological quality. Lastly, the indiscriminate use of relative risk reduction in most trials was proven as misleading for clinicians, who should properly interpret, for example a 18%-14% = 4% reduction as an absolute data, and not as a 21% relative risk decrease.

The ability to combine temporary "scientific truths" with a pragmatic patient-centered approach, the possibility to have intellectual autonomy, and the propensity to choose "in science and conscience" are all necessary factors that should always intervene in the physician's decision-making process, an undoubtedly complex task⁴⁴.

3. Discussion

The reductionism that characterizes areas of the current biomedical science that often focus too much on drugs and technology has been heavily criticized by several authors^{24,44-46}. Patients' lifestyle, diet, environmental and psychosocial conditions are in fact key elements in health and disease processes.

Translational medicine, epigenetics and integrative medicine are undoubtedly future areas of interest

3.a) Doctor-Patient Relationship

The adherence of patients to the medical advices has been long debated since the sixties and seventies^{49,50}. Interestingly, much fewer publications have been reserved to this issue in the last decades, as a more drug/technology-centred approach has been likely promulgated within the medical community; this way, physicians tend to bypass and somehow neglect the fundamental patient's involvement in the care project.

Whether justifiable or not, it is possible to speculate that this sub-optimal habit of most doctors, who just focus on symptoms and signs of the diseases, very often derives from their "impotence" to combat patients' inability to correct their lifestyle and all the other illness-related basic factors^{50,51}.

As possible consequences of this critical situation, on one side healthcare community should envisage a greater effort to increase patient's adherence to medical advices⁵¹, on the other side physicians arrive to hypothesize a sort of selection/denial of cures for the non-compliant patients; in fact, in a UK-based survey it was highlighted that 54% of the investigated NHS doctors considered appropriate

3.b) Biases in Biomedical Research

Also a recent systematic review of all Cochrane reviews indicated that the quality of evidence in EBM has not changed significantly over the past 17 years⁵⁴. The authors' conclusion points to the need for a major reassessment of scholarly research, with a focus on its several biases and shortcomings.

Interestingly, Cochrane reviewers also found that sponsored studies yield results that are more favorable towards certain therapies than unsponsored ones, which

in the treatment of chronic degenerative diseases. Incorporating these advanced approaches into the landscape of current biomedical science has the potential to be extremely beneficial and cost-effective, also in phlebology where significant changes have been recently advocated^{47,48}. A comprehensive approach that includes patient awareness and self-management can reduce the future burden of chronic diseases, which are destined to grow up in view of the increasing longevity.

to deny or differ the cures to non-collaborating obese or smoking patients⁵².

The integration of current medical knowledge with a broader functional and integrated approach to the whole psychobiological human reality can definitely contribute significant improvements against physicalism, reductionism, and poor decisions by caregivers and patients.

Also, a higher level of awareness among healthcare professionals can benefit patients and the future of medicine. A more ethical support from the industry is desirable, along with better health education for patients. The end goal would ultimately be to have a more patient-centric approach and the consequent socioeconomic sustainability of their treatment.

Citing M. Meissner, physicians can achieve the goal of a more balanced decision-making process between risks and benefits, "without being victims of a tyranny of the evidence, but integrating it with clinical expertise, the patient's values and preferences", especially before embarking on costly new diagnostics and treatments⁵³.

cannot be explained by standard risk biases¹⁹; in addition, a recent cross-sectional study highlighted that 24% of guideline writers had potentially relevant undisclosed ties to pharmaceutical companies⁵⁵. An example of this potential bias is also represented by the guidelines on lipid-lowering medications where contrasting interests tend to conflict, leaving little space to independent and reliable scientific literature⁵⁶.

4. Conclusions

In conclusion, while evidence retains its central role in guiding medical diagnosis and therapy, patient-related variables and socio-economic aspects should also be

included in the decision-making process to determine the best medical path for each specific case.

In clinical practice, bringing together evidence, ethics, and a broader view of the patient's clinical condition would lead to greater levels of appropriateness, cost-effectiveness, safety and ultimately efficacy.

The “choosing wisely” approach⁴⁵ addresses the problem of overtreatment and aims at improving the educational process for trainees who should have the skills to recognize and manage the so-called “therapeutic illusion”, one of the major biases that physicians in general have. A more transparent relationship with research-funding and health professional-paying organisms is also

endorsed, so to permit medical doctors to develop own beliefs and test own outcomes more thoroughly.

Overall, the future medical approach could involve a patient-centered vision that studies the underlying pathophysiological mechanisms of a given disease; as a result, therapies could be based on drugs, surgery, and technology but always in combination with good nutrition (and nutraceuticals if needed), proper lifestyle, attention to the environmental interfering factors, and proper stress management. Finally, a strict reference to the cost-effectiveness and appropriateness of the available diagnostic/therapeutic means should be an integral part of every medical decision-making process.

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