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Personalized medicine and proper dosage

Over- and undertreatment of chronic diseases endanger patients' health and strain public health systems

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Overtreatment and undertreatment of common medical conditions—such as diabetes mellitus, hypertension, or hypercholesterolemia—has become a major global health problem [1–3]. The past years have seen an—often unjustified—increased use of glucose-, lipid-, and blood pressure-lowering medications that is straining public healthcare systems with unnecessary costs. At the same time, "clinical inertia", namely a failure to initiate or intensify therapy, creates avoidable health risks for patients.

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Of these, undertreatment is much more dangerous as it contributes to the increasing incidence of common, chronic diseases. "Clearly, patients with significant disease should be treated when evidence indicates a possible benefit", commented Daniel Morgan, Associate Professor of Epidemiology and Public Health and Medicine at the University of Maryland. "If we undertreat populations with diabetes and hypertension, we are likely to see increased cardiac and vascular disease".

Overtreatment is a public health problem

But overtreatment has serious consequences, too. Glucose-lowering medications to treat diabetes have been blamed for up to 25% of emergency hospitalizations in the USA to treat hypoglycemia [3]. Diabetic treatments have also been implicated in cardiovascular events, cognitive impairment, fractures, and death [4]. Aggressive hypertension treatments often cause hypotension with potentially severe side effects, including acute renal failure, hyponatremia, hypokalemia, and syncope [1]. Statins to treat hypercholesterolemia also have numerous side effects: high blood glucose, which increases the risk for diabetes, abnormal liver enzyme levels, and muscle pain or—more rarely—muscle damage. "The outcomes of potential overtreatment for the individual and public health are enormous", commented Elbert Huang, Director of the Center for Translational and Policy Research of Chronic Diseases and Associate Director of the Chicago Center for Diabetes Translation Research at the University of Chicago, IL, USA. "Patients are exposed to the unnecessary risks of medications".

Overtreatment is particularly problematic for elderly patients with several medical conditions. The use of multiple drugs can trigger adverse reactions caused by drug–drug and drug–disease interactions and changes in pharmacokinetics and pharmacodynamics related to age. Additionally, the more the prescriptions, the higher the likelihood of an inappropriate medication or the risk of an emergency hospital admission [5]. "Patients and doctors need to be careful and individualized in how they pursue medical care, especially in the case of the elderly who are the least tolerant to medications", Morgan commented.

In addition to health risks for patients, overtreatment contributes to the excessive costs of health care. In the USA, for instance, unnecessary spending accounts for approximately a third of the total healthcare expenditure [6]. "Misclassifying who should be treated and who should not, will sometimes dramatically decrease the cost effectiveness of a treatment", said Timothy Hofer, Professor of Internal Medicine at the University of Michigan and Associate Director for Analytic and Information Resources at the VA Center for Clinical Management Research in Ann Arbor, MI, USA. "Moreover, this will obviously reduce the benefits and quite possibly increase the harms of the treatment".

Multiple causes of mistreatment

Numerous factors lead to over- and undertreatment: the structure of public healthcare systems, guidelines by medical councils, individual physicians' practices, and patients' attitude. A key cause is the indiscriminate implementation of treatment guidelines to prevent chronic disease, regardless of the patients' individual risks and benefits. "It is in many ways easier to maintain one set of targets for the whole population than to tailor targets from one patient to another", Huang commented.

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The lack of a more individualized treatment of chronic diseases is also caused by the naïve interpretation and incorrect adaptation of the results of clinical trials to the general population, favoring a one-size-fits-all recommendation, as Hofer reported. "For example, performance measures suggested that every diabetic should have a

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hemoglobin A_{1c} (HbA_{1c}) level below 7.0%, even though the intervention group in the clinical trial that supported that recommendation achieved an HbA_{1c} of only around 7.5%, limited by side effects from reaching their goal HbA_{1c} of 7.0%", he explained. "And that was in clinical trial subjects who are always more compliant and healthier than the general population". "Guidelines are short-sighted when extrapolating small potential benefits from carefully monitored trials to general populations—like the SPRINT trial", Morgan confirmed.

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Treatment guidelines for controlling glucose and cholesterol levels, and blood pressure have been based on low-risk factor levels, so as to reduce undertreatment of chronic diseases. For example, the UK National Institute for Health and Care Excellence (NICE) lowered the threshold for cardiovascular disease (CVD) risk QRISK2 in 2014, thus increasing the number of people who are eligible for cholesterol-lowering medication. Similar threshold reductions were suggested in 2013 by the American College of Cardiology and the American Heart Association [7]. This means that not only patients with severe hypercholesterolemia, but also those with slightly aberrant cholesterol levels will be treated with statins. "One of the main reasons of overtreatment is to confuse severe disease with mild disease or even variants of normal", Morgan commented. "In the USA, we have seen decreasing thresholds for what meets the criteria for hypertension or diabetes. Recently, we learned that with new criteria up to half of all Americans are hypertensive and one-third are diabetic or pre-diabetic".

Some of the guidelines for chronic diseases have been revised, but many physicians continue to apply outdated targets. "In the case of diabetes, we have specific public health efforts and guidelines that encouraged intensification of glucose control from over 10 years ago that still affect clinical practice today", Huang said. "There are multiple psychological biases such as anchoring and status quo bias that encourage this behavior". Clinicians tend to rely on earlier information and recommendations and do not always adapt to new data—the anchoring bias. The status quo bias describes patients' attitude to embrace the treatment option that is presented as default by a physician, despite possible alternatives.

Another aspect of the status quo bias is the patient's inertia: preferring the current condition even if changes would be beneficial. "Patients are less willing to take medicines, unless they feel symptoms or the anticipated pending complications of a chronic condition. That leads to people taking medicines only when complications have already occurred, which may be too late in many cases", Huang explained. Patients will not always comply with their doctor's instructions for a number of reasons, such as unbearable side effects or a complex medication regime or interaction with other drugs. But even when the treatment is not difficult *per se*, they often put other priorities higher than their health. "Patients have competing demands for the time and energy it takes to treat their medical conditions—like living their life, finding food, earning money, sorting out their personal life and families—and won't go along as a result", Hofer said.

On the other end of the spectrum, the medical culture itself can be "blind to harms and overly enthusiastic about possible benefits of treatments in patients at low risk", as Morgan noted. Patients with just mild symptoms would benefit more from lifestyle modification without any risks of harm or side effects. Cholesterol levels, for instance, can be lowered naturally by a healthy diet and physical exercise, which also reduce the risk of CVD. However, clinical practice seems to focus more on prescribing drugs rather than advocating a healthy lifestyle. "From a patient's perspective, drug treatments may seem easier and are generally perceived to be more effective than research indicates", Morgan explained. "I have observed a lot of clinical nihilism on the part of physicians regarding lifestyle change", Huang said. "We are not well trained in nutrition and exercise and that lead to clinical practices that emphasize medications". Moreover, medical treatments are considered part and parcel of the physician's job rather than lifestyle counseling. "You can get lifestyle advice from anyone, but you can only get drug treatments from a doctor. Anyway doctors aren't seen as being the source of the best advice on lifestyle", Hofer explained.

Another cause of over- and undertreatment is the lack of time for physicians to thoroughly discuss symptoms and recommend an appropriate treatment: The average patient–physician visit lasts 13–16 min, according to the 2016 Physician Compensation Report released by Medscape. "There is often a lot of competing demands for the time of the doctors to think about all the things that should be done for any given patient", Hofer commented. "We do not give physicians many tools that allow them to prioritize among the 20–30 recommendations they could make in any given primary care encounter".

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One cause of undertreatment specific to the USA is the healthcare system, which leaves millions of Americans uninsured and unable to get an early diagnosis and adequate treatment. "Lack of health insurance is one of the most important reasons of undertreatment in the US, even after the Patient Protection and Affordable Care Act (ACA)", Hofer said. In 2016, 27 million people were reported to be short of health insurance.

Addressing the problem

Reducing mistreatment and the health risks it causes would require various measures. A first step, according to Hofer, would be individualization of treatment not only to identify overtreatment, but also to better spot undertreated patients. Recent guidelines for treating diabetes and hypercholesterolemia already encourage setting individualized goals, but the challenge now, according to Huang, is to encourage physicians to adopt these guidelines. The American Geriatrics Society and the American Diabetes Association stress the increased risks of

hypoglycemia and reduced benefits of aggressive treatment in older patients with mild forms of the disease and endorse higher glycemic targets [4]. Likewise, the US Preventive Services Task Force's recent guidance on statin therapy recommended that adults aged 40–75 years without a history of CVD and 10-year risk of a cardiovascular event of 10% or greater should use a low- to moderate-dose statin to prevent CVD events. The latest guidelines for the UK by NICE also recommend a less aggressive glycemic control and prescription of statins as a preventive measure only for people with a 10% or greater 10-year risk of developing CVD.

> *"The personalized medicine we need now is that patients can understand and choose treatments they want."*

In parallel, improving randomized clinical trials, upon which guidelines and treatment targets are based, would help to increase benefits and reduce the harms of long-term treatments. This would require a change of how the results are analyzed and reported by using risk-stratified assessment: Patient subgroups with different benefits or risks from medication would be more easily identifiable [8]. "We suggest that payers and regulatory bodies motivate prompt, routine adoption of risk-stratified assessments of medical treatments' safety and benefits, since professional and economic incentives reward advocating treatments for as broad a patient population as possible", Hofer commented.

Moreover, the healthcare system should reward doctors for quality rather than quantity of medicines, medical tests, or other interventions. "We need to review medical reimbursement systems to stop rewarding overuse", Morgan recommended. Public healthcare systems need to encourage physicians to avoid overtreatment, while being careful not to increase undertreatment. "Crude utilization restraints, which have been used more or less aggressively as we contend with healthcare cost escalation, have been shown almost invariably to decrease necessary care at the same rate as unnecessary care, thus producing increases in undertreated patients", Hofer warned.

Above all, the culture of medical care needs to change: Both patients and physicians should be more skeptical and cautious, as Morgan suggested. The American Board of Internal Medicine (ABIM), originally established by the American Medical Association and the American College of Physicians launched the "Choosing Wisely" campaign in 2012 to reduce overtreatment by promoting a national dialogue between clinicians and patients. In addition, the ABIM founded the "Research Community on Low-Value Care" in 2015, a professional network for producers and users of medical research to eliminate low-quality health care.

An argument for personalized medicine

"A growing number of financial incentives is in place to avoid iatrogenic complications including adverse drug events", Huang said. "Our understanding of the safety and benefits of medicines has become complicated, but the availability of electronic medical records and computers in medicine can help us to personalize care. With technology, patients will also have more opportunities to be involved in the personalization process". "The personalized medicine we need now is that patients can understand and choose treatments they want", Morgan added. For this purpose, guidelines should emphasize and visualize the effects of a treatment in different populations, he suggested. "We need to have good evidence easily displayed and conveyed to the general public. Visual icon array representations of effect sizes would help educate both doctors and patients", he explained.

To improve treatment for the elderly, computerized tools to support decision-making by physicians have been developed, but are apparently not widely used. For instance, the "Fit fOR The Aged" (FORTA) list is a drug classification system developed as a clinical tool to assist in monitoring and optimizing drug therapy and care management of older patients [9]. Similarly, the "Tool to Reduce Inappropriate Medications" (TRIM) extracts patient data from an electronic health record to help identify treatment risks for aged patients [5].

An emphasis on personalized medicine combined with continuing medical education to keep doctors up to date with changing guidelines and developments in their field could go a long way to improve treatment of chronic diseases [10]. "Better education of health providers of all stripes will also help encourage safe use of medications", Huang commented. Moreover, healthcare professionals could improve the quality of service by receiving patient feedback on disease progression and outcomes. There is not a lack of solutions and suggestions to optimize treatment and thereby public health; the challenge is to implement these and individualize treatment to provide patients affected by diabetes, CVD, or hypertension with optimal medical care, tailored to their individual health background and needs.

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