EDITORIAL AND COMMENT

Evidence-Based Medicine and the Hard Problem of Multimorbidity

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Evidence-based medicine (EBM) rests on the proposition that questions in clinical medicine can be formalized, or reduced, into statistical questions. In the reductionist tradition, these statistical questions can then be addressed by studies designed to isolate the effect of a single exposure (typically an intervention) on a single disease outcome. While the results directly address the statistical question, inferences derived from the results are applied back to the complex clinical realm—where generalists live.

This reductionist “method of knowing” determines the form of our knowledge. When the foundational units of information come from trials carefully designed to isolate and measure the effect of a single treatment on a single disease, if only by force of parsimony, it may seem to follow that the optimal therapy for an individual with more than one disease (i.e. with multimorbidity) should be easily derived through the linear combination of recommended therapies for each component disease. Thus, if patients with Disease A (D_A) generally benefit from Treatments 1 and 2 ($T_{1,2}$), patients with D_B from $T_{3,4,5}$ and patients with D_C from $T_{6,7,8,9}$, then patients with D_{AB} should be treated with Treatments 1 to 5, those with D_{BC} with treatments 3 to 9, and those with D_{ABC} should receive all nine therapies.

While this may seem a scientific parody of EBM, and the antithesis of what thoughtful EBM-practitioners promote, it is unfortunately not as far from the current state-of-the-practice as many of us would hope. Clinical practice guidelines focus on the management of single diseases. It is not surprising that this approach has yielded guidelines that generally do not address how to optimally integrate care for individuals whose multiple problems can make guideline-recommended management impractical, irrelevant or even harmful.^{1,2}

We might be forgiven this “multimorbidity agnosia” if multimorbidity were an unusual condition, confined to the

occasional case report. Yet—as generalists well know—most patients with a chronic condition have more than one, and approximately half of older adults have three or more chronic medical problems.³

The root of the problem is not narrowly confined to guideline development, but is embedded in our very method of knowledge. At each phase of the translational path, including study design and analysis, the synthesis of results in meta-analyses and systematic reviews, and the guideline development process, the information necessary to support evidence-based care of the multimorbid patient is systematically suppressed or excluded.

How are we to address this problem? If this agnosia is in part a product of our “method of knowing” then additional methods alongside EBM may be necessary to address complex problems in real patients. No doubt, integrating knowledge through expert clinical judgment will always be central to the approach to complex patients. Yet, EBM has become the dominant paradigm in part because it has convincingly exposed the limitations of expert clinical judgment. Where wide variation in clinical practice has been construed as evidence of sub-optimal care, and where the need for greater standardization is widely accepted, a scientific basis is needed to achieve greater consensus about how complex patients (i.e. typical patients common in every generalist’s practice) should be managed.

To address these issues, we assembled a collaborative team with complementary expertise spanning the various phases of evidence development and translation to develop a comprehensive description of the problem and provisional recommendations. These were refined through an iterative process of feedback from researchers (from medicine, public health, biostatistics), guideline developers, and stakeholders from government, other payors and industry, which culminated at a conference on Improving Guidelines for Multimorbid Patients (Baltimore October 2010). The results of this project are presented in three papers in this issue, focused on the following three areas: 1) evidence generation (clinical trial and observational study design and analysis),⁴ 2) evidence synthesis (systematic review, meta-analyses),⁵ and 3) guideline development.⁶

Thus, our approach was to work within the existing framework of contemporary EBM, and to understand how this could be leveraged to create guidelines better fit to the needs of multimorbid patients. Our focus was on providing

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feasible, if provisional, recommendations targeted to people currently engaged in generating, synthesizing and integrating evidence into clinical practice guidelines. Each paper also suggests a “roadmap” that attempts to point the way toward more ambitious, longer range, goals.

Not surprisingly, an emergent theme from this project was that multimorbidity and its correlates should not be treated as nuisance variables. Rather, trials should be designed and conducted to maximize heterogeneity of multimorbidity among research participants. Analyses should be based on carefully considered ways to measure multimorbidity; heterogeneity of treatment effects (HTE) should be carefully explored across different subgroups of interest defined by specific comorbidities, or by fundamental dimensions of risk, such as outcome risk or competing risks. Evidence synthesis methodologies should evolve to capitalize on studies designed to address HTE, and to incorporate information from diverse sources. Further, to properly account for all sources of evidence, meta-analysts need to further explore whether and how to synthesize information across studies that differ in design (e.g., randomized trials and observational studies in mixed evidence or cross-design synthesis), or that differ in their internal validity or applicability.

Because the purpose of these trials is not to establish an overall effect, but to evaluate modification of treatment effects, trials may need to be much larger than conventional trials are currently—perhaps, far larger than even modern mega-trials—and thus our “roadmap” emphasizes the need for infrastructural changes that can support such studies. Such trials may only become possible when the clinical research and health delivery enterprises are fully integrated,⁷ with randomization (with informed consent) inserted widely into routine clinical encounters ensuring appropriate inclusion of patients with multimorbidity, since such patients are commonly encountered in routine care. Given the massive amount of data required for these analyses, this “disruptive” change⁸ may need to be accompanied by new concepts for data ownership that facilitate data sharing for pooling data across studies for meta-analyses of individual patient data.

To be sure, multimorbidity poses a fundamental challenge to the reductionist paradigm of EBM. Thus, our proposed solutions—firmly embedded within this paradigm—may simultaneously seem both unrealistically ambitious and woefully inadequate. New paradigms may be needed to address these challenges. What such a post-EBM paradigm might be is difficult to imagine from our vantage, since unpredictability is the essence of a new paradigm. New computational approaches may enable fundamentally different types of “evidence” based on a systems-level understanding of care. New forms of evidence will demand that guidelines themselves take new forms. For example, guidelines may take the form of an ever-expanding expert knowledge system not

compartmentalized by organ or disease. Based on specification of patient-specific characteristics (such as age, comorbidities and disease severities), customized patient-centered guidelines would prioritize among the multiple possible therapies those that likely to yield the greatest benefit, as defined by the patient’s own values and preferences.

This much is clear: the problem of multimorbidity will not be solved by ignoring it. It remains to be determined whether sustained and concentrated attention will permit us to satisfactorily address the problem of multimorbidity using the “normal science” available to us with the tools of EBM, or whether such attention will produce the sort of crisis that is the first prerequisite for a new paradigm.⁹

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