Medicine, Health Care and Philosophy (2020) 23:115–124
https://doi.org/10.1007/s11019-019-09915-5

SCIENTIFIC CONTRIBUTION

Mechanisms in clinical practice: use and justification

Mark R. Tonelli[1] · **Jon Williamson**[2]

Published online: 17 July 2019

Abstract
While the importance of mechanisms in determining causality in medicine is currently the subject of active debate, the role of mechanistic reasoning in clinical practice has received far less attention. In this paper we look at this question in the context of the treatment of a particular individual, and argue that evidence of mechanisms is indeed key to various aspects of clinical practice, including assessing population-level research reports, diagnostic as well as therapeutic decision making, and the assessment of treatment effects. We use the pulmonary condition bronchiectasis as a source of examples of the importance of mechanistic reasoning to clinical practice.

Keywords Mechanism · Mechanistic reasoning · Clinical judgment · Medicine

Introduction

With the advent of evidence-based medicine (EBM), the traditional role of mechanistic understanding and pathophysiologic reasoning in the clinical practice of medicine has been de-emphasized (Evidence-Based Medicine Working Group 1992). Considered less reliable than the results of population-based research, particularly for therapeutic decision making, mechanistic understanding and pathophysiologic reasoning have been relegated to the lowest tiers of "evidence" hierarchies (Guyatt and Rennie 2002; Clarke et al. 2013), excluded from clinical practice guideline development (Guyatt et al. 2008), and discouraged in clinical practice (Howick 2011). Much of the concern, caution, and criticism regarding mechanistic reasoning for clinical medicine relates to our often incomplete understanding of biological mechanisms and their complexity. In this paper, we argue that mechanisms remain central to clinical practice, and rightly so. Mechanistic reasoning enters into clinical decision making at multiple stages, with each use justified in a different manner.

For the purposes of this paper, we take the term 'mechanism' to refer to a complex-systems mechanism, i.e., entities and activities organized in such a way as to explain some phenomenon of interest (Illari and Williamson 2012), or a mechanistic process, i.e., a spatiotemporally contiguous process along which a signal is propagated (Salmon 1998), or a combination of the two. 'Mechanistic evidence' will be used to refer to evidence *of* a mechanism, i.e., evidence of either the existence or features of the mechanism. In contrast, we use 'mechanistic reasoning' to describe reasoning *from* previously established mechanisms or mechanistic hypotheses to other conclusions. Mechanistic reasoning in clinical practice, then, is reasoning from mechanistic understanding to conclusions regarding patient care. Reliance on such reasoning to warrant a clinical claim may be called the 'pathophysiologic rationale' for that clinical conclusion.

In the following sections we describe the ways in which clinicians rely upon mechanistic reasoning in practice. In each case, we provide contemporary examples and offer, or refer to, justification for the use of mechanistic reasoning in that context. In the "Bronchiectasis" section, we start by providing a brief background description of bronchiectasis, a medical condition that will serve as an example throughout the paper. In the "Assessing reports of clinical research" section we discuss the way clinicians use mechanisms in their assessment of the reports of population-based clinical research. We argue that mechanistic descriptions of biologic plausibility serve either to shift clinician's prior probability regarding an intervention or support a claim of causal effectiveness. In the "Clinical decision making" section, we look at several ways in which mechanistic reasoning enters into

✉ Mark R. Tonelli
tonelli@uw.edu

[1] University of Washington, Box 356522, 1959 NE Pacific St., Seattle, WA 98195-6522, USA

[2] University of Kent, Canterbury, UK

the provision of care for individual patients. Our primary focus centers on individualized diagnostic and therapeutic decision making ("Diagnostic and therapeutic choice" section). We argue that the use of mechanistic reasoning is warranted, regardless of whether clinicians are employing analogic reasoning ("Analogical reasoning and mechanism-based extrapolation" section) or extrapolating from reference classes ("Extrapolation from reference classes" section). In the "Problems for mechanism-based extrapolation" section we respond to objections to the use of mechanistic reasoning to extrapolate from population-level research. Clinicians also use mechanistic reasoning to aid the assessment of treatment effects ("Therapeutic assessment" section) as well as to bolster confidence in a particular decision ("Clinical confidence" section). We conclude ("Conclusion" section) that mechanistic reasoning will remain integral to the clinical practice of medicine.

Examination of the clinical reliance upon pathophysiologic rationale will be limited here to the care of individual patients—we will not consider guideline development nor medical science (see Parkkinen et al. 2018). This examination will not presuppose, in the manner of 'evidence' hierarchies, the superiority of population-level research over mechanistic reasoning in clinical practice. While we certainly acknowledge that mechanistic understanding in medicine remains incomplete and mechanistic reasoning remains fallible, neither of these features lead to the conclusion that mechanistic reasoning is strictly inferior to reasoning on the basis of clinical studies in clinical practice. Examining the roles pathophysiologic rationale continues to play in clinical medicine and the justification underlying such use is vital to ensuring that clinicians understand both the value and the limitations of this form of reasoning.

On the other hand, it is important to emphasize that we do not argue that the importance of mechanistic evidence obviates the need for clinical studies. Our claim is that *both* have a crucial place in clinical practice. Improvements to clinical practice can be better achieved by understanding the ways in which these two forms of evidence support each other than by taking one form of evidence to have primacy over the other.

Bronchiectasis

Bronchiectasis is a pulmonary condition characterized by chronic inflammation and infection of the airways. Persons with advanced bronchiectasis almost always have a chronic cough productive of large amounts of thick sputum resulting from persistent bacterial infection. This chronic infection can be suppressed but not eradicated with antibiotics. The airways themselves lose integrity, becoming dilated and mucus-filled, resulting in difficulty moving air in and, particularly, out of the lungs. Persons with bronchiectasis tend to experience episodes of worsening symptoms, often triggered by viral infections, termed 'exacerbations'. Once advanced, bronchiectasis is progressive and irreversible, resulting in gradual decline in lung function. The natural history of bronchiectasis may lead to death from progressive respiratory failure. End-stage bronchiectasis is thus an indication for lung transplantation.

Bronchiectasis can arise in a variety of ways, although in North America and Europe perhaps the most common single etiology is cystic fibrosis (CF). CF is a recessive genetic disorder that results in a loss or reduction of function in the CF trans-membrane conductance regulator (CFTR), a chloride channel protein that is normally present on the cell surface in a variety of tissues, including airway lining cells. The mechanisms by which loss of CFTR leads to the clinical manifestations of CF, including bronchiectasis, are not fully understood.

Bronchiectasis may also be the consequence of a myriad of other etiologies, including direct airway inhalational injury or obstruction, immune deficiencies resulting in recurrent airway infections, systemic inflammatory disorders, and genetic or acquired disorders of ciliary function. In clinical practice, the disorder is often divided into either CF or non-CF bronchiectasis. Bronchiectasis will provide a contemporary and clinically relevant illustration of the ongoing importance of a mechanistic understanding for clinical practice.

Assessing reports of clinical research

Reports of clinical research of new interventions or an expanded use of approved therapies virtually always contain some description of the biologic plausibility of the drug or device being studied. Biologic plausibility refers to the likelihood that a suggested mechanism of action can be posited by which the agent being studied affects the outcome being measured. For instance, in a recently published study of apalutamide for metastatic prostate cancer, the third paragraph of the introduction describes mechanistically the anti-androgen effects of the agent, explaining why that may be beneficial for disease treatment (Smith et al. 2018). The inclusion of a sentence or paragraph advancing a mechanism of action underlying the intervention is not an explicit requirement for medical publication, as are descriptions of the randomization protocol or details of the statistical analysis. Yet the ubiquity of these mechanistic preambles suggests they serve some important purpose.

Describing biologic plausibility might be seen as simply a justification on the part of researchers for why they chose to invest the time, energy and money to perform a particular study. In an era of targeted drug development, biologic plausibility may underlie the process of a drug's

development entirely. Rather than a simple description, however, these mechanistic justifications in published reports suggest an intention to influence and/or aid the primary readers, clinicians.

For studies reporting positive findings of a new intervention or application, advancing a mechanistic argument as prelude may serve two possible clinical functions. First, a mechanistic reason for why the treatment would seem likely to be effective may provide background knowledge for the reader. This background knowledge, particularly if new, serves to instill in the reader a high prior probability that the intervention is effective, making statistical evidence of effect more compelling. That is, a clinician is more likely to believe the results of any positive study, regardless of the associated *p* value, if she holds a strong prior belief that the treatment should work (Rubenfeld 2001). Convincing biologic plausibility makes for strong priors.

Alternatively, clinicians may view mechanistic rationale as explicit evidence supporting a causal effectiveness claim. Even in an era of EBM, the scientific training and biologic understanding of clinicians predisposes them to think of causes in mechanistic, rather than probabilistic, terms. Even when insisting upon statistical demonstration of effect, clinicians want to know why and how a treatment works. Indeed, plausibility was one of Bradford Hill's nine proposed types of evidentiary support for determining causation (1965). More recently, Russo and Williamson (2007) argued that to establish a causative claim in medicine, one normally needs to establish both that a cause makes a (statistical) difference to an outcome and that there is a mechanism from the cause to the effect (see also Williamson 2019). Clinicians may seek, and even demand, mechanistic evidence before believing that a statistical difference alone demonstrates that a study treatment caused the observed outcomes.

The importance of a mechanism for establishing causality may be easier seen in cases where there seems to be no plausible mechanism of action yet statistical evidence supports a claim of effectiveness. Failing to find a plausible mechanism of action may lead clinicians to view statistical associations as spurious (Jerkert 2015). Examples include ultra-high dilution homeopathy (where not a single molecule of the active ingredient remains in solution) and retroactive intercessory prayer (Williamson 2019). In these cases where basic principles of biology cannot accommodate a cause and effect relationship, the results of association studies are generally dismissed as the result of mere chance. Such examples are relatively rare in clinical medicine, as the total absence of a plausible mechanism to explain any discovered potential association serves to discourage clinical researchers from pursuing such studies. When a statistical association is discovered in population-level research despite strong biologic implausibility, for instance with acupuncture for pain relief, the result is often a search for a heretofore undiscovered mechanism to support a causal connection (Zhuang et al. 2013).

Not all claims of biologic plausibility are equally credible. While a complete understanding of mechanism is not necessary to assert biologic plausibility, mechanisms that are only hypothesized, poorly understood, or only peripherally related to the process being studied serve as weak influencers of prior probabilities or as weak support for a causal claim. For instance, the report of the initial randomized clinical trial of recombinant human activated protein C (drotrecogin alfa) for sepsis contained an extensive discussion, including a figure, regarding possible mechanisms of action (Bernard et al. 2001). The fact that the assertion of biologic plausibility in this case required tremendous effort, relying heavily upon speculation and emphasizing effects upon parts of the sepsis cascade not generally seen as crucial to outcome, meant that it was not particularly compelling to many clinicians. As critics of mechanistic reasoning rightly note, complex, highly redundant and incompletely understood mechanisms serve as unstable foundations for predictive mechanistic arguments (Howick 2011). Weak biologic plausibility likely contributed to slow uptake of the drug after approval in the US, caution that was appropriate given the subsequent withdrawal of the drug from the market as later clinical trials failed to demonstrate benefit.

A complete and detailed understanding of mechanism, however, is not necessary to infer biologic plausibility. In the treatment of bronchiectasis, the biologic plausibility offered for new, and ultimately successful, therapeutic interventions generally focuses on specific and limited portions of the causal pathway leading to the development and progression of bronchiectasis. Agents such as ibuprofen and azithromycin were advanced on the theory that the anti-inflammatory properties of each agent would decrease the severity of disease manifestations. Alternatively, the anti-bacterial effects of inhaled antibiotics, such as tobramycin, served as the basis for trials of these medications, some specifically formulated for inhalation. Biological plausibility in these instances proved compelling despite an understanding of the causal pathway of bronchiectasis that was far from complete.

Ivacaftor, a drug developed specifically to address one small ($<5\%$) subgroup of patients with CF deserves special attention. While there are now over 2000 different described mutations of the CFTR gene known to result in CF, not all of these mutations disrupt CFTR function in the same way. Most commonly, mutations result in very little or no CFTR reaching the cell surface in affected individuals. But some mutations allow for CFTR to make it to the cell surface and retain some activity, though ultimately insufficient to maintain normal airway function. Genetic variants of this type are termed 'residual function mutations.' Ivacaftor was designed and developed specifically to activate CFTR produced by a single, specific residual function mutation, allowing the

protein to function more normally in individuals with that variant. Clinical trials in that very narrowly defined population of patients with CF demonstrated improvement in multiple pulmonary and systemic outcome measures. Understanding an extremely small but crucial portion of the mechanism by which loss of CFTR function leads to bronchiectasis was sufficient to develop an effective treatment. We will return to the example of ivacaftor again.

In summary, assertions of biological plausibility are ubiquitous in clinical research reports of new treatments or treatment strategies. Arguing for biological plausibility serves to establish a greater prior probability of effectiveness on the part of clinicians and/or support suggestions of causation that follow from the statistical demonstration of improvement in outcome. The data do not speak for themselves.

Clinical decision making

Diagnostic and therapeutic choice

The application of the results of clinical research to the care of individual patients, as even thoughtful proponents of EBM acknowledge, is far from straightforward. Several clinicians and philosophers have suggested mechanistic reasoning as a way to help overcome the challenges of applying the results of a clinical study to a particular patient (Tonelli 2006; Andersen 2012). However, as a consequence of its de-emphasis of mechanistic reasoning, the EBM literature provides virtually no guidance to clinicians on when and how such knowledge should utilized (Sackett et al. 1997).

Not all are convinced that mechanistic reasoning can or should play this role. Howick and colleagues lay out four problems with using mechanistic reasoning to extrapolate from clinical research results (Howick et al. 2013) and Bluhm also shares their concerns (2013). We shall consider some of these criticisms in "Problems for mechanism-based extrapolation" section.

Population-based clinical research may be misconstrued as producing generalizable knowledge for use in clinical practice. For example, the results of a clinical trial may be promoted as demonstrating that "aspirin is effective for headaches", when the trial itself demonstrated only that "a majority of young patients in a select population with tension-type headache had a reduction in symptom scores after taking aspirin, compared to a placebo." Rather than generalizable knowledge, clinical research produces (1) an "average" case and/or (2) a reference class for comparison and/or extrapolation to a particular case. In either instance, mechanistic reasoning may help to optimally incorporate the results of clinical research into the care of a particular patient. While we are adopting the conventional language of the debate here, it is worth noting that one could rightly reframe the process as one by which population-level research can be used to help optimally incorporate pathophysiologic reasoning into the care of a particular patient. One is not always primary and the other adjunctive.

Analogical reasoning and mechanism-based extrapolation

Clinicians often employ analogical reasoning, comparing the case-at-hand to source cases, from their memory, published reports, or the "average" patient from a clinical study. Effective analogic reasoning largely depends upon the choice of appropriate source cases. Among the varied philosophical attempts to define criteria for justification of an analogy, three primary considerations appear in most, and are particularly relevant to reasoning from analogy in clinical medicine. A conclusion based on analogy is more probably correct when there are (1) meaningful material similarities, (2) a causal connection, and (3) no essential differences between analogs (Hesse 1966; Bartha 2016).

The 'no essential differences' criterion covers reasons, not in the causal pathway, to be considered when attempting to compare an individual patient to potential analog cases. Pediatricians warn us not to treat children as little adults; pregnant women differ in an essential way from their non-pregnant compatriots. Age, sex, pregnancy status, allergic history and a myriad of other personal attributes may be relevant to particular diagnostic and treatment decisions. Determining the relevance of these differences generally depends upon mechanistic reasoning and is case specific. Sex will be an essential difference when evaluating a patient for lower abdominal pain, but non-essential in considering treatment for acute pneumonia. Such distinctions are generally based upon mechanistic understanding and reasoning.

The 'causal connection' is crucial in both diagnostic and therapeutic choice. The approach to a person who is blue in the face and unable to speak depends greatly upon whether one is in the audience of a Blue Man Group performance or eating at a steak house. While patients with low blood pressure may share lethargy and confusion upon presentation, definitive treatment of their hypotension can only be instituted upon discernment of the cause. We compare a hypotensive heart failure patient with other patients with heart failure, not with those who have low blood pressure due to sepsis. Determining causes in clinical medicine relies upon clinical assessment and mechanistic reasoning in addition to clinical studies.

In evaluating a new patient with bronchiectasis, an initial clinical focus centers on determining the underlying cause. This approach is not primarily explanatory, but rather serves to help determine the source case(s) to which the patient will be most analogous. Knowing the etiology of bronchiectasis may be important to slowing disease progression. For instance, if the cause is recurrent infections due to a lack of

circulating immunoglobulins, then replacement of immunoglobulins is expected to improve outcomes. Such therapy makes no sense for other etiologies. Given the final common pathway in bronchiectasis, however, analogies are not limited to cases that share an etiology. As sputum production, inflammation and infection are features of bronchiectasis resulting from any underlying etiology, airway clearance, anti-inflammatory agents and anti-bacterials make mechanistic sense regardless of etiology. Given a robust clinical research infrastructure and funding source, many of these agents were initially studied in patients with CF (McShane et al. 2013). When found beneficial in that population, clinicians used pathophysiological reasoning to extrapolate to non-CF bronchiectasis, which is similarly characterized by inflammation and infection. Subsequent clinical studies, though not of the same rigor as those done in CF, have added support for the use of several of these agents in that broader population. Hence, non-CF bronchiectasis is analogous to CF-related bronchiectasis in some ways and not in others, depending upon which part of the causal pathway is invoked. Understanding mechanisms can both establish a 'causal connection' between patients with bronchiectasis and may also serve to define what is an essential difference between apparent analogs.

This role for mechanisms, then, can address a challenge that faces any attempt to represent diagnostic and therapeutic choice as instances of analogical reasoning. The inference in question might be represented as follows:

> The diagnosis/therapy choice was correct in a previous or exemplar case
> The current patient is causally similar to that case
> Therefore, the diagnosis/therapy choice is appropriate for the current patient

The challenge is that the current patient will differ to the previous or exemplar case, and something needs to be said about how to determine whether these differences are significant enough to block the inference.

We suggest that the challenge can be met by viewing the inference as a kind of mechanism-based extrapolation (Steel 2008). The source and target cases are sufficiently similar if:

(i) the mechanism of action (of the disease or of the therapy) in the source individual(s) is also instantiated in the target patient, and
(ii) there are no further counteracting mechanisms in the target patient that mask the effect of the mechanism of action.

Parkkinen and Williamson (2018) identify four ways of determining whether a mechanism of action in a source population is also present in a target population: enumerative induction, comparative process tracing, phylogenetic reasoning, and robustness reasoning. With enumerative induction, one can reason as follows: all previous patients who share certain characteristics with the present patient instantiate the mechanism, so it is likely that the target patient also instantiates the mechanism. Comparative process tracing requires showing that key features of the mechanism of action in previous patients are also present in the current patient, to conclude that it is likely that the target patient instantiates the same mechanism. Phylogenetic reasoning appeals to facts about common evolutionary ancestry, and mainly applies to extrapolation from animal models to humans. However, arguments from common human ancestry can also be used to extrapolate from humans to humans: for example, they are relevant to diagnosis of lactose intolerance and to choice of blood pressure treatment. With robustness reasoning, if the mechanism is instantiated in several individuals who vary in relevant respects then one can infer that it is likely that the mechanism is also exhibited in the target individual. See Parkkinen and Williamson (2018) for further discussion of these four modes of reasoning, and Steel (2008) for a detailed discussion of comparative process tracing.

This sort of mechanistic analysis helps to explain why mechanistic reasoning is central to diagnostic and therapeutic choice. Mechanistic evidence and mechanistic reasoning are required to ascertain both whether the proposed mechanism of action is present in the patient-at-hand, and whether there might be further mechanisms that counteract the effect of the mechanism of action.

Extrapolation from reference classes

Clinical research on selected population samples, utilizing inclusion and exclusion criteria, may define a reference class to which a patient-at-hand needs to be compared. Extrapolation from a reference class to an individual patient is fraught. Individual patients may belong to no pertinent reference class (they would not have been enrolled in any clinical trial) or belong to multiple reference classes. Research focused on a specific clinical question or therapeutic intervention may encompass multiple studies, each with a different reference class. Within any reference class there will likely be heterogeneity, with meaningful physiologic differences between members of the class. In this context, the reference class problem cannot be solved by purely statistical means; rather a clinician must utilize other approaches in determining the best course of action. Pathophysiologic rationale offers one such avenue, a way to assign patients to the most applicable reference class and to account for physiologic differences that might suggest the patient is not a typical member of any homogeneous reference class (Tonelli 2010; Andersen 2012; Wallmann and Williamson 2017). For instance, while there are evidence-based guidelines regarding the evaluation and

treatment of a middle-aged person who falls, those guidelines may not be helpful in the atypical case of a woman whose fall resulted from flying over handlebars on a bicycle at high speed (Greenhalgh 2018). The mechanism of injury matters. Guidelines do not tell you when the guidelines do not apply, but pathophysiologic reasoning may.

Mechanistic understanding is crucial for assigning a patient to a relatively homogeneous reference class. Persons with advanced bronchiectasis, regardless of cause, form a sufficiently homogeneous reference class with regard to inflammation and infection, making extrapolation from persons with CF-related bronchiectasis to persons with non-CF related bronchiectasis reasonable when considering anti-inflammatory and anti-bacterial agents. But patients with CF due to a residual function mutation form their own reference class with regard to treatment with ivacaftor. Unlike other treatments targeting the broader inflammatory and infectious pathways in bronchiectasis, there is no reason, given mechanism of action, to believe ivacaftor will benefit persons with non-CF bronchiectasis or even those with CF-related bronchiectasis not stemming from a residual function mutation (unless combined with some other agent that results in CFTR making it to the cell surface membrane). It is not simply that the drug has not been studied in these populations, there is simply no biologically plausible reason whatsoever to do so. The reference class here has been determined by a highly detailed understanding of a very small part of the causal pathway that leads to CF-related bronchiectasis.

Problems for mechanism-based extrapolation

Howick and colleagues suggest and examine four problems for using mechanisms to extrapolate from clinical research to other target populations (Howick et al. 2013). They suggest that these problems apply to extrapolating to individual patients as well, so we will consider their objections here.

First they cite the most common challenge to the use of mechanistic reasoning in medicine, the fact that our understanding of medically relevant mechanisms is incomplete and can be mistaken. This objection is typically supported by offering examples (the CAST trial is a favorite) where mechanistic reasoning has seemingly steered us wrong. While certainly there is much yet to learn about human biology and physiology, a full and complete knowledge of any particular mechanism is not necessary for sound mechanistic reasoning. As the example of ivacaftor demonstrates, understanding a crucial part of an otherwise complex and poorly understood mechanism can lead to a successful intervention. Furthermore, the fallibility of mechanistic reasoning as a guide to clinical practice would appear to be matched by the incompleteness and fallibility of clinical epidemiology (Ioannidis 2005, 2011). Just as examples of conflicting meta-analyses or randomized-controlled trials that cannot be reproduced do not lead to the dismissal of population-level knowledge as clinically irrelevant, nor do examples of mechanistic reasoning gone awry. The inability of either kind of knowledge to provide a thoroughly reliable base for clinical decision making is why clinicians continue to seek and appeal to both.

Howick et al.'s second objection claims that knowledge of mechanisms from tightly designed laboratory studies cannot be justifiably extrapolated outside of the lab. But this represents a misunderstanding of how clinicians come to their mechanistic understanding. Rarely can or does a clinician cite a specific basic research study to support a mechanistic clinical claim. Rather, mechanistic understanding is generated from a combination of sources that may include a wide variety of basic, animal and human investigations (Baetu 2016). For example, the belief that high tidal volume ventilation is injurious to lungs, particularly those already inflamed, comes not from any single study but from the aggregation of cellular, isolated lung, whole animal, and human observations and experiments aimed at elucidating the mechanism of such injury. (See, for example, Dreyfuss and Sauman 1998.) While Howick and colleagues are certainly right to point out that a carefully controlled laboratory study is unlikely to lead to an understanding of how a particular mechanism will behave in the wild, mechanistic understanding that rests upon multiple lines of independent investigation tends to prove more reliable and useful (Baetu 2016). Idealized cases, useful for clinicians, may derive from mechanistic understanding of disease, often in the form of medical models, generally based upon research in the basic sciences (Ankeny 2007).

The observation that mechanisms can appear to behave in paradoxical ways represents Howick et al.'s third problem with using them as a tool of extrapolation. Paradoxical effects are those that run directly counter to that predicted by mechanism of action, for instance an anti-epileptic medication that increases seizure frequency in an individual. But mechanisms themselves do not really behave paradoxically, rather individuals may have a paradoxical reaction to an intervention. Such reactions, however, actually demonstrate incomplete understanding of mechanisms and, hence, this third objection is really a variant of the first. Indeed, the effects of an intervention only seem paradoxical where there is no mechanistic explanation, or an inadequate mechanistic explanation, of those effects. Mechanistic reasoning is thus essential to dissolving these apparent paradoxes.

Howick et al. identify a fourth problem for mechanism-based extrapolation, which was called the *extrapolator's circle* by Steel (2008). A first attempt at understanding the logic of extrapolation might construe it thus:

> A causal relationship holds in the source case/population

The source and target cases/populations are similar in causally relevant respects
So, the causal relationship holds in the target case/population

As it stands, this inference is circular because one cannot establish the second premise without already establishing the conclusion. This motivates Steel to develop an account of mechanism-based extrapolation (see above). On Steel's account, the source and target are shown to be similar by comparative process tracing, i.e., by showing that the key points of the mechanism of action in the source are also present in the target. However, Howick et al. argue that Steel's account does not avoid the extrapolator's circle: they suggest that establishing that key points of the mechanism of action are instantiated in the target is enough to establish causation in the target, making the source redundant. In response to this concern, it suffices to note that establishing causality requires more than establishing the existence of a possible mechanism of action that connects the putative cause to the putative effect—one also needs to establish that there is a net association across this mechanism, i.e. that the cause makes an overall difference to the effect. Therefore, establishing the existence of a mechanism in the target does not establish the causal relationship in the target and there is no extrapolator's circle here. Williamson (2019) explores this point in more detail.

Therapeutic assessment

Even when providing support for a claim of efficacy, population-level studies provide very circumscribed information that may be only marginally useful in clinical practice. Not all subjects in a study population benefit from the intervention being tested, even one demonstrated to be effective across the sample. In addition, clinical research tends to be protocolized, time limited, and to measure only a few predetermined end-points. Few clinical research studies allow for changes in treatments (other than withdrawal of the intervention) based upon the responses of individual subjects. In clinical practice, however, end-points and treatment durations are not usually fixed. Mechanistic reasoning aids in assessing the effect, or more importantly the lack thereof, of therapeutic interventions once chosen.

Most therapeutic decisions are followed by some re-evaluation of that clinical decision for a particular individual. This re-evaluation may occur within minutes or hours for acutely and critically ill patients, over days for milder acute or severe chronic diseases or at a subsequent clinic visit for less severe chronic diseases. The assessment of therapeutic effect in an individual relies heavily on pathophysiologic reasoning regardless of the strength of the population-level research that supported the initial therapeutic choice. In acute, critical illness, the clinician will monitor the patient's physiologic responses in order to judge whether the intervention seems likely to improve the patient's odds of recovery. While improvement of physiologic end-points itself is not the goal of therapy, lack of improvement of parameters thought or known to be important in terms of recovery precipitate a re-evaluation of the treatment choice. For example, there is strong population-level research (as well as pathophysiologic rationale based upon human and animal studies, noted above) that using a low tidal volume (as compared to a significantly higher tidal volume) for mechanical ventilation in patients with acute respiratory distress syndrome results in lower ICU mortality. Not all patients, however, tolerate low tidal volumes. If after being placed on low tidal volume ventilation a particular patient develops life-threatening cardiac arrhythmias that are eliminated by using a slightly higher tidal volume, a prudent clinician using pathophysiologic reasoning will increase the delivered tidal volume. Such a change is justified primarily on the basis of a mechanistic argument: a minimal increase in tidal volume will only negligibly increase risk of mortality while refractory cardiac instability will dramatically increase that risk.

Outside of the intensive care unit, monitoring physiologic response will be less continuous, but remain vital to providing optimal care. If a patient with an acute pneumonia is being treated according to evidence-based guidelines yet is persistently febrile and has worsening respiratory parameters several days into treatment, her clinician will need to consider alternative diagnoses and treatments based upon the physiologic trajectory. In the outpatient setting, assessing treatment effects in chronic diseases, such as diabetes and hypertension, that increase risk of major complications, cannot wait until those complications occur. Rather, clinicians will use intermediary measurements and pathophysiologic reasoning to judge whether a treatment should be continued, augmented or abandoned. Since high blood pressure itself generally causes no distress to patients, treatment is rightly directed at decreasing late complications of high blood pressure for which individuals are at risk. Population-level studies can provide initial guidance with regard to treatments that can, on average, mitigate those risks. But if blood pressure continues to increase at subsequent clinic visits, pathophysiologic reasoning suggests another intervention is in order, as high blood pressure is not simply a marker of risk but in the causal pathway.

Evaluation of therapeutic effect in an individual seeks to answer the question, "Is the intervention working?" While a positive answer to this question would require some determination of single-case causality, it is a negative answer that is clinically actionable. That is, when a patient is responding as expected to a therapeutic intervention, this suggests that the initial diagnosis and understanding of disease mechanism is correct, though does not guarantee this. Regardless, if

the patient is progressing as anticipated, neither patient nor physician will generally be compelled to alter care. As the examples above demonstrate, interim assessments that reveal therapeutic ineffectiveness generally necessitate change in diagnosis (the presumed mechanistic cause was wrong) and/or in the treatment plan (unanticipated mechanisms are at play). Proper mechanistic reasoning in the assessment of therapy requires the use of appropriate intermediary measurements. Analogous to surrogate outcomes in population-level studies good interim measures will be those clearly in the causal pathway of well understood mechanisms, close to the targeted endpoint, and consistent across patients (Aronson 2005). Utilizing multiple signs, symptoms and laboratory/radiographic testing as interim measures, as clinicians generally do, facilitates the detection of cases where a change in treatment strategy is warranted.

Certainly pathophysiologic reasoning in clinical practice remains fallible. Additional population-level research could augment clinicians pathophysiologic understanding for several of the examples provided above, particularly those related to intermediary measures in common, chronic illnesses, by demonstrating close association between interim measures and long-term outcomes. Yet individual patients will remain particulars, with variable responses to therapeutic interventions. Just as individualizing treatment choice usually requires mechanistic reasoning, so too does assessing the effects of treatment on particular patients.

Returning to the example of bronchiectasis, response to treatment is assessed and changes to the therapeutic regimen are guided by mechanistic understanding. For instance, there are multiple methods for persons with bronchiectasis to perform airway clearance, a therapy itself based on mechanistic reasoning. All airway clearance techniques aim to assist the patient in expectorating sputum, clearing the airway to improve airflow and decreasing the bacterial load. Clinical response to various airway clearance maneuvers is highly idiosyncratic. Providers and patients often trial several different strategies before finding one that works best for the particular patient. The best option is not determined through clinical research, but rather through assessment of patient symptomatology, volume of sputum production and measures of airflow. Mechanistic understanding, in this case the notion that an airway clearance technique will provide the most long-term benefit for a particular individual when it provides the most effective short-term results, leads clinicians and patients alike to individualize the treatment choice around airway clearance. No population-level trial would reasonably change this approach.

Clinical confidence

Pathophysiologic reasoning and the utilization of population-level research, despite the tone and format of much of the philosophical debate, are clearly not mutually exclusive nor does priority need to be assigned to one or the other. In clinical practice both approaches are considered and used concomitantly. When understanding of mechanism and the results of clinical research both support a clinical judgment, the clinician's confidence in that judgment is rightfully increased as compared to relying on only one or the other. Just as basing a clinical decision on mechanism alone can be fraught and fallible, so too is relying entirely on population-level research, given that conclusions drawn from such studies are tightly constrained, fallible and not directly applicable to particular patients. While there may be examples where mechanistic reasoning or population-level research alone can be sufficient, in general both lines of support are required to inspire a high level of confidence in the treating physician. As noted above, Russo and Williamson (2007) contend that normally both statistical difference-making evidence and evidence for the existence of a mechanism are necessary to establish a causal claim in medicine. A clinical corollary of this thesis is offered here: both the results of clinical research and mechanistic understanding are normally required for a clinician to have a high level of confidence in a particular clinical decision. Mechanistic reasoning can provide additional support to weak population-level evidence and vice versa.

As discussed above, extremely weak mechanistic support inspired little confidence in human activated protein C (drotrecogin alfa) for many clinicians, rightly contributing to the slow uptake of the drug, ultimately abandoned, for use in sepsis despite the positive results of a rigorous clinical trial. Alternatively, while observational studies and several small trials suggested that aspirin was associated with a decreased incidence of colorectal cancer, elucidating the anti-neoplastic mechanisms of the drug provided clinicians with an important additional reason to use it for this indication (Neugut 2009). While many factors beyond study design impact the acceptance and incorporation into practice of clinical research results by clinicians (Tonelli 2012), mechanistic evidence and understanding appear to be particularly important.

In treating exacerbations of bronchiectasis in specific patients, a clinician will have more confidence when choosing an antibiotic that is active in the laboratory against bacteria obtained from that patient's sputum, confidence stemming from mechanistic understanding of how antibiotics work. Similarly, the strong mechanistic support for the use of ivacaftor in CF patients with a specific residual function mutation contributed to the rapid clinical uptake of the drug despite its exorbitant cost after a randomized controlled trial in only 213 subjects. The United States Food and Drug Administration (2017) expanded the indications for the drug to patients with other residual function mutations not studied in randomized controlled

fashion based upon mechanistic reasoning. In sum, mechanistic reasoning and population-level studies may provide independent and additive support for a clinical decision, with a clinician's confidence in that decision being related to the presence and strength of both.

Conclusions

Mechanistic understanding and pathophysiologic reasoning remain an integral part of clinical practice for evaluating reports of clinical research, arriving at diagnostic and treatment decisions and assessing treatment effects. Some account of biologic plausibility in the form of a putative mechanism of action accompanies virtually every clinical trial describing a new intervention. This mechanistic description provides support for making a causal inference regarding a positive statistical association. A lack of a convincing mechanism linking treatment to effect, on the other hand, leads to clinicians discounting such an association. In coming to diagnostic and therapeutic decisions regarding patients, clinicians will use mechanistic reasoning to extrapolate from population-level research. Pathophysiologic rationale is necessary for both analogical reasoning from 'average' or former patients and for extrapolating from reference classes determined by population-level research. Finally, mechanistic reasoning is crucial for assessing whether a medical intervention is working as anticipated in particular individuals. When it is not, changes in treatment strategy are usually necessary, changes that will also be guided by pathophysiologic reasoning. These uses of mechanistic reasoning in clinical practice are epistemically justifiable and remains a crucial skill of clinicians aiming to optimize the care of individual patients. While some forms of artificial intelligence being introduced in medicine forego reliance upon mechanisms (London 2019), there is also a sustained interest in developing expert systems that retain mechanistic features, making them explainable (Samek et al. 2017). Furthermore, the focus upon the individual in the precision medicine movement necessitates mechanistic reasoning (Tonelli and Shirts 2017). We anticipate both an ongoing dependence upon mechanistic understanding and reliance on pathophysiologic rationale in clinical practice, as well as an ongoing debate regarding their proper place.

Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

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