Certainty of the evidence

From: Key Concepts for assessing claims about treatment effects and making well-informed treatment choices (Version 2022)

3.2d Consider how certain you can be about each advantage and disadvantage.

Explanation

The certainty of the evidence (the extent to which the research provides a good indication of the likely effects of treatments) can affect peoples' treatment choices. For example, someone might decide not to use or to pay for a treatment if the certainty of the evidence is low or very low. How 'certain' the evidence is depends on the fairness of the comparisons, the risk of being misled by the play of chance, and how directly relevant the evidence is. Systematic reviews provide the best basis for these judgements and based on these judgements, should report an assessment of the certainty of the evidence. Unexplained inconsistencies in effect estimates from different studies can also affect the certainty of the evidence.

The use of hydroxychloroquine (HCQ) and chloroquine (CQ) to treat Covid-19 illustrates the importance of considering the certainty of the evidence when making decisions about treatments. On March 28, 2020, the US Food and Drug Administration (FDA) issued a letter granting an Emergency Use Authorization for use of HCQ and HQ for treating Covid-19 [*Thomson 2020*], and the use of HCQ and HQ surged [*Vaduganathan 2020*]. The letter did not describe the evidence underlying the decision. It stated that the authorisation was supported by recommendations "for treatment of hospitalized COVID-19 patients in several countries, and a number of national guidelines" based on "limited in-vitro and anecdotal clinical data in case series". By June, controlled trials had shown that the FDA guidelines had been misleading – no beneficial effects on morbidity or mortality had been detected. On June 15, the FDA revoked the Emergency Use Authorization. A systematic review published in April 2021 included 14 unpublished trials (1,308 patients) and 14 publications/preprints (9,011 patients) [*Axfors 2021 (SR)*]. It found that HCQ increased deaths in Covid-19 patients, and no benefit of chloroquine had been demonstrated.

Basis for this concept

The certainty of evidence is low for many decisions about treatments. Of 9,451 recommendations in UpToDate, a widely used digital medical textbook, about half were based on low-certainty evidence (see table below) [*Agoritsas 2017 (RS)*]. Most (92%) of the recommendations based on low-certainty evidence were weak recommendations. Weak or conditional recommendations apply to most, but not all patients [*Andrews 2013a*]. Decisions depend on the preferences of patients more than when there is a strong recommendation and require more effort by health professionals to ensure that decisions reflect patients' values (see Concept 3.2c).

Table 3 Distribution of the strength of the recommendations in UpToDate according to the certainty in evidence			
	Weak recommendations	**Strong recommendations**	**All recommendations**
	n (%)	**n (%)**	**n (%)**
Low certainty	4335 (66.7)	366 (12.4)	4701 (49.7)
Moderate certainty	2019 (31.1)	1740 (59.0)	3759 (39.8)
High certainty	147 (2.3)	844 (28.6)	991 (10.5)
Total	6501 (68.8% of all rec)	2950 (31.2% of all rec)	9451 (100)

Sometimes it is appropriate to make a strong recommendation despite low-certainty evidence [_Andrews 2013b_]. That is, there are some treatment decisions where nearly everyone would make the same choice, despite the uncertainty. That was the case for about 2% of the UpToDate recommendations. Reasons for this include low-certainty evidence that suggests:

- a possible benefit – and high-certainty evidence of harm or high cost
- two treatments may be equivalent – and there is high-certainty evidence of less harm for one of the treatments, or there is high-certainty evidence of equivalence and low-certainty evidence suggests harm for one of the treatments
- a possibility of catastrophic harm – and high-certainty evidence of modest benefits

The reason for about one-third of UpToDate's strong recommendations based on low-certainty evidence was a life-threatening or catastrophic situation when low-certainty evidence suggests benefit. However, as illustrated by the hydroxychloroquine example above, such decisions can sometimes be deadly.

When there is moderate- or high-certainty evidence, different people will nonetheless sometimes make different choices. In UpToDate, 54% of recommendations based on moderate-certainty evidence and 15% of recommendations based on high certainty were weak or conditional recommendations. Often this is because of differences in the relative importance of desirable and undesirable outcomes (see Concept 3.2c). In addition, even when there is high-certainty evidence, there is almost always some uncertainty about who will benefit, who will not, and who will be harmed (see Concept 1.1d). People vary in terms of how risk averse or risk taking they are in relation to the desirable and undesirable effects. Lower comfort with uncertainty has been found to be associated with overutilization of diagnostic tests, but there is sparse evidence of the effects of uncertainty or attitudes towards uncertainty on health professionals' decisions about treatments [_Saposnik 2016 (SR)_, _Tubbs 2006 (SR)_].

Similarly, a variety of research has addressed how people respond to and deal with uncertainty generally, but relatively little has focused specifically on uncertainty about the effects of treatments. How patients respond to health professional expressions of uncertainty varies [_McGovern 2017 (SR)_]. This may depend on how the uncertainty is communicated, but few studies have investigated this. Although there are recommendations on how to orally communicate uncertainty, most of these lack an evidence base [_Medendorp 2021 (SR)_].

Uncertainty of the effects of treatments is often inadequately reported in news reports, including uncertainty due to the play of chance (imprecision), the risk of bias, unexplained inconsistencies in effect estimates from different studies, and extrapolation (indirectness of the evidence) [_Oxman 2022 (SR)_]. A systematic review of the effects of uncertainty in public science communication found that most findings of negative effects (such as reduced credibility and beliefs) were from experiments that operationalised uncertainty as disagreement or conflict in science ("consensus uncertainty") [_Gustafson 2020 (SR)_]. Consensus uncertainty was not found to have positive effects. In contrast, uncertainty in the form of quantified error ranges and probabilities ("technical uncertainty") had positive effects, if any, and not negative effects.

Few studies have investigated the impacts of communicating the certainty or quality of the evidence. Two online experiments compared presenting the effect of face shields on reducing the risk of Covid-19 with and without a message that the certainty or quality of the evidence was low [_Schneider 2021 (RS)_]. Participants who were told that the certainty of the evidence was low rated the evidence less trustworthy and rated facemasks as subjectively less effective. When there is a public health emergency, it may be appropriate to persuade people to change their behaviour – for

example, to wear facemasks – despite important uncertainties about the potential benefits and harms. However, when there are important uncertainties, they should be acknowledged. Not disclosing uncertainties distorts what is known, inhibits research to reduce important uncertainties, and can undermine public trust in health authorities *[Oxman 2022]*.

Several cognitive biases can affect decisions by both health professionals and patients when there is uncertainty *[Blumenthal-Barby 2015 (SR), Kahneman 2017 , Saposnik 2016 (SR), Tversky 1974 (OR)]*. However, most studies of cognitive biases in healthcare decision making are based on hypothetical scenarios *[Blumenthal-Barby 2015 (SR)]*. The extent to which these biases affect actual decisions is uncertain. Evaluations of interventions to counter cognitive biases suggest that these interventions may be helpful *[Ludolph 2018 (SR)]*. Interventions that have been evaluated include cognitive strategies, primarily aimed at improving people's critical thinking skills, and communication strategies, such as providing graphical information in addition to statistical information. The cognitive biases that have most often been targeted in evaluations of these strategies in the context of health-related judgements are "optimism bias" (being overly optimistic) *[Chalmers 2006]*, "framing effects" (choosing among options based on whether they are presented with positive or negative connotations, e.g., as a loss or as a gain) *[Akl 2011a (SR)]*, and base-rate neglect (paying too much attention to numerators and insufficient attention to denominators) *[Ludolph 2018 (SR)]*. "Relative risk bias" (a stronger inclination to choose a treatment when presented a relative effect than when presented an absolute effect), which is similar to base-rate neglect, has also often been targeted *[Akl 2011b (SR)]*.

More broadly, tolerance of uncertainty has been found to be associated with emotional well-being *[Strout 2018 (SR)]*. However, the certainty of this evidence is low. Intolerance of uncertainty, on the other hand, may cause anxiety *[Rosser 2019 (SR)]*. Studies have found a strong association between intolerance of uncertainty and both anxiety and worry in young people *[Osmanağaoğlu 2018 (SR)]*.

Studies have investigated choices made after laboratory-induced stress versus a nonstress condition. A systematic review of those studies found that overall, stress conditions led to decisions that were more disadvantageous, more reward seeking, and more risk taking than nonstress conditions *[Starcke 2016 (SR)]*. A variety of strategies have been evaluated to help patients and their families manage uncertainty *[Zhang 2020 (SR)]*. On average, these strategies had small to moderate beneficial effects for both patients and their family members. However, the certainty of this evidence is low. Uncertainty is a ubiquitous concern in health professional education, with students experiencing different forms of uncertainty at many stages of their training. However, strategies that directly support learning around uncertainty are taught infrequently *[Moffett 2021 (SR)]*.

Implications
Consider the certainty of the evidence when choosing treatments.

References

Systematic reviews

Akl EA, Oxman AD, Herrin J, Vist GE, Terrenato I, Sperati F, et al. Framing of health information messages. Cochrane Database Syst Rev. 2011a(12):CD006777. https://doi.org/10.1002/14651858.cd006777.pub2

Akl EA, Oxman AD, Herrin J, Vist GE, Terrenato I, Sperati F, et al. Using alternative statistical formats for presenting risks and risk reductions. Cochrane Database Syst Rev. 2011b(3):CD006776. https://doi.org/10.1002/14651858.cd006776.pub2

Axfors C, Schmitt AM, Janiaud P, Van't Hooft J, Abd-Elsalam S, Abdo EF, et al. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. Nat Commun. 2021;12(1):2349. https://doi.org/10.1038/s41467-021-22446-z

Blumenthal-Barby JS, Krieger H. Cognitive biases and heuristics in medical decision making: a critical review using a systematic search strategy. Med Decis Making. 2015;35(4):539-57. https://doi.org/10.1177/0272989x14547740

Gustafson A, Rice RE. A review of the effects of uncertainty in public science communication. Public Underst Sci. 2020;29(6):614-33. https://doi.org/10.1177/0963662520942122

Ludolph R, Schulz PJ. Debiasing Health-Related Judgments and Decision Making: A Systematic Review. Med Decis Making. 2018;38(1):3-13. https://doi.org/10.1177/0272989x17716672

McGovern R, Harmon D. Patient response to physician expressions of uncertainty: a systematic review. Ir J Med Sci. 2017;186(4):1061-5. https://doi.org/10.1007/s11845-017-1592-1

Medendorp NM, Stiggelbout AM, Aalfs CM, Han PKJ, Smets EMA, Hillen MA. A scoping review of practice recommendations for clinicians' communication of uncertainty. Health Expect. 2021;24(4):1025-43. https://doi.org/10.1111/hex.13255

Moffett J, Hammond J, Murphy P, Pawlikowska T. The ubiquity of uncertainty: a scoping review on how undergraduate health professions' students engage with uncertainty. Adv Health Sci Educ Theory Pract. 2021;26(3):913-58. https://doi.org/10.1007/s10459-021-10028-z

Osmanağaoğlu N, Creswell C, Dodd HF. Intolerance of Uncertainty, anxiety, and worry in children and adolescents: A meta-analysis. J Affect Disord. 2018;225:80-90. https://doi.org/10.1016/j.jad.2017.07.035

Oxman M, Larun L, Gaxiola GP, Alsaid D, Qasim A, Rose CJ, et al. Quality of information in news media reports about the effects of health interventions: systematic review and meta-analyses. F1000Res. 2022;10:433. https://doi.org/10.12688/f1000research.52894.2

Rosser BA. Intolerance of uncertainty as a transdiagnostic mechanism of psychological difficulties: A systematic review of evidence pertaining to causality and temporal precedence. Cognit Ther Res. 2019;43(2):438-63. https://doi.org/10.1007/s10608-018-9964-z

Saposnik G, Redelmeier D, Ruff CC, Tobler PN. Cognitive biases associated with medical decisions: a systematic review. BMC Med Inform Decis Mak. 2016;16(1):138. https://doi.org/10.1186/s12911-016-0377-1

Starcke K, Brand M. Effects of stress on decisions under uncertainty: A meta-analysis. Psychol Bull. 2016;142(9):909-33. https://doi.org/10.1037/bul0000060

Strout TD, Hillen M, Gutheil C, Anderson E, Hutchinson R, Ward H, et al. Tolerance of uncertainty: A systematic review of health and healthcare-related outcomes. Patient Educ Couns. 2018;101(9):1518-37. https://doi.org/10.1016/j.pec.2018.03.030

Tubbs EP, Elrod JA, Flum DR. Risk taking and tolerance of uncertainty: implications for surgeons. J Surg Res. 2006;131(1):1-6. https://doi.org/10.1016/j.jss.2005.06.010

Zhang Y, Kwekkeboom K, Kim KS, Loring S, Wieben AM. Systematic Review and Meta-analysis of Psychosocial Uncertainty Management Interventions. Nurs Res. 2020;69(1):3-12. https://doi.org/10.1097/nnr.0000000000000368

Other reviews

Tversky A, Kahneman D. Judgment under uncertainty: heuristics and biases. science. Science. 1974;185(4157):1124-31. http://www.jstor.org.ezproxy.uio.no/stable/1738360

Research studies

Agoritsas T, Merglen A, Heen AF, Kristiansen A, Neumann I, Brito JP, et al. UpToDate adherence to GRADE criteria for strong recommendations: an analytical survey. BMJ Open. 2017;7(11):e018593. https://doi.org/10.1136/bmjopen-2017-018593

Schneider CR, Freeman ALJ, Spiegelhalter D, van der Linden S. The effects of quality of evidence communication on perception of public health information about Covid-19: two randomised controlled trials. PLoS One. 2021;16(11):e0259048. https://doi.org/10.1371/journal.pone.0259048

Vaduganathan M, van Meijgaard J, Mehra MR, Joseph J, O'Donnell CJ, Warraich HJ. Prescription fill patterns for commonly used drugs during the Covid-19 pandemic in the United States. JAMA. 2020;323(24):2524-6.

Other references

Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013a;66(7):719-25. https://doi.org/10.1016/j.jclinepi.2012.03.013

Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013b;66(7):726-35. https://doi.org/10.1016/j.jclinepi.2013.02.003

Chalmers I, Matthews R. What are the implications of optimism bias in clinical research? Lancet. 2006;367(9509):449-50. https://doi.org/10.1016/s0140-6736(06)68153-1

Kahneman D. Thinking, Fast and Slow. New York: Farrar, Straus and Giroux; 2017.

Oxman AD, Fretheim A, Lewin S, Flottorp S, Glenton C, Helleve A, et al. Health communication in and out of public health emergencies: to persuade or to inform? Health Res Policy Syst. 2022;20:28. https://doi.org/10.1186/s12961-022-00828-z

Thomson K, Nachlis H. Emergency Use Authorizations during the Covid-19 pandemic: lessons from hydroxychloroquine for vaccine authorization and approval. JAMA. 2020;324(13):1282-3. https://doi.org/10.1001/jama.2020.16253