Do Pills Have No Ills?

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Do pills have no ills? Capturing the impact of direct treatment disutility

1. Introduction

Model-based economic evaluations of interventions should capture the impact on all the costs and outcomes relevant to the chosen study perspective and time horizon. In a number of jurisdictions, the quality adjusted life year (QALY) is the recommended measure of benefit given its potential to capture both quantity and health-related quantity of life in a single metric [1]. When calculating QALYs, the impact on health-related quality of life is valued using utility values, which are sourced from preference-based exercises, and then attached to specified condition-related health states or, where relevant, adverse drug reactions. In general, taking the medicine itself is assumed to cause no inconvenience to the patient, or in other words, have no direct treatment disutility. This editorial will define what is meant by direct treatment disutility and highlight why it is an important attribute which should be considered for integration within model-based economic evaluations, particularly for medicines used for primary prevention that require patients to take a daily pill for very long periods for relatively small lifetime benefits.

2. Direct treatment disutility

The traditional approach in economic theory is to assign no overall value to the direct impact of the healthcare intervention. Instead the value is derived from the subsequent health-related outcomes reflecting the use of those interventions. This impact on health-related outcomes can be positive or negative (reflecting the impact of adverse treatment effects).This focus on health-related outcomes has been criticised as being narrowly consequentialist [2]. By focusing attention entirely on the subsequent health-related outcomes, some key attributes which patients may value are missed. The useful concept of *process* utility has been put forward [3] as the means to think about attributes of an intervention, like the way in which healthcare information is delivered or maintaining dignity, which may not affect the final health outcome but which are still valued by patients.

There is also the potential for interventions to have *negative* attributes associated with their use. Obvious examples of such interventions are those which are invasive such as surgical procedures, screening programmes and biopsies. In addition, interventions which place a considerable burden on patients such as the need to undergo frequent injections or routinely attend a clinic, to have chemotherapy or a biologic administered, may have negative process utility. Brennan and Dixon provide a useful systematic review of such process utilities [4].

In this editorial we highlight the potential relevance of direct treatment disutility (hereafter termed DTD). Our focus is on long-term medication use, such as statins for the primary prevention of cardiovascular disease, which requires daily treatment over many years for benefits to be realised and translated into health gain. Taking statins would generally be considered to be non-invasive in the traditional sense and is believed to have low day-to-day treatment burden on patients. However, with a relatively small absolute benefit from treatment which accrues over very long periods, patient preferences regarding use of the medicine over a life-time could be important in determining patients' take-up of the intervention [5,6] as well as its cost-effectiveness.

For a particular medicine we define direct treatment disutility as representing an individuals' strength of preference for not taking the medicine, which may arise for a number of reasons. Patients are likely to value negatively the inconvenience of obtaining prescriptions and collecting the medicine from pharmacies, taking it every day and then having to undergo ongoing maintenance in terms of visiting general practitioners and other health care professionals for monitoring. For some patients the requirement to take an intervention for life is an unpalatable prospect in its own right. Preventative medicines do also have the potential for adverse drug reactions or out-of-pocket costs but these attributes are outside of our definition of DTDs as there are other mechanisms by which these attributes can be included within decision-models. DTDs are possible for a range of interventions and do not specifically have to be associated with a medicine. There is no reason why the concept of DTD could not be extended to other interventions. However, here we focus on DTDs associated with long-term medication use because there is evidence that even small DTDs when they occur over a long period are likely be important for cost-effectiveness.

Our rationale for suggesting the term DTD as a subset of process utility is to make clear the obvious negative value associated directly with the use of a medicine in general, and a long-

term preventative medicine in particular. Previous efforts to identify process utility studies in the literature have been hindered by a lack of consistent terminology and indexing [4], and the use of the term DTD would facilitate easier sourcing of values from the literature for inclusion in future decision models.

3. Current evidence from the literature

A rapid review of the literature was conducted on 1st July 2015, using a parsimonious search strategy (available on request) in four databases (Medline, Embase, PsyINFO and Econlit) in OVID. We sought to find studies which elicited DTDs from patients or the general public, and evidence on the use of treatment disutilities included within model-based CEAs for statins for prevention of cardiovascular disease or with a focus on cardiovascular disease. We chose this exemplar case because with falling costs of statins as they come off patent, new clinical guidelines including the one published by the National Institute for Health and Care Excellence (NICE) in 2014 are recommending their use in people at much lower levels of baseline risk of cardiovascular disease [7], in whom absolute benefit over a lifetime of treatment is relatively small. In this context, DTD may therefore have significant impact on the overall relative cost-effectiveness of the healthcare intervention.

3.1 Elicitation of DTDs

Three published empirical studies that relate to the concept of DTD were identified through the search strategy [6,8,9]; and one was found via reference list searching [10]. Gage et al find a disutility directly associated with taking warfarin of 0.003 and no disutility associated with taking aspirin when using a time-trade off method in patients (n=70) with atrial fibrillation [10]. More recently, using time trade off (TTO) methods to elicit values, Hutchins et al found DTDs of 0.01 (95% CI: 0.008 to 0.013) in US residents (n=1000) and 0.003 (95% CI: 0.002 to 0.004) in US healthcare employees (n=708) for a scenario involving one pill per day for life which had no costs or side effects [8,9]. In both papers, standard gamble and willingness to pay methods were also used to elicit disutilities and gave comparable results.

Fontana et al (2014) use DTD values to inform a patient-accessible tool to encourage shared decision-making. They use a TTO method and find that two-thirds of the general public interviewed in London (n=360) would require a gain of more than one-month at the end of life in order for them to be willing to take a pill per day for life. For a perfect pill with no

ongoing maintenance or side effects, that would represent a DTD of at least 0.00274 per year if patients were assumed to live for another 30 years.

All four papers find significant heterogeneity in the preferences of the participants. For example, Fontana finds evidence of individuals with 'extreme' values of DTD who would require greater than 10-years life-gain to take a tablet every day (a DTD of approximately 0.033) whilst there is also evidence of a class of individuals who would only need less than 1-month of extra-life in order to undergo treatment (a DTD of near-zero). Hutchins et al (2014) also finds evidence of class of reluctant pill-takers with 30% of their sample being willing to trade time versus 70% of their sample being unwilling to trade any time at all (equivalent to a DTD of zero).

3.2 Inclusion of DTDs in model-based economic evaluations

Model-based evaluations provide a structured and explicit framework in which to synthesise data inputs, including potential DTDs, from a range of sources within the same analysis [11]. A total of seven studies were found which included DTDs in decision-analytic model-based economic evaluations of statins [12–18]. The DTDs used were typically assumed, rather than based on values sourced from the literature, with DTD typically applied in sensitivity analysis, with values ranging from 0.00384 (equivalent to 2 weeks of full health traded to avoid 10-years on statins) to 0.02 (10 weeks of full health to avoid 10-years on statins). The assumed values were often smaller in magnitude than those elicited in empirical studies, meaning the impact of DTDs on cost-effectiveness results could have been underestimated. Even at the levels assumed the inclusion of DTDs had a marked effect on whether the interventions proved to be cost-effective. Often treatment strategies which were highly cost-effective in the base-case analysis ceased to be cost-effective once DTDs had been integrated, although the reporting within the sensitivity analysis was often insufficiently detailed to draw firm conclusions. It was clear from the review that there was methodological uncertainty regarding the best approach for incorporating DTDs into the QALY and model-based economic evaluations. On-going work in the literature, such as the appropriate methods for the calculation of joint health state utility values where patients have multiple conditions [19,20], could be useful in providing a methodological framework for properly accounting for DTDs within the QALY calculation.

4. Conclusions

This editorial has suggested the potential need to incorporate DTD into model-based economic evaluations of long-term preventative interventions. A review of studies eliciting, and using, DTD found evidence of a measurable and important impact on populations taking a preventative medicine. Currently, where DTDs had been included in primary preventative model-based economic evaluations, their inclusion could change whether treatments were judged to be cost-effective even using values of DTD at the lower range of those found in the elicitation studies. The inclusion of DTDs is therefore likely to make it harder for long-term medication use to be cost-effective. However, the scope for the inclusion of DTDs should not be confined to economic evaluations for long-term preventative interventions and could also play an important role in other areas. Therefore considerations regarding the need for the inclusion of DTDs should ideally play a routine role in the conceptualisation stage for model-based economic evaluations.

There is a need for using appropriate elicitation methods, such as discrete choice experiments, in relevant populations to produce robust point estimates of DTDs together with a measure of uncertainty around the point estimate. Existing studies for the elicitation of DTDs find evidence of heterogeneity in preferences implying that the use of mean population values would underestimate and overestimate DTDs for many individuals. Consequently classes of individuals should therefore be identified where possible using appropriate regression-based methods and reflected in sub-group analysis in model-based evaluations. Fundamentally however, the concept requires decision-makers to recognise the potential relevance and impact of DTDs in general and for long-term preventative interventions in particular.

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References

[1] International Society for Pharmacoeconomics. Pharmacoeconomic Guidelines Around The World 2015.

[2] Brouwer WBF, van Exel NJA, van den Berg B, van den Bos GAM, Koopmanschap MA. Process utility from providing informal care: the benefit of caring. Health Policy 2005;74:85–99.

[3] Mooney G. Economics, medicine and health care. FT PrenticeHall; 3 edition; 2003.

[4] Brennan VK, Dixon S. Incorporating process utility into quality adjusted life years: a systematic review of empirical studies. Pharmacoeconomics 2013;31:677–91.

[5] Goldacre B, Heneghan C. How medicine is broken, and how we can fix it. Bmj 2015;350:h3397–h3397.

[6] Fontana M, Asaria P, Moraldo M, Finegold J, Hassanally K, Manisty CH, et al. Patient-accessible tool for shared decision making in cardiovascular primary prevention: balancing longevity benefits against medication disutility. Circulation 2014;129:2539–46.

[7] National Institute for Health and Care Excellence. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (CG1818). London: 2014.

[8] Hutchins R, Pignone MP, Sheridan SL, Viera a. J. Quantifying the utility of taking pills for preventing adverse health outcomes: a cross-sectional survey. BMJ Open 2015;5:e006505–e006505.

[9] Hutchins R, Viera a. J, Sheridan SL, Pignone MP. Quantifying the Utility of Taking Pills for Cardiovascular Prevention. Circ Cardiovasc Qual Outcomes 2015:1–10.

[10] Gage BF. The Effect of Stroke and Stroke Prophylaxis With Aspirin or Warfarin on Quality of Life. Arch Intern Med 1996;156:1829.

[11] Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? Health Econ 2006;15:677–87.

[12] Greving JP, Visseren FLJ, de Wit G a, Algra a. Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis. BMJ 2011;342:d1672.

[13] Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation 2011;124:146–53.

[14] Pignone M, Earnshaw S. Aspirin, statins, or both drugs for the primary prevention of coronary heart disease events in men: a cost–utility analysis. Ann Intern … 2006.

[15] Pletcher MJ, Pignone M, Earnshaw S, McDade C, Phillips K a, Auer R, et al. Using the coronary artery calcium score to guide statin therapy: a cost-effectiveness analysis. Circ Cardiovasc Qual Outcomes 2014;7:276–84.

[16] Pletcher M, Lazar L. Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern … 2009.

[17] Roberts ET, Horne A, Martin SS, Blaha MJ, Blankstein R, Budoff MJ, et al. Cost-Effectiveness of Coronary Artery Calcium Testing for Coronary Heart and Cardiovascular Disease Risk Prediction to Guide Statin Allocation: The Multi-Ethnic Study of Atherosclerosis (MESA). PLoS One 2015;10:e0116377.

[18] Timbie JW, Hayward RA, Vijan S. Variation in the net benefit of aggressive cardiovascular risk factor control across the US diabetes population. Arch Intern Med 2010;170:1037–44.

[19] Ara R, Wailoo A. Using health state utility values in models exploring the cost-effectiveness of health technologies. Value Health 2012;15:971–4.

[20] Ara R, Wailoo AJ. Estimating health state utility values for joint health conditions: a conceptual review and critique of the current evidence. Med Decis Making 2013;33:139–53.