Using absolute risks to assess the risks and benefits of treatment

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Health providers and their patients are accustomed to taking risks and benefits into account when deciding whether or not to use a particular treatment. In some instances the choice is clear cut, as when the treatment has few side effects or the patient has a strong aversion to a particular health outcome. When an intervention has favourable effects on some health outcomes and unfavourable effects on others and patient preferences regarding particular outcomes are unclear, the decision becomes more difficult. Part of the difficulty is simply gathering relevant information for the decision. Most healthcare providers do not have the time to compile information on the effects of an intervention on each health outcome as well as on the absolute risk (or probability) of that outcome in the absence of intervention, which are necessary ingredients for a formal approach to decision making. Yu *et al*¹ have provided such information to help inform the decision of whether or not to use roflumilast to suppress exacerbations of COPD. They also address whether that decision should be 'yes' for some patients and 'no' for others.

Yu *et al*¹ used summary data from the US Food and Drug Administration to evaluate the risks and benefits of roflumilast to prevent exacerbations of COPD. They distinguished between moderate exacerbations and severe exacerbations, defined by hospitalisation or death. They concluded that roflumilast provided a net benefit only to patients at high risk of severe exacerbations. Here I review their methods and

assumptions and indicate some opportunities for using additional data for treatment decisions.

The essential ingredients for a treatment decision are: (1) A list of the adverse health outcomes affected by the treatment. We denote the number of such health outcomes by K . For example, Yu *et al* studied $K=11$ outcomes, including COPD exacerbation and various gastrointestinal, neurological and psychological outcomes (see their table 2). (2) Estimates of the absolute risks (probabilities) of each adverse outcome in the absence and presence of intervention. We use the symbol P_{0k} to denote the probability of outcome k in the absence of treatment and P_{1k} to denote the probability of the outcome in the presence of treatment. (3) The loss (or weight or severity), w_k , associated with each adverse outcome. The treatment has a beneficial effect on outcome k if $(P_{0k} - P_{1k}) > 0$ because treatment reduces the probability of the adverse event. If $(P_{0k} - P_{1k}) < 0$, the treatment is harmful for outcome k . A criterion for recommending treatment² is: treat if

$$\sum_{k=1}^K w_k P_{0k} - \sum_{k=1}^K w_k P_{1k} > 0. \quad (1)$$

The overall decision for treatment from equation (1) requires that the weighted sum of probabilities of adverse events without treatment is greater than the weighted sum of probabilities of adverse events with treatment. Another way to think about equation (1) is to consider the term $w_k(P_{0k} - P_{1k})$. This quantity is proportional to the weighted number of adverse events of type k that will be prevented by treatment (if

treatment is beneficial) or caused by treatment (if treatment is harmful). If one imagined a population of 10 000 people with COPD as in table 2 of Yu *et al*, then equation (1) could be multiplied by 10 000, and terms like $10000 \times w_k(P_{0k} - P_{1k})$ would represent the weighted number of events of type k that were prevented (or caused) by treatment. Thus, equation (1) implies that one should treat if the weighted sum of adverse events prevented by treatment exceeds the weighted sum of adverse events caused by treatment. Equation (1) is the criterion used by Yu *et al* to determine whether roflumilast has a net benefit. Note that absolute risks for each outcome, not relative risks, are needed for this decision. Moreover, absolute risks are needed for the outcome against which the treatment was primarily directed (eg, COPD exacerbation) and for the other outcomes affected by treatment.

Yu *et al* clearly describe their data sources and methods. The risks of adverse outcomes when roflumilast is not given, P_{0k} , were estimated, where possible, from observational cohorts, which were thought to be more representative of the general population than the control group in a randomised intervention trial. Such control groups may be healthier or sicker than the general population of patients with COPD, and they may receive non-representative care. Cohorts are needed to estimate absolute risks of an adverse outcome in the absence of treatment, P_{0k} . Even a large cohort may yield too few events for some outcomes to estimate P_{0k} precisely. Ideally, large registries of patients with COPD would be available for this purpose. As we move into the era of electronic health records and record linkage, it may be possible to obtain better estimates of P_{0k} from very large data sets that represent experience in the general population.

Estimates of the probability of an adverse outcome if treated, P_{1k} , should be based on randomised controlled trials whenever possible, to avoid confounding of treatment effects by patient selection.

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Although the treated group in a randomised trial yields estimates of P_{1k} directly, a more generalisable approach is to estimate a relative risk, rr_k , namely the ratio of the probability of the adverse event in the treated group to that in the control group in the trial. Then, assuming that this same relative risk applies to the general population, we set $P_{1k} = rr_k \times P_{0k}$, where recall P_{0k} is obtained from the more representative observational data. The idea is that the relative risks from the trial are 'transportable' to the general population, but that the absolute risk obtained directly from the intervention arm of the trial might not be, because trial participants might be healthier (or sicker) than in the general population. I have expressed the calculation of the absolute risk P_{1k} as a simple product above. The actual calculation in the presence of competing risks is more complicated, but still depends on the relative risks.¹⁻³

Table 2 of Yu *et al* gives the net number of outcomes caused or prevented by roflumilast in a hypothesised population of 10 000 patients with COPD in 1 year, based on P_{0k} and P_{1k} . For example for insomnia in table 2, $10000 \times (P_{0k} - P_{1k}) = 170 - 509 = -339$ implies that roflumilast causes 339 additional cases of insomnia. Likewise roflumilast causes 1180 additional cases of diarrhoea and 3369 such adverse events altogether, while only preventing 321 moderate or severe COPD exacerbations, assuming that the probability of such an exacerbation is 0.90 (or 90%) without roflumilast. A patient and physician could look at this table and apply their own weights for various adverse outcomes to decide whether roflumilast has a net benefit, according to equation (1). Let $k=1$ correspond to a COPD exacerbation. Using any of the four weighting systems proposed by Yu *et al*, one finds no net benefit for all exacerbations (moderate and severe combined), even when the baseline risk of exacerbation in the absence of intervention is $P_{01}=0.90$ (or 90%). However, if one restricts consideration to severe exacerbations and lets $k=1$ correspond to a severe exacerbation, then

if the probability of a severe exacerbation without roflumilast, P_{01} , is above 0.22 (or 22%) (table 3 and figure 1), roflumilast has a net benefit. This benefit is found in men and in women, regardless of age group. An important feature of the work of Yu *et al* is their examination of four possible systems of weighting, to help assure that their conclusions are robust.

Yu *et al* did not personalise the treatment decision beyond age and gender, perhaps because only summary outcome data were available. If individual level data were available, one could construct risk models for the probability of a severe exacerbation and for the probabilities without roflumilast of the ten other adverse outcomes in table 2 of Yu *et al*. A risk model that predicted the probability of severe exacerbations, P_{01} , based on the patient's previous history of exacerbations and other risk factors, could be used to identify patients with the highest risk of severe exacerbations in the absence of roflumilast, who stand to benefit most. The decision making could be further personalised and potentially improved⁴ by also developing models for the risks $P_{02}, P_{03}, \dots, P_{011}$ in the absence of roflumilast of the other outcomes that are affected by roflumilast.

Individual level data could also be used to estimate the joint probabilities of two or more adverse outcomes, which would be necessary to compute expected losses that do not conform to the linear structure in equation (1). For example, if the loss from having insomnia and anxiety is greater than the sum of the losses for insomnia and for anxiety separately, then one would need information on the joint probability of insomnia and anxiety.

The decision paradigm used by Yu *et al* is to give treatment only when it reduces expected losses (equation (1)). This is an accepted approach, but there are other justifiable ways to make treatment decisions. The aphorism (often attributed to Hippocrates) 'First, do no harm,' if strictly construed, would eliminate most interventions. But given data on the net numbers of adverse outcomes prevented

or caused by the intervention, as in table 2 of Yu *et al*, Hippocrates would probably make a helpful treatment recommendation. Compiling reliable data of this type, based on absolute risks for various outcomes in the absence and presence of intervention, requires care and effort, but it is itself an important aide to clinical management. Such tables have been used to guide treatment decisions after the diagnosis of an illness such as COPD, and to inform decision making for preventive interventions, such as the use of tamoxifen to prevent breast cancer.²

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