



Speech followed by discussion:

“Comparisons enable better treatment – evaluating therapeutic advances in patients’ best interests”

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How, and on whose behalf, should the “added therapeutic value” of a new drug be assessed?

Abstract

- Knowledge of the “therapeutic value” brought by a new drug is a core element supporting treatment decisions at both individual and group level.
- By comparing a new drug with the best available treatment option, it can be deemed a therapeutic advance if it is proved to affect patient-relevant endpoints and demonstrates a relevant level of effectiveness.
- Counter-intuitively, not every “new drug” represents a “therapeutic advance”. More exacting requirements and incentives are needed to stimulate the development of drugs that would represent greater therapeutic advances in patients' best interests.
- Continuous monitoring of the “therapeutic value” of drugs is needed in order to categorise both new and established medicines in the changing therapeutic landscape. This monitoring will be all the more powerful and informative when based on comparative studies and the evaluation of all the available data.

In medicine, ultimately, you always have to make a decision. Whether the patient has diabetes, depression or cancer, there are nearly always several treatment options for patients and health professionals to choose from nowadays – including the option of not using a drug treatment.

Such decisions are made on two levels. The first is a joint decision between the patient and the health professional who have to decide which of the available options is best for the individual. Three aspects come into play here: the current status of knowledge about the different treatment op-

tions, particularly in comparison with one another, the health professional's experience and the patient's preferences.

The second level relates to the healthcare system in general: to enable patients and medical professionals to choose a treatment, it must first of all have a marketing authorisation. Secondly, it has to be affordable – in other words, covered by the health insurance system.

In the past few years it has become increasingly clear that different criteria often apply to granting marketing authorisations on the one hand and the decision as to whether a drug should be reimbursed on the other. And this brings us to the task of Health Technology Assessment (HTA) institutions such as the *National Institute for Health and Clinical Excellence* (NICE) in the UK, the *Haute Autorité de Santé* (HAS) in France and the *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (IQWiG) in Germany. Their work often begins where that of the licensing bodies ends.

What is a therapeutic advance?

Health Technology Assessment organisations actually ask the same questions that health professionals ask themselves: for the patient, what are the tangible benefits and drawbacks of one particular treatment compared to another?

This “added therapeutic value” was proposed as far back as 2001 by the independent *International Society of Drug Bulletins* as the definition of a therapeutic advance. (1) Organisations like the IQWiG are firmly rooted in the methods of evidence-based medicine (EBM).

An initial core element here is the focus on patient-relevant endpoints.

The definition is basically very simple: “patient-relevant endpoints measure how patients feel, function or survive”. (2) But this definition is more complicated than it appears: changes in parameters such as blood pressure, blood glucose levels or cholesterol (also known as “intermediary criteria”) are not patient-relevant as such. They only become relevant when it is proven that “tangible” complications of a disease are reduced or the patient's quality of life is improved. “Tangible” also implies that the change in the patient's health effected by a treatment reaches a level where the patient actually feels it. Apart from the type of change, then, a drug's level of effectiveness is also important.

Another core element in understanding the nature of a therapeutic advance is that a patient is almost always interested in the difference between the “best” options. If the possibility of treatment is already available, a new treatment must measure up well to the existing “best” one.

A therapeutic advance is characterised by proven effects of a treatment on patient-relevant endpoints, a relevant level of effectiveness, and both in comparison with the best available treatment option.

Not every “new drug” is a “therapeutic advance”

Not all new drugs granted a marketing authorisation meet these criteria of a therapeutic advance. This can partly be explained by the history of the legislation related to the granting of marketing authorisations. Marketing authorisation criteria have definitely been shaped in some measure all over the world by the *thalidomide* (Contergan^o) disaster. When we remember that in the 1960s thousands of children were seriously damaged by the

adverse effects of *thalidomide* (malformation in the womb causing atrophied limbs), it is understandable that the primary aim is, above all, to ensure drug safety, and that the comparison of beneficial effects is only a secondary goal. The example of *benfluorex* (Mediator[®]) demonstrated just how difficult even simply guaranteeing drug safety still is difficult.

Even today, marketing authorisation focuses mainly on preventing harm and is intended primarily to ensure that a drug will not cause too unacceptable damages. Moreover, the authorisation process asks whether a drug is at least as effective and well tolerated as existing drugs (non-inferiority). In addition to that, a drug should have more positive than negative effects overall, in other words demonstrate an acceptable risk-benefit balance for the indication in question. It should be mentioned here that surrogate parameters, in other words substitute parameters for relevant endpoints, are often used as a benchmark rather than patient-related endpoints, because information for these surrogate parameters can be gathered more easily and quickly.

Apart from the requirement of non-inferiority, the marketing authorisation process mostly focuses on the “new” drug. The primary goal of the marketing authorisation process is not to rank new drugs within the existing range of treatments. As a result, new drugs for authorisation are often not compared with existing ones. Out of 122 drugs containing new active ingredients which were authorised in Europe between 1999 and 2005, only 58 (48%) were compared with other drugs for the purposes of the process. (3) A marketing authorisation is therefore no guarantee that a new drug represents a therapeutic advance. It comes as no surprise, then, that evaluations of newly authorised drugs repeatedly come to the conclusion that many of them do not represent a therapeutic advance – or at least, that this question has not been answered because there is no comparative data available.

In total, only a few percent of the new drugs that receive a marketing authorisation every year are of real benefit to patients compared to those already on the market. For example, in 2009 *Prescrire* evaluated 104 drugs that had been newly launched on the

French market. None of them was classed as a real advance, 3 were assessed as “*offering an advantage*” and 14 as “*possibly useful*”. The majority of products (62/104) were rated as “*nothing new*.” (4) Likewise, an evaluation by German scientists of the substances newly authorised in 2009 classed 13 out of 36 as having an “innovative structure” (a new mechanism of action with clinical relevance) but came to the conclusion that two of these 13 substances offered no advantage compared to established preparations and that the therapeutic status of one of them was unclear. Fifteen substances were classed as improvements on the pharmacodynamic or pharmacokinetic properties of previously known substances, and eight as me-tooos with no advantage compared to already available medicines. (5)

How can we achieve greater therapeutic advances?

In this situation, it is essential to be more exacting of new drugs and put incentives in place for the development of drugs that lead to greater therapeutic advances in patients’ best interests.

The conditions for cost reimbursement of a new drug are becoming an increasing incentive. In many countries, the prices that pharmaceutical companies can obtain for a drug now depend on proof that it represents a therapeutic advance. France already has a system of this kind (rating the “improvement of therapeutic benefit”, in French “*Amélioration du Service Médical Rendu*”, ASMR) and Germany is to introduce one from January 2011 onwards. It seems still too soon to judge whether these incentives will be enough. More far-reaching proposals have already been made, demanding evidence of a therapeutic advance as a condition for granting a marketing authorisation. (6)

Continuous monitoring of the therapeutic status of drugs

However, in order to support health professionals’ and patients’ decisions and those at the healthcare system level as well, the therapeutic value brought by drugs should be continuously monitored, and to categorise both new and established medicines within the changing therapeutic land-

scape. This is the task performed, among others, by HTA organisations. However, what makes sense in theory meets with obstacles in practice.

Insufficient number of comparative studies. In some fields of medicine we cannot find enough studies that compare the available drugs head to head or with non-drug therapies and that measure patient-relevant endpoints. For example, the work of the IQWiG on glinides met with this obstacle. Between 1998 and 2001, two substances from this class of anti-diabetic drugs were authorised: *repaglinide* and *nateglinide*. The marketing authorisation studies examined a surrogate parameter, i.e. whether glinides reduced blood glucose levels, and what adverse effects such as hypoglycaemia they caused. When the IQWiG assessed glinides in 2009, 10 years after authorisation, no new studies were available which examined the benefit of glinides on the relevant clinical parameter that is reducing diabetes-related complications (heart attacks, strokes or kidney damage). In addition, relevant comparative studies were only available with two other classes of diabetes drugs. Because of the lack of studies, the “therapeutic value” of glinides compared to the many other treatment options for diabetic patients is still unclear. (7)

That said, at least for new drugs, we can expect the new price incentives to lead to more comparative studies in the future. Nevertheless, we will still be dealing with drugs that are already on the market for decades to come. For these drugs, we may need studies that are independent of pharmaceuticals companies.

All study results should be publicly available. The second hurdle to the meaningful evaluation of drugs is the availability of data. We have been familiar with the problem of publication bias for around 30 years now. Publication bias means that the publication of studies depends on their results. We know that positive studies are published more frequently and sooner than negative ones. As a result of publication bias, the public is presented with a distorted picture. The positive effects of a drug are harms overestimated and potential harms underestimated. (8,9)

The dramatic impact that publica-

tion bias can have is demonstrated by the assessment of the anti-depressant *reboxetine*. IQWiG research had shown that the majority of data on *reboxetine* had not been adequately published. Following intensive public debate on this case, the manufacturer made all the data available for the evaluation, despite its initial refusal. Analysis of the full data showed that *reboxetine* was no more effective in treating the symptoms of depression than placebo and that it had been proved to be less effective than other anti-depressants. (10, 11) The published studies, in contrast, had drawn a picture of a drug that was effective compared to other antidepressants.

It is therefore an important prerequisite for the assessment of drugs to be valid to have all the data available. Experience over the past few years has shown that this problem can only be resolved by legislation requiring the publication of all study results. Here, too, transparency is not only needed for new drugs, but for those that are already on the market. This transparency is indispensable in order to allow HTA organisations as well as players like *Prescrire* and other independent drug bulletins to have an adequate starting point for their work.

Outlook

Critical evaluation of drugs supplies up-to-date information for decision-making on the use of new drugs. At the same time critical evaluation of drugs provides incentives for the targeted development of drugs meeting

patients' real needs and can therefore make its own contribution to therapeutic advances. In this sense, *Prescrire's* work also helps to improve the quality of healthcare provided to patients in the future.

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Conflict of interests statement:

Beate Wieseler: « I hereby confirm that I have no interests or connections which could cast doubt on my independence. IQWiG as an organisation is independent of the pharmaceuticals and medical devices industry. IQWiG is financed by the Foundation for Quality and Efficiency in Health Care. The Foundations budget consists of contributions from the members of all German statutory health insurance funds (GKV).»

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The IQWiG is an independent scientific institute that investigates the benefits and drawbacks of medical interventions for patients. We regularly provide information about the potential advantages and disadvantages of different diagnostic and therapeutic interventions. For more information visit: www.iqwig.de