Integrating Patient Preferences into Benefit-Risk Analyses

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How Do We Get Patient Input? And Should We Do More?

We're talking here about 2 major B/R decisions.

1. Yes/No approval decision, i.e., is the risk of a drug acceptable in lights of its benefit?

NB. This does not arise if the risk are not serious. That is, we approve drugs with frequent, bothersome side effects, truthfully labeled. Patients and physicians can decide.

Even for more serious risks, our bias is in favor of giving a choice, UNLESS we think there is no rational reason to use the drug, usually because there is a fully adequate alternative without the liability.

2. Labeling or REMS directing treatment to patients in whom risk is worth it. Need to decide on how strong to be, whether to have procedures in place to direct treatment, etc.

We Often Do Not Seek Input

I think this is because we think the answer is apparent, i.e., that the risk involved is acceptable to an informed patient, OR is never acceptable, but perhaps that is not always so, and there could be close cases. Consider:

1. Clozapine

Clozapine causes agranulocytosis at 1.5%, potentially lethal.

BUT, it was shown (not just assumed) to work in people failing other anti-psychotic treatment and was labeled for such people.

I'd say we thought it was completely obvious that the risk of the drug in this devastating disease was acceptable AND we required close monitoring of white count – no blood, no drug with limited distribution.

More generally even considerable risks are often acceptable when a drug clearly treats the otherwise untreatable.

Suppose it might have been an alternative treatment for such people, but had not been shown to work in non-responders. Would we then have given people the choice (probably not).

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2. Bepridil

Bepridil, a CCB, prolongs the QT and clearly causes TdP, sometimes fatal. It was shown to be more effective than diltiazem in non-responders to diltiazem (trial randomized to diltiazem and bepridil), and therefore was an option for people with unresponsive angina who could not benefit from or not be given bypass or angioplasty.

Angina is somewhat under patient control (don't exercise), but can greatly limit activity and impair QOL.

Is bepridil's effect worth the risk?

We thought it was, but it seems a close case. Could patient input have helped?

We Often Do Not Seek Input

3. Dabigatran

In a study of 150 mg and 110 mg vs coumadin in atrial fibrillation, dabigatran was clearly superior to coumadin and to 110 mg on preventing stroke. It prevented embolic stroke better than either (preventing embolic stroke is the reason for using an anticoagulant) and caused far less hemorrhagic stroke than coumadin and about the same rate of hemorrhagic stroke as 110 mg.

But it caused more severe bleeding than 110 mg (not significantly more fatal bleeding, however).

There was no doubt 150 mg would be approved. What about 110 mg? The CRAC was divided, at least partly because of concern that bleeding anxiety (which the committee did not necessarily consider rational) would cause people not to use the drug, and it was thought possible that there might be very high risk people who should get a lower dose, even if they were not identified. We were also of 2 minds internally, and most other countries approved the 110 mg dose.

Dabigatran (cont)

If you think strokes are clearly worse than serious, but non-fatal bleeds, which I must admit I do, it seems clear that it would be irrational to use the lower dose in anyone (at least anyone identified). We also found that people who bled on either dose were not more likely to bleed again if they resumed 150 mg than if they resumed 110 mg (not randomized, though).

Yet people may have a real terror of bleeding, perhaps making them willing to have a stroke.

I believe that is not rational but should we have given patients and physicians a chance?

And if you wanted to ask people about this matter, how would you do it?

We Do Seek Input Sometimes (But how reliable is it?)

4. Tysabri

Tysabri is a dramatically effective drug for MS that causes a rare fatal complication, PML (progressive multifocal leukoencephalopathy) at about a rate of 1 per 1000. Alternatives are less effective (interferon, copaxone) or too new to know risks (fingolimod).

We invited patients to speak at an advisory committee meeting, and many did. They strongly expressed the view that an informed patient should be able to choose the drug, agreeing with what we believed, but this was hardly a scientific survey. And what kind of information could/should have affected our decision? Note that many people and organizations write to us about these matters.

How Good Must Evidence Be

The NSAID Bextra was removed from market after a finding that it could cause Stephens-Johnson Syndrome. There was no evidence of an advantage over alternatives but some individuals were quite sure there was.

In general we would argue that a lethal risk, not present for alternative drugs, would doom a drug with no documented advantage over alternatives.

But when there is no alternative we often leave such drugs alone, even if they provide only symptomatic benefits and let people choose.

- Terfenadine (TdP) stayed on the market till fexofenadine became available (note that loratadine was available but we still left terfenadine on the market, with Warnings, of course).
- Troglitazone (liver failure) stayed until rosiglitazone and pioglitazone were shown not to be hepatotoxic (took about 9 months)

More Input?

The cases that could call for more input are those where a drug has a major effect/benefit but major toxicity (e.g., Tysabri).

More commonly, serious toxicity emerges for a drug without a clear advantage, over alternatives, and those drugs usually go away. But how clear and documented does the advantage have to be?

A problem is that all too often potential advantages are not looked for very well, are not seen as important enough for the overall population to warrant the risk, and are not studied in the population where the risk might be acceptable (alosetron, Zelnorm). This seems to be an area where patient input could be important.