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Therapeutic value (TV) of treatments with pharmaceutical drugs. Rough estimates for all clinical conditions based on Cochrane reviews and the ratio: Number Needed to Harm/Number Needed to Treat (TV=NNHtotal/NNT).

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BMJ-deputy editor Trish Groves writes about the great problems related to medical evidence, putting the whole project of evidence-based medicine in danger (1). Bias in pharmaceutical studies have been known for a long time, as the randomised clinical trial (RCT) is very easy to manipulate, to make a drug treatment look better and safer (2).

Treatment efficacy can in general be expressed as NNT: Number [of patients] Needed to Treat [for one to reach the treatment goal], and treatment harm can be expressed as NNH: Number [of patients] Needed to treat to Harm [one patient with a specific side/adverse effect].

Mostly pharmaceutical drugs have one positive outcome and a number of adverse effects, so the total likelihood to get one adverse effect can be calculated from the list of adverse effects taking the specific likelihood for each adverse effect. We call this total likelihood for getting one adverse effect for NNHtotal (3). The ratio benefit to harm can thus be calculated as TV=NNHtotal/NNT.

Obviously NNHtotal/NNT is a fairly rough estimate of the therapeutic value (TV) of a treatment as beneficial effects and mortal and insignificant adverse effects are all attributed equal importance. But this is not as meaningless as it might look for a first glance, for in most industrial RCTs the treatment goal is not a cured patient, but only a clinically significant improvement (often the smallest improvement you can argue has clinical significance, or an indicator of such an improvement (4)), and adverse effects are only included and counted when they are found clinically significant to the patient. So for practical reasons -

the pharmaceutical industry trying to maximize NNT and minimize NNH - this measure of therapeutic effect ends up pretty meaningful after all.

Therapeutic value of pharmaceutical drugs

To estimate the size of the Therapeutic Value (TV) for a pharmaceutical drug you need to know the NNT and NNHtotal(3). These numbers are easily collected from Cochrane reviews when such exists listing all the positive and negative effects and the likelihood for a patient to get them. It is worth noticing that while the industrial trials often give a NNT of 5, 10 or 20 for a drug (5), the Cochrane reviews of a single drug often give NNTs of 20 or 50 (6), while the meta-analyses of whole groups of drugs often give NNT of 100 or more, as we recently have seen it for the outcome "improvement of mental state" (mental health) for the whole group of antipsychotic drugs (7) and the whole group of antidepressant drugs (8).

It's a paradox that the pharmaceutical companies again and again find their new drugs to be efficient and relatively safe, while independent meta-analyses later again and again document whole classes of drugs to be of modest value for the patients, and harmful. It is also sad that such thorough analyses often have little impact on our medical reality, as the drugs often just continues to be used, in spite of meta-analyses concluding that the drugs are of little therapeutic value if any, as we saw it with Abel's famous study of anticancer chemotherapy 20 years ago (9). Able concluded that anti-cancer chemotherapy when compared to no treatment, for most types of cancer shortened life and destroyed quality of life. In the history of medicine the commercial interests have often trumped science, and we need to learn from that so we can make medicine more rational in the future.

Typical values of NNT, NNHtotal and TV for some drug groups are listed in Table 1.

Table 1: Typical values of NNT, NNHtotal and (Therapeutic Value TV= NNHtotal//NNT) for pharmaceutical drug (single drugs and drug-groups) (Typical numbers from industrial trials, Typical numbers from independent analyses of single drugs and Typical numbers from independent analyses of whole groups of drugs).

Drug-type	Typical numbers from industrial trials (RCTs) (see text)			Typical numbers from Cochrane/ independent metaanalyses (of single drugs, see text)			Numbers from Cochrane/ independent metaanalyses (of whole groups of drugs, see text)		
	NNT;	NNH_{total};	TV	NNT;	NNH_{total};	TV	NNT;	NNH_{total};	TV
Antidepressant drugs (less depressed)	3-20;	2-4;	?0.67	>20;	1-2;	<0.10	>100;	1;	<0.01
Antipsychotic drugs (mental state improved)	3-20;	2-4;	?0.67	>20;	1-2;	<0.10	>100;	1;	<0.01
Anticancer chemotherapy (survival, treatment vs. no treatment)	20-50;	1-2;	?0.1	>20;	1-2;	<0.10	>100;	1;	<0.01
Antibiotics	1-20;	1-20;	1	20;	10;	0,5	20;	10;	0,5

Source: Independent meta-analyses of single drugs and drug groups (mostly Cochrane reviews) (see text)

The NNT and NNH numbers from the pharmaceutical industry's RCT tests are often of such a size that one safely can argue that the benefits might be worth the risk (TV?1); the numbers from independent metaanalysis of the same drugs often makes this unlikely to be the case, as a typical ratio of benefit/risk here is only about 2:20 (TV?0.1) (6).

If you go to the metaanalyses of the whole drug-group you sometimes see that practically all effect is lost while the drugs are likely to harm almost all patients (TV<0.01) (7,8,9).

DISCUSSION

Some drug-groups seem to "pass" the tough test of the high level metaanalysis, like the antibiotics, while other drug-groups "fail" the test, like the antidepressants (8), the anti-psychotics (outcome: mental state) (7) and anti-cancer chemotherapy (9) (see Table 1).

The rule is that the more data that is included in a study and the more rigid the protocol of the analysis is, the smaller is the treatment effect and the larger is the harm. The reason for this effect is easy to understand: just think of inducing bias with the selection of small (appropriate) samples and with test-methods you can influence to get the result you want (1,2).

If the patients were informed that the risk of being harmed is about 100% and the likelihood of gaining a benefit is below 1% they would probably not choose such a treatment.

CONCLUSIONS

In general pharmaceutical drugs have a therapeutic value TV=NNHtotal/NNT=0.67-0.01.The future of pharmaceutical medicine will be determined by which source of information we accept as valid. If we accept the data coming from Cochrane metaanalyses and similar independent research institutions, most drugs in use today will not be used in the future as their therapeutic value is too modest (TV= NNHtotal/NNT=0.1- 0.01).

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