Tough Calls: When a Drug Causes Rare and Serious Adverse Effects, But Offers Only Symptomatic Benefits

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Why Would Rare Serious Risk Be Acceptable at All

One could ask why a symptomatic benefit (i.e., not life-saving or disease modifying – a special kind of symptomatic benefit) is ever worth a fatal risk.

The answer is that all too often there's no real choice. All the drugs have some low level of serious risk.

- Diuretics cause arrhythmias, gout; ACEI's cause angioedema; CCB's cause heart failure; BB's cause (and treat) heart failure, bradycardia
- All non-selective NSAIDs cause fatal GI bleeds (we're thinking about what COX-2 selectives do)
- All other pain meds also have lethal consequences
- AEDs universally have a range of serious effects
- Antidepressants, AED's cause suicidality
- Antibiotics have severe allergic reactions and many other problems
- Hypnotics cause auto accidents

But a problem arises when a drug has a worse serious effect than alternatives or has such an effect when alternatives do not. Those are the cases where a drug is often withdrawn.

What Goes into B/R

In some sense all B/R decisions are similar, B has to outweigh R for some defined population

And similar variables apply

Benefit

- Magnitude compared to no Rx
- Magnitude compared to alternatives
- Whether it can add to existing Rx
- Subgroup of very high level responders
- Tolerability (lack of annoying side effects)
- Working in failures on other Rx
- Tolerated by people who can't tolerate other Rx
- Different mechanism
- Convenience (less often, oral route)

An advantage in any of these areas can at least sometimes let a drug survive despite a serious rare toxicity

What Goes into B/R

Risk

Rate

Severity (fatal, irreversible)

Preventable, in advance or by watching

- Control dose
- Early warning
- Only with another drug
- Lab or other test

Risk compared to alternatives

Special Symptom Cases

Some "symptomatic" cases are special, notably when the drug is disease modifying. For these, much more serious and frequent adverse effects can be accepted, e.g. in RA, Crohn's Disease, MS (consider Tysabri).

AEDs are "symptomatic," but seizures are life-threatening as well as life-damaging, and much more serious toxicity is accepted for AEDs than for most drugs.

Basic Case

If a drug cause rare serious adverse effects and there are alternatives that do not cause these ADE's and have no other serious adverse effects, the drug is in trouble. Why, after all, would anyone use the drug?

But it can depend on the alternatives. If the drug with the AE is in a different (new) pharmacologic class, the drug probably has a greater likelihood of survival, because of the perceived benefit of providing alternatives, although there are not many examples of this.

Troglitazone, after hepatotoxicity at pretty high rate was found (> 1/5,000, probably), was allowed to stay marketed for second line use, because it represented a novel treatment modality, until pioglitazone and rosiglitazone were shown not hepatotoxic (then troglitazone removed).

Basic Case

If drug is just another number of a class and it has a significant problem and no advantage. Why accept the risk? We often don't, but sometimes we do.

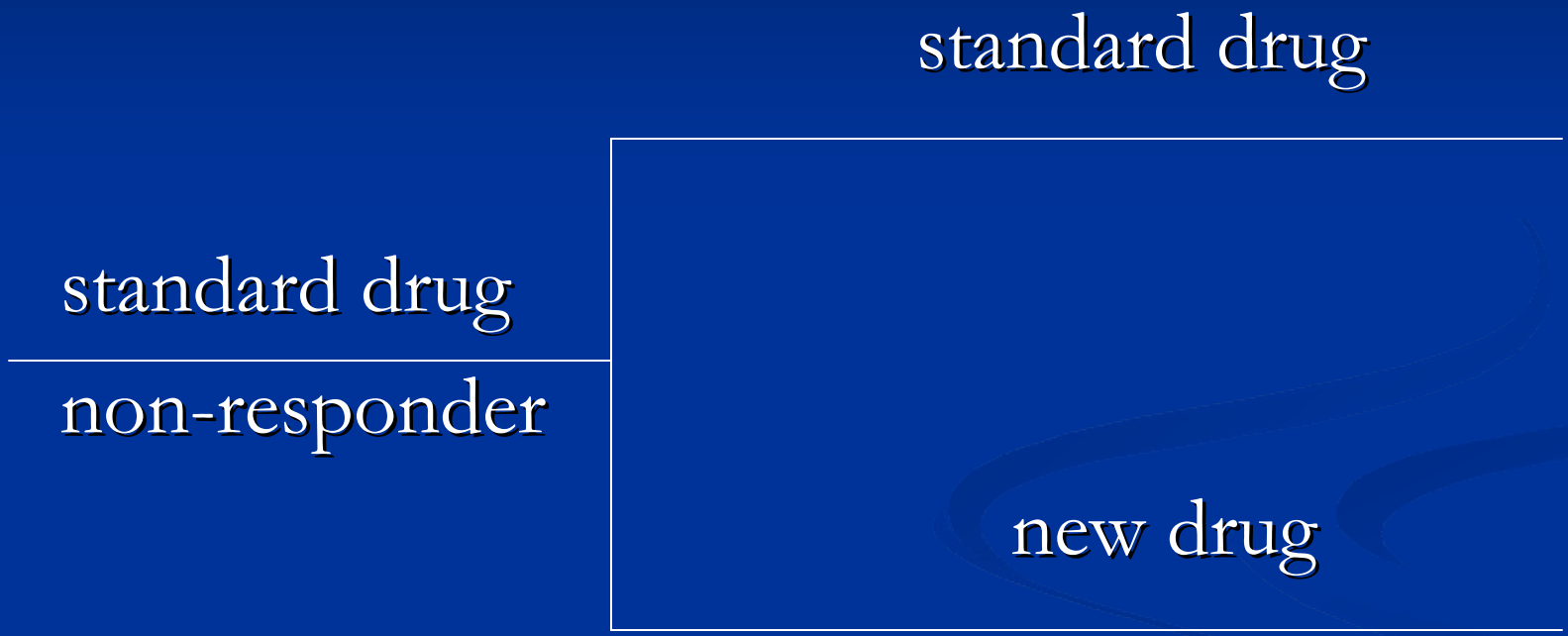
It can have to do with people's impressions of response variability. In past advisory committee discussions of NSAIDs, e.g., experts clearly believed that people differed in their responses to NSAIDs, so that a variety of drugs was necessary. They may be right but there is in fact no evidence that this is so. Nonetheless, NSAIDs vary in liver and perhaps renal effects, and in how likely they are to cause major GI bleeds. But drugs with varying degrees of these problems remain available (not if they're too much worse however).

Individual Variability

As noted, we presume/believe responses among individuals are variable and that many (or at least several) drugs in a class are needed to account for this.

This is actually a testable hypothesis, although it is rarely tested. The way to do it is to carry out a study in non-responders, randomizing patients to the failed drug and the new drug.

Studies in Non-Responders



Clozapine

Too toxic unless clear clinical advantage

Study in schizophrenics unresponsive to standard therapy

History of poor response to neuroleptics

Diagnosis of schizophrenia, hospitalized

6 week failure on haloperidol

4 week, double-blind comparison of clozapine
vs. chlorpromazine plus benztropine

Results

	Response (%)	
	Clozapine	**CP2**
CGI (decrease ≥ 1)	71	37*
BPRS items (dec ≥ 1)		
concept disorganization	60	39*
suspiciousness	64	42*
hallucinations	59	51
thought content	65	40*
CGI and BPRS	15	2*

*$p \leq 0.05$

Studies in NRs

It does not always work, though. In discussions of NSAIDs, as noted, all arthritis doctors said many drugs are needed because responses are individual. This was plausible, but at a COX2 meeting a few years ago I suggested a study in NRs.

Merck in fact did such a study, comparing rofecoxib 25 mg and celecoxib 200 mg in celecoxib non-responders.

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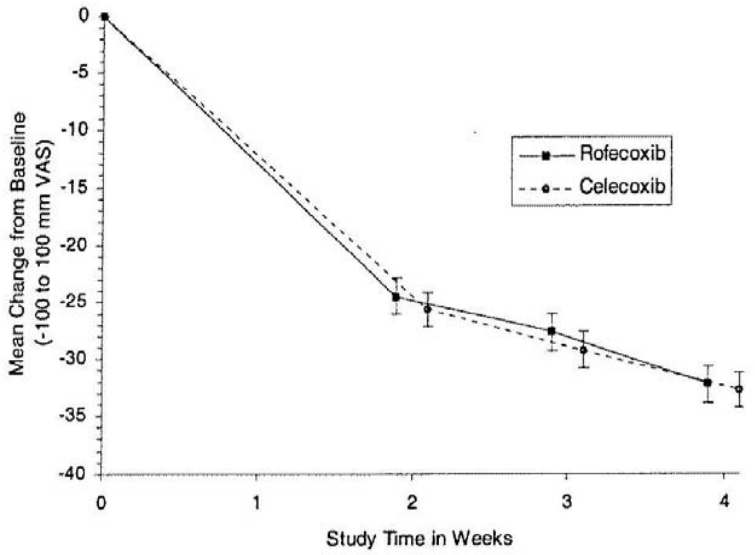
Figure 1

Pain at Night while in Bed (WOMAC)
Mean Change from Baseline ± SE by Timepoint
(Primary Per-Protocol Approach)



Note that without a celecoxib control, rofecoxib would have appeared VERY effective in this NR population.

Individual Variability

I'm aware of just 4 studies (there could be more, of course) in non-responders, the 2 cited and

- Bepridil was effective in angina in diltiazem non-responders. We approved it, even though it is a torsadegen
- Captopril was effective in hypertension in triple therapy (diuretic, reserpine, hydralazine) non-responders. We approved it despite agranulocytosis

When we withdraw Zomax in 1980 (allergic reactions), there was some sense of its superiority in acute pain, and a study in non-responders was considered, but one was never performed.

What Usually Happens

Withdrawals over the years show that, as a rule, a drug with a very serious, even if quite rare, ADR that other drugs of its class don't have, is withdrawn.

NSAIDs: bromfenac (DILI); benoxaprofen (DILI), valdecoxib (SJS), zomepirac (anaphylaxis); suprofen (ARF)

Antihistamines: terfenadine, astemizole (both T&P)

Statin: cerivastatin (rhabdo)

Diuretic: ticrynafen (DILI)

Antibiotics: grepafloxacid (TdP), trovan (DILI), temafloxacin (hemolysis, ARF)

Some single member of class drugs, if not perceived as sufficiently valuable, were also withdrawn (tegaserod, alosetron).

Short of Withdrawal

If a drug has known or possible advantage, there may be labeling or other attempts to avoid problem (avoid CYP450 3A4 inhibitors with terfenadine, cisapride, astemizole), but these often fail.

Bottom Line

When a symptomatic treatment causes even quite rare, very serious ADE's, it is not likely to survive if it is a member of a class where other drugs do not have the effect. There is some deference to a new pharmacologic effect, but even here, the effect has to be perceived as valuable.

Backup Slides

History of Drug Withdrawals

Drug	Date App'd	Date WD	Data: 1, 2, 3	Adverse Effect
iproniazied (Marsilid)	1950 (?)	1956	1	DILI
azarabine (Triazure)	1977	1977	1	Arterial thrombosis
phenformin		1978	2	Lactic acidosis
ticrynafen (selacryn)	1979	1980	1	DILI
Benoxaprofen (Oraflex)	1982	1982	1	DILI
zomepirac (Zomax)	1980	1983	1	Anaphylaxis
methaquolone (Qualude)	1960's	1984	1	OD very hard to treat
nomifensine (Merital)	1984	1986	1	hemolytic anemia
suprofen (Suprol)	1985	1987	1	ARF
** encainide (Enkaid)	1986	1991	3a	CAST; mortality (HR=2)
temafloxacin (Omniflox)	1992	1992	1	Hemolysis, renal failure
flosequinan (Manoplax)	1993	1992	3a	Mortality (HR – 1.5)

* 1= individual cases
  2 = epidemiologic data
  3 = RCT's: 3a large trials; 3b MetaA
** NOT withdrawn, but limited
*** Returned to market

History of Drug Withdrawals

Drug	Date App'd	Date WD	Data: 1, 2, 3	Adverse Effect
fenfluramine (Pondimin)	1973	1997	2	Valvulopathy
terfenadine (Seldane)	1985	1997	1	TdP
mibefradil (Posicor)	1998	1998	1	Interactions; TdP
bromfenac (Duract)	1997	1998	1	DILI
** trovafloxacin (Trovan)	1997	1998	1	DILI
astemizole (Hismanil)	1988	1999	1	TdP
grepafloxacin (Raxar)	1997	1999	1	TdP
troglitazone (Rezulin)	1997	2000	1	DILI
cisapride (Propulsid)	1993	2000	1	TdP
*** alosetron (Lotronex)	2000	2000	1	ischcolitis; constip'n
PPA	<1962	2000	2	hemorrhagic stroke
rapacuronium (Raplon)	1999	2001	1	bronchospasm
cerivastatin (Baycol)	1997	2001	1, 2	rhabdomyolysis

* 1= individual cases
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History of Drug Withdrawals

Drug	Date Approval	Date WD	Kind of Data: 1, 2, 3	Adverse Effect
levacetyl methadol (orlaan)	1993	2003	1	TdP
rofecoxib (VIOXX)	1999	2004	3a	AMI
*** natalizumab (Tysabri)	2000	2005	1	PML
pemoline (Cylert)	1975	2005	1	DILI
valdecoxib (Bextra)	2001	2005	1	Stevens-Johnson
pergolide (Permax)	1998	2007	2	Valvulopathy
tegaserod (Zelnorm)	2002	2007	3b	CV events