Update on Mini-Sentinel Activities
A New Tool to Assess Safety

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A New Tool

What will we be able to do with it? Dr. Platt has described the many possibilities. Let me focus on a few of the major attractions.

1. Size

Eventually it will be very large, getting close to the population contributing to AERS (i.e., everybody), large enough to detect rare events, at least if they are captured properly in the database, and there will be data from a non-exposed group. In some sense, this is one of the basic features of "active surveillance."

2. Multiple sites/analyses

If you believe, as I do (JAMA, 1999), that no epidemiologic study should be published until it is replicated at at least one more site, we have a huge opportunity here to look at multiple databases.

3. Use data

It should be possible to quickly look for changes in use in response to labeling changes, drug safety communications, concomitant treatments. Can also be used to see if contraindications and other labeling advice is being observed.

What We Can Do

4. Effectiveness

Some epidemiologists think you can evaluate effectiveness with such systems but if, like me, and like most epidemiologists, you do not give much credibility to RR's < 2 (or < 1.5 if you're an optimist) this will NOT be possible. Hardly any drugs have effect sizes near 50%.

5. Finding large increases in risk of common events

AERS is hard to interpret for relatively common events (heart attacks, depression, violence, suicide attempts) and interpreting reports is a major problem,. You need a reference group. It's worth remembering that epidemiologic studies have found such major, but not previously recognized, risks reliably:

- Thromboembolic disease with OC's
- Endometrial cancer with unopposed estrogens
- Valvulopathy with fenfluramine

Finding/Confirming Large Increases in Risk

How have we found the large risks that cause removal of drugs from the market? Most commonly, especially in the past, by detecting uncommon serious and fatal events that are extraordinarily rare without a drug, reflecting RR's of > 10, perhaps 100, especially when one considers time of event in relation to drug user. In those cases, drug-relatedness "speaks for itself"

- Major hepatic injury
- Torsade de Pointes arrhythmia
- Stevens-Johnson Syndrome
- Acute renal failure
- Hematologic abnormalities (aplastic anemia, agranulocytosis, hemolytic anemia)

It would be of interest to do a similar analysis of findings that have led to Boxed Warnings, major limitations of use.

Drug	Date Approved	Date Withdrawn	Data: 1, 2, 3	Adverse Effect
azaribine (Triazure)	1975	1976	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
methaqualone (Qualude)	1960's	1984	1	overdose 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)	1992	1993	3a	Mortality (HR – 1.5)
fenfluramine (Pondimin)	1973	1997	2	Valvulopathy
terfenadine (Seldane)	1985	1998	1	TdP
mibefradil (Posicor)	1997	1998	1	Interactions; TdP and
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	isch colitis; constip'n needing surgery
PPA	<1962	2000	2	hemorrhagic stroke
rapacuronium (Raplon)	1999	2001	1	bronchospasm
cerivastatin (Baycol)	1997	2001	1, 2	Rhabdomyolysis >> other status
Etretinate	1986	2002	1	Birth Defects
Levacetyl methadol (0rlaam)	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
gatifloxacin (Tequin)	1999	2006	1	hyperglycemia and hypoglycemia
pergolide (Permax)	1998	2007	2	Valvulopathy
tegaserod (Zelnorm)	2002	2007	3b	CV events
aprotinin (Trasylol)	1993	2008	3a	Increased mortality
sibutramine (Meridia)	1997	2010	3a	CV events

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

DILI = drug induced liver injury
TDP = Torsade de Pointes
PML = progressive multifocal leukoencephalopathy

Large Risks

Most of the withdrawals were discovered by AERS reports (sometimes with literature support). But there are many other serious events where it is not so easy to know the background rate, e.g., pancreatitis, suicidal or violent behavior or how it relates to the condition being treated. In all these cases, we must decide

- Whether there is some other explanation for the event (case by case). You always need to do that.
- Whether the events we see are compatible with the background rate of the event, a very hard task, especially when we don't really know the reporting rate
- So what do we do now:
  - See if it's a good case (exclude other causes, look at timing, good description)
  - Evaluate timing; close to use increases causal likelihood; look for dechallenge, rechallenge
  - Use data mining to help decide if rate is higher than expected (but it's relatively crude, not usually population specific); i.e., look for large differences in observed vs expected
  - Worry if it seems likely that the risk is > background. Unfortunately, this is very hard to know.

Large Risks

Sentinel gives us one more thing to do, and it is very exciting.

What I believe is possible is that Sentinel can rapidly assess likely causality when

- The cases are good (well-described, well-timed)
- The rate seems much higher than expected (e.g., survives data mining analysis)
- There is uncertainty about reporting artifacts (new drug, publicity, comparator agents have been around long) and what the real background rate in the specific population getting the drug

We have a recent example: dabigatran, an anticoagulant for use to prevent thromboembolic disease in people with AF.

Dabigatran

It's an illustration – no data yet because approval too recent.

In 2011 we received 100's of reports of serious bleeding, far more than we received for coumadin, the traditional anticoagulant used in AF, an established cause of serious bleeding, and with far greater use.

An 18,000 patient study in AF (RE-LY) showed very similar bleeding rates for dabigatran at its approved dose (150 mg) and coumadin, each about 5%). If we got all reports of major bleeding on coumadin, we would have many, many thousands of reports.

So, why would we see so many reports with dabigatran? Reporting artifact, wrong population, something add about people in trials vs real world?

Dabigatran

The reporting rate of serious bleeds is so much greater than it is for coumadin that a RR of 5 or more is suggested (if it is all true).

If that is true, Sentinel will be able to detect it. A smaller RR would not be so easy.

So, what Sentinel can find, and check out, is AERS findings that reports many serious events, and where there truly IS a large excess risk, something we most definitely need to know about.

Other candidates would seem to include

- Psychiatric problems with drugs, always difficult because of the background rate
- Celiac disease with ARBs (olmesartan)
- PML with drugs for MS (when databases get large enough

Long-standing Problem

There is a second potential benefit, as noted earlier. What the background rate of serious events is can be very hard to know. Even for an obvious, and often drug related, event like severe hepatic injury, when the rate associated with drug use is low (1/50,000) it can be hard to decide whether this is above background, as a long-standing issue with nefazodone illustrates. When (if) Sentinel becomes large enough, it should be able to help with even these rare events because it will have good data on background rates.