Preclinical pharmacology approaches in the NIH Medicines Development Program and lessons for the future.

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4 May 2012

Disclaimer:

- Much of the opinion expressed in the talk is mine. It is not a consensus of those who worked with us on this delightful program over the years.
- I haven't had the opportunity to discuss all the issues with very many of the CPDD participants nor to pass my notes to them prior to this meeting.

The history, scope, and major findings of the preclinical narcotic evaluation program of the CPDD.

In the beginning the program was conceived to provide predictions about human narcotic drug evaluation with the prime target of producing a strong pain reliever without abuse liability.

The Eddy standards:

- Evaluations done by blinded observers.
- Public disclosure of findings.
- Funding was not “fee for service” – it was a public health standard of service.
- Service was coordinated through a “biological coordinator” - the submitter never dealt directly with those involved with compound evaluation.

The standards:

- Were never violated.
- They worked.
- Reliable results were obtained.
- The biological coordinator insured reliability by resubmitting compounds for reliability assessments. Complementarity was assessed as well.

The product:

- The submitter needed the findings for regulatory assessment of abuse liability.
- It was extremely difficult to obtain the information in any other way.
- The regulatory bodies (FDA and WHO) “abided” by the findings.

Initial workings of the narcotic program:

- Observational studies of morphine dependent rhesus monkeys (circa 1952)
- Different conditions of intoxication, fully dependent: Nonwithdrawn, 12 hr. withdrawn, and nonintoxicated monkeys. In some cases, a primary dependence study was carried out in narcotic free monkeys.
- Built by Maurice Seevers to be parallel to human studies at Lexington facilities.

In the 1970s and early 1980s: significant changes in personnel and protocols.

- Additions of MCV group, headed by Dr. Harris as a complement to the unsure situation at Michigan with Dr. Seevers' retirement.
- Protocol additions of dependence induction and measurement in rats, self-injection procedures in rhesus monkeys, drug discrimination, analgesia in rodents and monkeys, respiratory function in primates, and in vitro measures of opioid activity.

Logical principles in play and major findings:

- Pharmacological equivalence (W.R. Martin), explicitly employed in dependence assessment
- Receptor selective effects
- Efficacy
- Applications of in vivo antagonist potency
- Three major receptor types: mu, kappa, and delta
- Buprenorphine: characteristics of action.

The beginnings of the decline:

- Cessation of human drug evaluation for opioid dependence liability
- Very gradual decline in active drug discovery programs in pharmaceutical industry
- Compound rates of submission were maintained for long periods of time in the face of the above problems

- The DEC closed its public program on 28 February 2007, and published its last report the following year.
- It is, to our knowledge, a unique public health program featuring drug discovery in drug dependence and, perhaps, more broadly.

Key References:

- N.B. Eddy. The National Research Council Involvement in the Opiate Problem, 1928-1971. National Academy of Sciences, Washington, D.C., 1973.
- E.L. May and A.E. Jacobson. The CPDD: A legacy of the NAS. A historical account. Drug and Alcohol Dependence. 23: 183-218 (1989).
- A.E. Jacobson. The history and current activities of the DEC of the CPDD. NIDA Res. Monog 174: 314-322 (1997).