

## STATEMENT BY THE AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

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The American College of Neuropsychopharmacology (ACNP) is devoted to promoting the interaction of a broad range of scientific disciplines of brain and behavior in order to advance the understanding of prevention and treatment of diseases of the nervous system including psychiatric, neurological, behavioral and addictive disorders. This ACNP statement focuses on key issues in system development for objectively evaluating medication safety and effectiveness.

### EVALUATING HARMS

The central issue is that harms may occur to patients while being treated with medications. These may (infrequently) be reported to the FDA as Adverse Event Reports via its voluntary system (MedWatch) or by industry.

However such reports are only of concomitance and do not establish causality. The usual difficult case is that the harm in question often occurs in the absence of treatment and may actually occur with increased frequency in the untreated patient. Therefore definitive causal attributions are unwarranted. Even the proportion of medicated patients supposedly affected is unknown because reporting is incomplete. Such reports have been negotiated between industry and the FDA as to their labeling inclusion as concerns and warnings. However, this practice was recently brought into question when public concern was incited by a controlled clinical trial yielding a clear causal inference of a rare, possibly lethal, effect of an FDA approved medication, Vioxx (rofecoxib).

The complex chain of events with regard to public warnings and marketing of COX-2 inhibitors and NSAIDS are available at <http://www.fda.gov/cder/drug/infopage/COX2/default.htm>).

A major point is that the inference that this drug caused rare but potentially lethal effects was based on a large clinical trial conducted for other purposes. Therefore, questions about FDA effectiveness in recognizing safety issues gained in substance.

Such concerns were further reinforced by the FDA review and eventual warning actions concerning anti-depressant treatment and "suicidality" in children. The issue of firm causality was, again, central.

I submitted to an IOM committee on The Assessment of the U.S. Drug Safety System a personal critique of the data and analyses used by the FDA in justifying its Black Box warning and public statements. This review concludes: The central concern of the FDA and its advisory boards was whether antidepressants could be lethal, by causing suicide in children and adolescents. Since no suicide occurred in these clinical trials that studied approximately 4,400 children, the analyses relied upon "suicidality" as a surrogate.

The classification of adverse events by the Columbia group necessarily relied on shaky inferences, because the available evidence was not prospectively collected for this purpose; and thus does not fulfill requirements for evaluating "suicidality" e.g., direct interview as well as circumstantial evidence concerning necessary intent to die, self harm, lethality of attempt, required medical attention, definite plan, concealment etc. The threshold used for the crucial inference of intent to die seems to have been even the slightest suspicion.

Strategies used in data analysis: The data analysis relied on a composite marker of "suicidality" including "ideation". This was an inappropriate, misleading surrogate for completed suicide that grossly overestimates potential risk for a rare event.

The failure of the FDA's post-marketing surveillance system is evident. Accusations about the FDA's structure, bungling or industry influence deflect attention from the central issue.

## THE CENTRAL LACK OF RELEVANT DATA

The FDA cannot, objectively or timely, detect or evaluate rare or delayed toxicities because of the limited safety information it relies upon, spontaneous adverse event reports or short term, necessarily underpowered, clinical trials. Since most prescriptions are "off-label" even minimal clinical trial signals re possible harms rarely exist. Therefore recommendations that all approved medications require prompt large-scale post-marketing trials would serve quite incompletely besides being impractical.

Unfortunately, the FDA's ability to rapidly communicate about realistic possible harms, worthy of public concern, is limited to the problematic information it can obtain from Adverse Event Reports. Further, the public often reacts to such warnings, despite FDA qualifications, as if they were firmly established. The FDA does not know whether such communications are helpful or have a net negative public health effect by frightening public and professionals from availing themselves of safe, useful treatments.

## PHARMACOVIGILANCE/PHARMACOEPIDEMOLOGY

Alternative methods for systematically collecting evaluable safety data must be developed. Proper post-marketing surveillance by linked computerized medical records is a leading possibility that deserves major public and political attention and appropriate action. Unfortunately, it has not received any public attention. Therefore we present a concrete example of a well functioning current system - PHARMO.

Also, we present a concrete example how a complex cross-linked database – such as PHARMO - would have helped clarify any causal relationship of SSRIs to suicidality.

PHARMO-Institute for Drug Outcome Studies.

PHARMO, a system developed in the Netherlands, is reviewable at: (<http://www.pharmo.nl>).

"The PHARMO Institute is an independent scientific research organization dedicated to study drug use and outcomes in daily practice. The PHARMO Institute has direct access to large and high quality pharmacoepidemiological databases, is staffed with academic trained specialists in epidemiology, pharmacotherapy, medicine and informatics, and works closely together with the international renowned department of Pharmaco-epidemiology and Pharmaco-therapy of the University of Utrecht ([www.pharm.uu.nl](http://www.pharm.uu.nl)). This unique combination of expertise and access to patient-based data enables fast and professional handling of research questions meeting state-of-the-art research standards. The PHARMO databases constitute a well-defined population including one million residents in the Netherlands and enable us to follow-up drug use and hospitalizations in patients for an average of ten years. Access to medical charts and other clinical data is available within the prerequisites of the Dutch privacy regulations. Studies and results are representative for the whole Dutch population. For optimal transparency, we strive to publish the results of studies in order to fulfill our mission to learn and disclose more about the safety, effectiveness and costs of drugs for implementation in current pharmacotherapeutic practice. Clients are amongst others: universities, governmental agencies and pharmaceutical companies."

## THE COMPLEX PHARMO DATABASE

"The PHARMO Institute has direct access to the data source PHARMO Record Linkage System that was established at the Dutch Universities of Utrecht and Rotterdam in the early nineties. This PHARMO system links patients' medical histories to the use and cost of prescription drugs (U-Expo database), diagnostic/therapeutic data from hospitals (LMR), clinical lab and pathological findings, GP records and drug histories in hospital. The PHARMO Institute has access to a variety of databases, each of them having their relevant and specific items to link them to the PHARMO database on patient level, following the history of drug use and other medical events of an anonymous patient. Currently, data are collected from a population of about two million residents in the Netherlands and are representative for the Netherlands."

Since reinventing the infrastructure needed for appraising each treatment or indication is too costly and prohibitive for timely results, the only feasible procedure is a standing high quality cross-linked computerized general medical data base.

Epidemiological approaches attempt to contrast samples matched except for treatment exposure. However since receiving treatment is not a random event analyses are not straight forward. Analyses must pay particular attention to selection biases and confounding to avoid false positive relationships. Given a vast population based data base numerous possible comparison groups can be constructed via stratification, regression etc. to allow for these problems. This complex area should be at the forefront of methodological development, combined with specific clinical/biological understanding of disease processes.

#### EXAMPLE OF POTENTIAL UTILITY - MEDICATION INDUCED SUICIDALITY

Given national concern about suicide, a specific file would accumulate longitudinally, by anonymized individual, all reports that specify self-harms, suicide attempts or attempted suicides gathered from computerized, structured:

- Diagnoses and demographics in medical records
- Specification of illness severity and functional impairment
- Clinical lab and pathological findings
- Emergency room records
- Diagnostic/therapeutic data from hospitals
- Death certificates
- Census records

These would be correlated and contrasted, using various analytical methods e.g. time series, case controls, cohort analyses, etc. with prescription records and toxicology tests to search for beyond base-rate and beyond chance differences attributable to various treatments. Textbooks of Pharmacoepidemiology address these issues.

Following the marketing of a medication, a focused comparative analysis cross-linked to the developing prescriptive data base may yield an early signal of problems. Detection of such signals would lead to even more refined, medically informed, analyses to further rule out possible confounds and selection biases. These analyses would estimate the actual risk/benefit ratio because the utilization denominators are known, which not the current case is. Therefore the magnitude of public health concern can be estimated much more firmly. Public communications and warnings would have a much firmer, more timely, and more informative basis.

### PRACTICALITY FOR USA

It might be thought that such a system would not be feasible within the private practice network of the U.S. or by federal budgetary constraints. However, the billions already lost by industry, and the likelihood that a crescendo of such losses are forthcoming, places in perspective costs to industry and the public of providing a safety/effectiveness program adequate to current requirements. Further, there would be huge advantages for individuals' medical care since they would have available to them a completely detailed medical record. This is far advanced beyond the current reality.

### FOSTERING CHANGE

However, the need for such systems is simply not on the public radar screen. The political will for drastic change is often stirred by catastrophes revealing the gross inadequacies of current safety nets. The Elixir Sulfanilamide catastrophe of the 1930's and the thalidomide tragedy of the 1960's are almost entirely responsible for the current system of pharmaceutical regulation re safety and efficacy---not just in the USA but across the developed world. In addition to the drug safety issue the mounting crescendo of medical costs, as well as ensuring that individual treatments are immediately informed of all past evaluations and care, has brought Health Information Technology into the political arena. However, current efforts focus narrowly on technical problems such as facilitating inter-computer communication.

There is a fortunate confluence of interests here since cross-linked computerized medical records may provide the crucial advance needed for ameliorating these tremendous problems.

## RECCOMENDATIONS

Federally directed complex medical systems such as the VA, Armed Forces, and PHS provide entry points for legislatively mandating a cross-linked computerized surveillance system that speaks objectively to both safety and effectiveness. The Veterans Administration has already made substantial strides in Health Information Technology use. This should be carefully reviewed.

The ACNP believes that developing the public understanding and political will necessary to realize such medical documentation innovations via cross-linked computerized Health Information Technology, requires ongoing public discussions by the range of stakeholders. In particular, detailed analyses of PHARMO and similar systems are required.

Work groups should proffer plans and analyses. Conflicting views are inevitable. Public meetings organized by a variety of patient support groups, academics, professional, and political organizations, etc., should accelerate public debate.

The FDA can foster this democratic process by initiating such meetings in the near future. The ACNP is actively considering promptly sponsoring a Washington DC meeting for analysis of pharmacovigilance systems promoting medication safety.

*ACNP, founded in 1961, is a professional organization of more than 700 leading scientists, including three Nobel Laureates. The mission of ACNP is to further research and education in neuropsychopharmacology and related fields in the following ways: promoting the interaction of a broad range of scientific disciplines of brain and behavior in order to advance the understanding of prevention and treatment of disease of the nervous system including psychiatric, neurological, behavioral and addictive disorders; encouraging scientists to enter research careers in fields related to these disorders and their treatment; and ensuring the dissemination of relevant scientific advances.*