

Developing Methodologies for Monitoring Long-Term Safety of Psychotropic Medications in Children: Report on the NIMH Conference, September 25, 2000

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ABSTRACT

Objective: To improve the methods for long-term assessment of drug-associated side effects and advance knowledge of the safety profile of psychotropic medications in children and adolescents. **Method:** A multidisciplinary, interactive workshop was hosted by the National Institute of Mental Health (NIMH) and the Research Units on Pediatric Psychopharmacology network. Participants were experts in child and adolescent psychiatry, psychopharmacology, pharmacoepidemiology, and statistics from academia, the pharmaceutical industry, the Food and Drug Administration (FDA), and the NIMH. Evaluation of drug safety was examined from five perspectives: research design and methods, industry, regulatory requirements, bioethics, and practice settings. For each of these areas, special emphasis was placed on identifying barriers and generating solutions. **Results:** A major obstacle is the lack of standardization of the methods used for collecting safety data. The limitations of both randomized clinical trials and passive postmarketing surveillance in assessing long-term safety were recognized. The need to consider alternative approaches, such as registries and trend analysis of population-based databases, was highlighted. Recommendations were proposed together with possible approaches to implementation. **Conclusions:** A concerted effort by academic researchers, industry, FDA, practitioners, and NIMH is needed to standardize methods and lay the foundations for systematic research on the long-term safety of psychotropic medications in children. *J. Am. Acad. Child Adolesc. Psychiatry*, 2003, 42(6):651–655. **Key Words:** children, psychopharmacology, treatment, adverse events, drug safety.

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The study of the long-term safety of psychotropic medications in children is important for two main reasons. First, treatment with psychotropic medications is often continued for long periods of time, during critical stages of development, because psychiatric disorders themselves are often chronic. In contrast, most of the available safety data on these agents are derived from short-term studies, often gathered only in adults. Second, exposure of a developing organism to a medication, even for a brief period of time, may have effects that are long-lasting or that emerge later in life (Vitiello and Jensen, 1995).

The lack of established methods for investigating the long-term safety of psychotropics in children is both a

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reason and a consequence of the limited research devoted to this area (Greenhill et al., 2003; Vitiello et al., 2003). Given the considerable public health relevance of drug safety in children, and the potential effects of psychotropic medications on physical growth and brain development, it is important to identify valid methods for detecting possible drug-induced adverse events during early and/or prolonged exposure (Vitiello and Jensen, 1995).

The Research Units on Pediatric Psychopharmacology (RUPP), a research network funded by the National Institute of Mental Health (NIMH), convened a workshop titled "Medication Safety Monitoring 2000: Developing Methodologies for Monitoring Long-Term Safety of Psychotropic Medications in Children" in September 2000. The organizers used a consensus-building forum for developing new research methods and organizational approaches to long-term drug safety evaluation in children.

The participants of the workshop quickly agreed that there is no universal definition for "long-term effects." Still, this term was used to indicate an extended period of time—from 12 months to several years—needed to evaluate possible effects of treatment on development. Although animal models can substantially contribute to the understanding of long-term effects of psychotropic medication and the interaction between developing brain and pharmacological treatment, even long-term effects noted in other species may not be relevant to humans.

METHOD

The workshop convened 135 experts in child and adolescent psychiatry, developmental psychopathology, clinical psychology, psychopharmacology, pharmacokinetics, experimental design, epidemiology, biostatistics, bioethics, regulatory affairs, and policymaking. To maximize interaction, participants met in plenary sessions and five smaller, multidisciplinary workgroups devoted to research designs and methods, regulatory aspects, bioethics, pharmaceutical industry considerations, and practice network research. Each workgroup was charged with three main tasks: (1) to identify possible approaches to studying the long-term safety of psychotropic medications in children; (2) to highlight obstacles to implementing these approaches; and (3) to recommend possible solutions for overcoming the obstacles.

Emphasis was put on setting realistic goals and approaching tasks from a multidisciplinary perspective. To this end, specific questions were raised: (1) How can clinical researchers collaborate with practitioners, epidemiologists, and biostatisticians to enhance the detection of possible drug toxicity in a prompt and efficient manner? (2) What can regulatory agencies do to address the research, ethical, financial, and traditional barriers to improve long-term adverse event collection methodology for children? (3) What can the pharmaceutical industry do to improve the collection of long-term adverse events in children? (4) How can NIMH foster research in this area?

RESULTS

RESEARCH DESIGN CHALLENGES

Obstacles

- Because it is difficult to enroll large samples of children in controlled trials, the small samples used in these studies may detect only the most common drug-related side effects.
- Sensitivity is lost because there is no empirically validated method for gathering side effect data in children, leading to diverse ascertainment and recording methods for drug safety.
- The child populations involved in short-term clinical trials may not be representative of the usual real-world clinical populations of children.
- While adverse events that are circumscribed and have clear onset are relatively easy to identify, toxicities that emerge slowly and insidiously (e.g., cognitive impairment) may escape detection. At the moment, with the exception of the Food and Drug Administration (FDA) MedWatch program, there are no publicly available, large databases of adverse events that are easily accessible for retrospective searches.

Recommended Solutions

- New clinical trials should be encouraged to use cohort sequential designs with subject enrollment blocked by age (grouping every 3 to 5 years of age) to identify common drug-related adverse events by developmental stage in children. This design should be controlled in the short term as it occurs in traditional randomized clinical trials used to establish efficacy. However, the study samples should be systematically monitored beyond the initial acute phase of treatment and prospectively assessed during long-term maintenance. The original randomization, together with the initial controlled phase and the systematic, prospective assessment, will help control selection biases and detect possible drug-related toxicities. If the sample size of these studies is in the hundreds, at least the most frequent adverse events could be identified.
- To detect unexpected but serious adverse events, retrospective designs could be used to gather data from larger child populations (in the thousands). This might be best done by conducting cohort studies in practice settings, thus enhancing recruitment and sample representativeness. This would lead to the creation of reg-

istries of patients of different ages who are representative of diverse children treated with a certain medication. These registries can provide long-term prospective monitoring.

- To facilitate meta-analyses, standardized methods should be used to assess safety and common variables across studies should be selected.

PHARMACEUTICAL INDUSTRY CHALLENGES

Obstacles

- The use of instruments and methodologies of unproven validity may lead to false-positive results by implying a causal association between toxicity and drug exposure based merely on temporal association. This would have damaging consequences for the company marketing the drug.
- Drug-related side effects may take months or years to surface, such as the rare occurrence of hepatic failure during pemoline treatment.
- Industry gets no financial incentive for launching an active postmarketing safety initiative.
- If data were gathered and shared among members of industry, inappropriate use of the resulting database could occur, leading to spurious associations between drug and toxicities. As it is, competing companies are not often willing to share safety data.

Recommended Solutions

- There should be standardized definition about what constitutes "long term" among industry and regulatory representatives. This would make it easier to reassure families and the government that a new therapeutic drug was safe for developing children.
- The FDA should be encouraged to provide appropriate incentives through the use of the Food and Drug Administration Modernization Act (FDAMA) legislation to extend patent exclusivity in exchange for research on safety in children. This authority has already been used to study efficacy and pharmacokinetics in children.
- Industry should make proprietary databases of clinical trials available to independent investigators for studying drug safety.
- "Active" postmarketing surveillance should be conducted on newly marketed drugs that are given to children.
- There should be an effort across industry to standardize methods of safety evaluation, in collaboration with FDA and NIMH.

REGULATORY CHALLENGES

Obstacles

- Clinicians underutilize MedWatch because there is the lack of incentive in using it and the perception that reporting a drug-associated adverse event may increase the risk of malpractice litigation.
- FDA cannot mandate industry to establish registries. To give FDA such a power would require a legislative change.
- The heterogeneity in reporting adverse events to FDA is a limiting factor in creating large databases.

Recommended Solutions

- Education should be provided to clinicians about the importance of MedWatch, and the fact that anonymous reporting does not increase litigation risks for the clinician could improve utilization.
- Through new legislation, Congress should encourage the FDA to use the FDAMA (now reauthorized by Congress for 2002) to increase industry's incentive to study long-term safety in children (FDAMA, 1997). FDAMA, which allows a 6-month extension in patent exclusivity to be granted to a pharmaceutical company in return for research on its pediatric use, has been successfully utilized for increasing research on the efficacy of medications in children.
- FDA can be encouraged to work with industry, investigators, and NIMH to standardize the methods for assessing drug-associated adverse events in children.
- MedWatch's ability to detect rare and unexpected adverse events should be improved. Currently, its use is limited because clinicians do not systematically report drug-associated adverse events.
- A national policy should be developed to establish registries for studying long-term drug safety of newly introduced medications in children.

ETHICAL CHALLENGES

Obstacles

- It is difficult to estimate the risk-benefit ratio for children entering into clinical trials of medications because the long-term adverse event profile for a new drug is not known for children.
- Volunteer studies cannot be conducted in children, so the optimal dose range that provides the greatest safety is not known.

- For studies to be conducted in clinical practice settings, the local institutional review board (IRB) may not always be available for monitoring the re-consent process.
- Long-term placebo-controlled treatments are often unacceptable from an ethical point of view because they may expose children to suboptimal treatment for extended periods of time.

Recommended Solutions

- The IRB of an academic institution could function as a coordinating center in multisite studies.
- Centralized IRBs could provide greater standardization across university and clinical settings.
- Alternatives to placebo-controlled designs must be considered.
- When registries are used, or when patients in naturalistic practice settings are studied for extended periods of time, special attention must be paid to ensuring that appropriate informed consent for participation is obtained and that patients' confidentiality is protected.
- In prospective studies of long-term safety, the process of obtaining informed consent should be repeated as the child may participate for several years and the information available on risk and benefits is likely to change over time.
- Findings of long-term safety should be routinely made available to research participants after the clinical trial is completed.

PRACTICE NETWORKS

Obstacles

- No standardized instruments are used in practice for assessing drug-associated adverse events.
- No accepted definition of "long-term" exists.
- It is difficult to motivate practitioners to participate in research studies.

Recommended Solutions

- Large simple trials of drug safety in practice settings should be considered. Large simple trials are randomized studies in which treatment interventions are standard interventions that can be delivered in the practice setting. Outcome measures are clear-cut and simple to define and ascertain.
- A network of child and adolescent psychiatrists in practice who are willing to participate in research should be created.

- Standardized adverse events assessment instruments that can be used in practice settings should be developed and validated. To determine feasibility and acceptability, practitioners should be involved in the development of these instruments.
- Studies on long-term safety should be conducted in practice settings to take advantage of large sample size and patient representativeness. The utilization of both pediatrics and child and adolescent psychiatry practices could be considered.
- Existing health maintenance organization and Medicaid databases should be used for pharmacoepidemiological studies focused on ascertaining drug utilization as a measure of drug exposure in a population. Extent of drug exposure is essential in interpreting the rate of adverse events, especially the less frequent events.

CONCLUSIONS

While there are many issues relevant to safety of psychotropic medications in children, the main effort should be directed at identifying rare but serious adverse events and identifying common toxicities that may be associated with prolonged use of psychotropics, as well as those that may emerge later after early drug exposure at critical times of development. Because it is not always possible to predict which toxicity a drug may induce without extended use in thousands of patients, the approach to identifying rare and serious adverse events must be broad and open-minded.

Children should be evaluated on the following domains: (1) physical growth (i.e., weight and height); (2) pubertal development (to examine whether the drug affects timing and course of puberty); (3) cognitive development; and (4) mental health development (to examine whether the drug induces or worsens certain types of psychopathology).

These recommendations and possible solutions are being considered for implementation at different levels. Some academic investigators in collaboration are proposing the formation of a practice network for large simple trials with the American Academy of Child and Adolescent Psychiatry (AACAP). A Pediatric Psychopharmacology Initiative group has been formed by the AACAP which includes representatives of the AACAP, American Academy of Pediatrics, FDA, NIMH, industry, and patient advocacy. The RUPP network has started the development and testing of a unified assessment instrument that could be used as standard way of collecting safety data in research and practice settings.

REFERENCES

Food and Drug Administration Modernization Act of 1997. 27 USC 321, 1997
 Greenhill LL, Vitiello B, Riddle MA et al. (2003). Review of safety assessment
 methods used in pediatric psychopharmacology. *J Am Acad Child Adolesc
 Psychiatry* 42:627-633

Vitiello B, Jensen PS (1995). Developmental perspectives in pediatric psy-
 chopharmacology. *Psychopharmacol Bull* 31:75-81
 Vitiello B, Riddle MA, Greenhill LL et al. (2003). How can we improve the
 assessment of safety in child and adolescent psychopharmacology? *J Am
 Acad Child Adolesc Psychiatry* 42:634-641

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