

Review of Safety Assessment Methods Used in Pediatric Psychopharmacology

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ABSTRACT

Objective: Elicitation is an essential and critical step in ascertaining adverse events (AEs). This report reviews elicitation methods used in published clinical trials of psychopharmacological agents in children. **Method:** Pediatric psychopharmacology reports were reviewed for safety methods in the *Medline* database. Studies were included if they were published 1980 or later, provided data on AEs, and described the ascertainment methodology used for determining them. **Results:** A review of 196 pediatric psychopharmacology articles depicting safety assessments in clinical studies over the past 22 years revealed that there was no common method used for eliciting or reporting AE data. **Conclusion:** The current inconsistency in safety data ascertainment is a major limitation that likely impairs the ability to promptly and accurately identify drug-induced AEs. Research on how best to standardize safety methods should be considered a priority in pediatric psychopharmacology. *J. Am. Acad. Child Adolesc. Psychiatry*, 2003, 42(6):627–633. **Key Words:** children, adverse events, drug safety, treatment, psychopharmacology.

Pharmacological interventions have become mainstay therapeutic modalities for the treatment of childhood psychiatric disorders. For example, there has been a three-fold increase in psychotropic drug use in preschool chil-

dren aged 2 to 4 years (Zito et al., 2000). Many of these medications have not been tested in youths for acute or long-term safety (Jensen et al., 1999; Vitiello and Jensen, 1995, 1997). The impact of psychotropic medication on development and the timing of puberty, physical growth, and cognitive development are not well known.

When collecting reliable pediatric safety data, one encounters special methodological challenges. There has been no standard for how to collect adverse events (AEs) in children and adolescents, nor has the most sensitive and reliable method for inquiring about side effects from parents or from pediatric patients been determined. Multisite child psychopharmacology trials have used safety questions without training. In addition, no agreement exists on a universal glossary of preferred terms to be used for coding the information for this age group.

Postmarketing reports of rare but serious AEs in children and adolescents taking psychopharmacological agents have been first detected by the Food and Drug Administration's (FDA) passive surveillance system, MedWatch. These events vary in dangerousness, producing a range of outcomes from a trip to the emergency room to death. Their rarity means that they are unlikely to be detected

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in a controlled trial. If the AE occurs in a negative clinical trial, it may never be published. Furthermore, it is difficult to determine the risk of such events because spontaneous reports do not indicate the size of the population exposed. Over the past decade, there have been at least five serious but rare AEs associated with psychotropic medications used in children and adolescents, including the sudden deaths of 3 children taking desipramine for attention-deficit hyperactivity disorder (ADHD) (Medical Letter, 1990); the deaths of 4 individuals taking methylphenidate, clonidine, and other drugs (Swanson et al., 1995); 25 deaths from hepatotoxicity (Scheffner et al., 1988) and 4 deaths from hemorrhagic pancreatitis in pediatric patients taking valproic acid (Cooper and Groll, 2001; Otsubo et al., 1995); and 11 cases of extreme hepatotoxicity—resulting in death or liver transplant—in individuals being treated with pemoline for ADHD (Safer et al., 2001).

Randomized, double-blind, industry-sponsored trials of new psychotropic agents in children often use a single-page Case Report Form that records spontaneous AE complaints from the patient's parents (Greenhill et al., 2002). General-inquiry prompts (e.g., "How has your child's health been since the last visit?") are not often specified in the methods sections of reports on the study, nor are the methods listed to interpret and code the answers. The sensitivity of such general-inquiry, spontaneous-report techniques for detecting AEs in children and adolescents is unknown.

Drug-specific checklists that collect commonly occurring AEs related to a specific drug have been used in child and adolescent studies. Whether these are more valid than general-inquiry methods has not been formally tested. These drug-specific lists differ from broader symptom checklists and from a review-of-systems format that asks about a range of bodily dysfunctions by body area.

Problems were revealed during a review of psychostimulant trials of children with ADHD (Jadad et al., 1999). Of 2,402 articles identified, only 32 reports and 29 studies yielded useful safety data from ADHD patients treated with psychotropic medications. Eleven of the trials failed to indicate the number of patients randomized to one or more of the treatment arms, making it impossible to table the AE rates. There was marked heterogeneity in methods to elicit, measure, and present AEs. There was no information on interactions between the child's developmental state and AEs. Standardized glossaries were not used, and terms were not defined. The

estimates of the occurrence rate of AEs were limited by small sample sizes.

Many different methods have been used to gather AEs from children, including waiting for spontaneous reports, general inquiry, specific inquiry, and specific inquiry following general inquiry (Vitiello et al., 2003). The relative advantages and disadvantages of different elicitation approaches in adult patients were tested during development of the National Institute of Mental Health's (NIMH) Systematic Assessment for Treatment Emergent Events (SAFTEE) (Levine and Schooler, 1986). This instrument included both a simple, three-question general inquiry and a 78-item structured inquiry which addressed 29 body systems. While the specific inquiry elicited more AEs than did the general inquiry from 226 adult patients, there was no difference between the two methods if one examined the number of changes in clinical management that resulted (Rabkin and Markowitz, 1986). Even so, the investigators on this project disagreed, with some concluding that the general inquiry was able to detect all the clinically important AEs, while other members of the team wrote that the specific inquiry was required to pick up the clinically significant AEs that the general inquiry had missed (Levine and Schooler, 1986). No further research involving children or adolescents has been able to determine which elicitation method and which informant—parent or child or both—might yield the most clinically relevant AE data during drug trials with children.

Industry-sponsored, multisite, randomized controlled trials are now being conducted with pediatric populations. These offer an opportunity to bring improvements in the methods of collecting AEs during early clinical investigations of these psychotropic agents. A systematic literature review was conducted to compare methods of eliciting safety data in these new multisite medication treatment studies with previously published, single-site, university-based trials.

METHOD

Search Strategy

Eligible reports were identified from a systematic search of *Medline* from 1980 to present, *PsycINFO* from 1984 to present, and *EMBASE* from 1984–1997. The search strategy used included the terms *psychotropic drug-related adverse events, child, adolescent, stimulants, neuroleptics, lithium, anticonvulsants, benzodiazepines, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), clonidine, and guanfacine*. In addition, articles published since 1980 included large, multisite, placebo-controlled pediatric trials of new psychotropics now in press. Full reports were eligible if they were published in English peer-

TABLE 1
Adverse Events Methods: Number of Published Reports Meeting Search Criteria

Medication Studied (No. of Papers)	Case Study	Chart Reviews	Single Site RCTs	No. of Multisite Trials	General/No Elicitation Method Stated	Drug- Specific AE Checklist	Lab Test AE Methods
Stimulants (65)	7	12	47	6	22 (34%)	27 (41%)	16 (24%)
Anticonvulsants (37)	16	14	7	0	5 (14%)	0	32 (86%)
Neuroleptics (31)	20	6	4	1	6 (19%)	7 (23%)	18 (58%)
Tricyclics (24)	7	3	14	0	13 (54%)	1 (4%)	10 (42%)
SSRI (16)	4	5	2	5	11 (69%)	2 (12%)	3 (19%)
Pemoline (4)	4	0	0	0	0 (100%)	0	4 (100%)
Lithium (13)	4	0	9	0	3 (23%)	7 (54%)	3 (23%)
Benzodiazepines (6)	2	0	4	0	5 (87%)	1 (13%)	0
All medications (196)	63	40	87	12	65 (33%)	45 (23%)	86 (44%)

Note: RCT = randomized controlled trial; AE = adverse event; SSRI = selective serotonin reuptake inhibitor.

reviewed journals, focused on the psychotropic medication treatment of children or adolescents, and reported AEs.

Definition of Terms

Terminology was defined before data extraction began. "Adverse event" (AE) refers to any negative occurrence in mental or physical functioning that occurred during the conduct of a pediatric psychopharmacology trial. AEs may be "unrelated," "likely related," or "definitely related" to the drug being taken. Their occurrence during a clinical trial can be judged "frequent" (more than 5% of subjects are affected), "infrequent" (more than 2% but fewer than 5% are affected), or "rare" (fewer than 1% are affected). Severity of AEs can range from "mild" through "moderate" to "severe." According to FDA definition, "serious" is any AE that is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in a congenital malformation, or results in a persistent significant disability (Castle, 1999).

Data Extraction

Safety data were extracted independently from full reports by two reviewers (L.L.G., E.S.). All selected articles had to have at least one paragraph devoted to a report of AEs during the period of observation. Articles were classified on the basis of whether the study was single site or multisite, was open or controlled, whether AEs included primarily laboratory data or patient subjective report of new signs or symptoms, and the method of elicitation of the AEs (general, drug-specific, and specific body-system AE questionnaires). Differences were resolved by consensus. The authors' names on the original reports were not concealed, and this could have led to a bias.

RESULTS

Yield of the Search

Electronic database searches, review of reference lists of review articles, and referrals from experts yielded 196 citations, as shown in Table 1. Of these AE reports, 65 described stimulants, 16 reported on selective serotonin reuptake inhibitors (SSRIs), 31 reported on neuroleptics, 24 reported on tricyclic antidepressants, 13 reported on lithium carbonate, 37 reported on anticonvulsants, 4

reported on pemoline, 6 reported on benzodiazepines, and 4 reported on α_2 -reuptake inhibitors (clonidine and guanfacine). A listing of these references is available from the corresponding author.

Elicitation Methods Used in Studies of Stimulant Medications

Studies were identified as those that used general-inquiry elicitation methods (22), those that focused on laboratory tests (16), and those that used drug-specific checklists (27). All but 4 of these studies state the duration of observation, but only 11 had a year or more duration of observation for children on stimulant medication. This means only a small proportion of reports in the literature address long-term (more than 1 year) use of stimulants in children with ADHD. All but two of the studies questioned only one informant, the parents. Using a 17-item list of stimulant-related AE symptoms, the investigators found a wider range of AEs when children were asked than either parents or teachers (DuPaul, 1996). The data analysis of the titration trial of the NIMH Collaborative Multisite Multimodal Treatment Study of Children With ADHD (MTA study) showed that the largest source of variance in the AE data, when a drug-specific checklist was used, came from the type of informant (Greenhill et al., 2001).

The stimulant pemoline was on the market for 20 years before a rare, unexpected, serious AE was discovered: hepatic failure. Four of the five pemoline reports concentrate on single-case studies of laboratory and pathology values during hepatic failure, plus one review of MedWatch postmarketing data suggesting that signs of its presence were available before reports began to appear in the gastroenterology literature (Safer et al., 2001).

Elicitation Methods Used in Studies of SSRIs

SSRIs have become the second most prescribed psychotropic agents in the United States (Jensen et al., 1999). There have been 16 studies, with 5 of them being multisite trials (DeVaugh-Geiss et al., 1992; Keller et al., 2001; March et al., 1998; Research Unit on Pediatric Psychopharmacology [RUPP] Anxiety Study Group, 2001; Riddle et al., 2001), as shown in Table 1. The remaining published reports that describe AEs consist of two single-site randomized controlled trials and nine case or retrospective studies. Only 11% of these studies used a drug-specific method of elicitation, two thirds used a general-inquiry method, and 15% reported laboratory data.

Elicitation Methods Used in Studies of Tricyclic Antidepressants

Tricyclic antidepressants have been used to treat children with enuresis, ADHD, anxiety, and depressive disorders. This search identified 14 single-site, placebo-controlled randomized controlled trials and one large multisite trial. General-inquiry method predominated in 54% of all the reports, while 42% presented laboratory data, particularly changes in electrocardiogram readings. Only 4% of the studies used drug-specific AE checklists.

Elicitation Methods Used in Studies of Neuroleptics

Slightly more than 22% of the 31 publications on neuroleptic-related AEs in children used drug-specific symptom checklists, particularly focusing on abnormal involuntary movements. Laboratory measures figured in the reports of 58% of these articles. The remaining 19% featured single-case reports. Only one study—examining the effects of risperidone on the behavior and mood of children and adolescents with autism—was designed as a multisite randomized controlled trial and used a mixture of general-inquiry and drug-specific AE checklists (RUPP Autism Network, 2002).

Elicitation Methods Used in Studies of Mood Stabilizers

Anticonvulsant AE reports included those that did not specify the elicitation method (14%) and those that were based on laboratory values (86%). Because the medical events (pancreatitis, liver failure) led to emergency hospitalization, these AEs were deemed serious and related to the anticonvulsant being taken. The majority of the publications were single-case studies or chart reviews, with a smaller number of single-site trials.

Lithium carbonate has been studied in nine single-site randomized clinical trials and five case reports or case

series. Although it is essential to monitor laboratory values in patients using this medication, only 23% of these articles identified abnormal laboratory values for the children and adolescents who had drug-related AEs. More than 50% of these published reports used drug-specific rating scales to elicit AEs.

Elicitation Methods Used in Studies of Other Medications

This group constitutes 24 reports (12% of the search) and consists of 1 multisite trial, 13 single-site randomized controlled trials, and 10 case reports. Benzodiazepines were reported in two case studies and four single-site randomized controlled trials in this survey. Only one study (13%) used a drug-specific elicitation checklist, with the majority not defining the method of inquiry. Clonidine has been examined in two controlled trials. These trials used drug-specific inquiry elicitation methods.

Elicitation Methods Used in Randomized Multisite Studies

The pediatric psychopharmacology literature over the past 10 years was surveyed to identify published multisite clinical trials. Table 2 reviews the outcome of this search: 15 multisite randomized controlled trials. Some served as phase III registration trials for New Drug Applications for the FDA, so they involved intensive monitoring and surveillance of all aspects of the trial. Only 3 of these 13 trials—the NIMH MTA study, the RUPP Autism Network study of risperidone (RUPP Autism Network, 2002), and the Tourette's study group trial of clonidine and methylphenidate (Tourette's Syndrome Study Group, 2002)—used drug-specific checklists for their AE elicitation. The methods sections of these papers do not detail training for the AE raters, nor do they explain the methods of the AE coding, tabulating, and reporting. Most of these multisite papers detail those patients who dropped out of the study because of medication-related AEs.

DISCUSSION

Review of 196 published drug safety reports extracted from the pediatric psychopharmacology literature reveals that most used general-inquiry questions as the main elicitation method. Occasionally, a few studies used drug-specific AE checklists. Studies of stimulant medications and neuroleptics have most often used drug-specific checklists. Other than one placebo-controlled study of a stimulant-related AE checklist (Barkley et al., 1990) and another two studies comparing differences among informants dur-

TABLE 2
Adverse Events Methods: Multisite, Randomized Controlled Trials (RCTs) in Children and Adolescents

Author / Year	Medication Studied	No. of Subjects	No. of Sites	Treatment Arms	Duration	Elicitation Method	AE Report Table
Biederman et al., 2002	SL1381 (Adderall-XR)	584	47	2 arms: SL1381 10, 20, 30 mg, placebo	3 weeks	General inquiry, probe not specified	AE report table but no report of dose lowering for AE
Conners et al., 2002	d-MPH	67	7	2 arms: d-MPH 10 mg b.i.d., placebo	6 week open-label titration, 2 week controlled; 44 week open-label follow-on	General inquiry, probe not specified limited dose given	AE report table for AEs > 5% prevalence, no. of cases where AEs
De Vaughn-Getts et al., 1992	Clomipramine	60	5	2 arms: clomipramine, placebo	10 weeks	General inquiry, probe not specified	Small AE table reported all AEs, but no listing of cases of discontinuation or dose lowering from AEs
Gillberg et al., 1997	d-Amphetamine	62	5	2 arms: amphetamine, placebo	60 weeks	Inquiry method not given	All AEs discussed, but no table; cases described where AEs limited dose increase or discontinued
Greenhill et al., 2002	Beaded MPH (Metadate-CD)	321	32	2 arms: beaded MPH, placebo	3 weeks	General inquiry, probe not specified	No sleep problems
Keller et al., 2001	Paroxetine, imipramine	275	16	3 arms: paroxetine, imipramine, placebo	3 weeks	Parents, specific	Weight reduction, appetite loss, dry mouth, slakiness
March et al., 1998	Serrraline	187	12	2 arms: serrraline, placebo	4 weeks	Parents, specific	Heart rate increased
Michelson et al., 2001	Atomoxetine (Strattera)	297	13	3 arms: MPH, atomoxetine, placebo	8 weeks	Parents, spontaneous	Cleaning, drumming, agitation, compulsive behaviors
MTA Cooperative Group, 1999	MPH	579	6	4 arms: MPH 15-60 mg t.i.d., behavior management, combination, community care	56 weeks	Drug-specific inquiry using Pittsburgh Side Effect Scale and Medication Visit Form Side Effect Scale	No table of adverse events listed: no placebo control for AEs; cases specified where dose could not be raised because of AEs
Riddle et al., 2001	Fluvoxamine for OCD	120	17	2 arms: fluvoxamine, placebo	6 weeks	Parents, spontaneous and general inquiry	All AEs listed whose prevalence is greater than 0%, but no listing 1 of cases whose AEs limited dose increases
RUPP Autism Network, 2002	Risperidone for autism	101	5	2 arms: risperidone, placebo	8 weeks	General inquiry plus drug specific inquiry	No table of AE vs. placebo, just one paragraph
RUPP Anxiety Study Group, 2001	Fluvoxamine for anxiety disorders	128	5	2 arms: fluvoxamine, placebo	8 weeks	General inquiry, probe not specified	All AEs listed for placebo and active: no listing of patients whose AEs limited dose increases

— Continued

TABLE 2
(Continued)

Author / Year	Medication Studied	No. of Subjects	No. of Sites	Treatment Arms	Duration	Elicitation Method	AE Report Table
Swanson et al., 2005	d-MPH	143	12	2 arms: d-MPH, placebo	4 weeks	General inquiry	Table of AE > 5% prevalence for placebo and d-MPH; listing of patients whose AEs limited dose increases
Tourette's Syndrome Study Group, 2002	Clonidine, MPH	136	11	Clonidine, methylphenidate, combination, placebo	8 weeks	Drug-specific inquiry (tics)	All AEs listed for placebo, clonidine, MPH, combination, and cases whose AEs limited dose increases
Wolraich et al., 2001	OROS-MPH (Concerta)	282	13	OROS-MPH (18, 36, 54 mg), placebo	4 weeks	General inquiry	No table of AE vs. placebo

Note: MPH = methylphenidate; OCD = obsessive-compulsive disorder; AE = adverse event

ing a stimulant treatment study (DuPaul, 1996; Greenhill et al., 2001), there have no psychometric studies to optimize AE inquiry methods or identify the best informant. This suggests that the methodology used to elicit and report AEs in children has been less tested than that used to ascertain the drug's efficacy (Laughren et al., 1994).

Drug safety monitoring does present a different set of challenges than efficacy research. Unlike tests of efficacy, which can pose a single specific research question and then test it, safety monitoring has to use a flexible vigilance method for detecting any safety issue, expected or unexpected, from mild to serious. This may explain why serious AEs reported since 1980 have appeared in small-number, anecdotal reports. Lack of agreement about exact definitions of AEs, passive elicitation methods, different measurement strategies, and variations in dimensions measured characterize these reports (Rabkin and Markowitz, 1986).

Do Reports of Adverse Events Impact on Clinical Practice?

For serious but rare AEs related to psychotropic drug use in children and adolescents, spontaneous, passive anecdotal reports gathered during the postmarketing phase have been the main sources of new AE information. Sparse participation by practitioners produces a biased pattern of AE reports (Hollister et al., 1994).

A bigger problem in pediatric psychopharmacology is how these reports—which are unprotected from the biases inherent in their collection—are used. A handful of patients experiencing a serious AE—often with too few subjects to establish a causal link between the medication and the AE—may effectively stop the use of a psychotropic drug on a national level. For example, practitioners stopped prescribing desipramine to treat ADHD after the report of four sudden deaths over a 3-year period (Biederman et al., 1995).

FDA Response to Lack Of Safety Data

During the past decade, the FDA encouraged more pharmaceutical research with vulnerable age groups, especially children, to determine safe doses of psychotropic medications for children. The goal was to provide age-specific dosing and safety information for the package insert that accompanies packaged drugs. Similarly, the package insert now includes common, infrequent, and rare AEs associated with use of the drug in children. To encourage private pharmaceutical companies to gather such information, Congress passed two initiatives. The first is the Pediatric Rule. If a company requests approval

for a new drug, or asks for a new indication for an already-approved drug, the FDA can require additional pediatric studies before approval is granted. The second method involves a 6-month extension of patent exclusivity under the Food and Drug Modernization Act (FDAMA) if the company does an additional study in children. More recently, FDAMA has been reauthorized by Congress in the Best Pharmaceuticals for Children Act.

However, the development of new elicitation and reporting methods of safety data needs to be encouraged. Studies of adult randomized clinical trials across seven different medical areas have revealed that safety data are given minimal space in the published paper and are not collected in a systematic manner (Ioannidis and Lau, 2001). Similarly, most of the multisite randomized clinical trials involving children also devoted less than a page to AEs. We agree with Ioannidis and Lau that new methods of active surveillance for adverse reactions are needed. Specifically, clinical investigators should be encouraged to use rigorous, standardized, drug-specific questionnaires rather than passive surveillance and general-inquiry methods.

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