Psychoactive Medication Prescribing Practices for U.S. Children: Gaps Between Research and Clinical Practice

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ABSTRACT

Objective: To determine national pediatric prescribing practices for psychotropic agents and to examine these practices in view of the available evidence concerning their safety and efficacy in this age group. **Method:** Prescribing data from 2 national databases based on surveys of office-based medical practices were determined and reviewed vis-à-vis available safety and efficacy evidence. **Results:** Data indicate that levels of psychotropic prescribing in children and adolescents are greatest for stimulants, resulting in nearly 2 million office visits and 6 million drug "mentions" in 1995. Selective serotonin reuptake inhibitors were the second most prescribed psychotropic agents, while anticonvulsant mood stabilizers (prescribed for a psychiatric reason), tricyclic antidepressants, central adrenergic agonists, antipsychotics, benzodiazepines, and lithium were also prescribed for a substantial number of office visits. Comparison of prescribing frequencies with available safety and efficacy data indicates significant gaps in knowledge for commonly used agents. **Conclusions:** Most psychotropic agents require further sustained study to ensure appropriate health care expenditures and vouchsafe children's safety. Recommendations for researchers, parents, federal agencies, and industry are offered as a means to accelerate the pace of research progress. *J. Am. Acad. Child Adolesc. Psychiatry,* 1999, 38(5):557–565. **Key Words:** pharmacoepidemiology, psychopharmacology, medication safety and efficacy, childhood mental disorders, prescribing practices.

Reports in this Special Section (Campbell et al., 1999; Emslie et al., 1999; Geller et al., 1999; Greenhill et al., 1999; Riddle et al., 1999; Ryan et al., 1999) have documented the safety and efficacy data available to inform psychoactive medication prescribing practices for children with mental disorders. As these and other reports (Vitiello and Jensen, 1997) have described, many psychotropic medications are used in youth with insufficient evidence of safety and efficacy. The possibility of substantial prescribing rates of psychotropic medications for children and adolescents and the lack of data on their effects (adverse or beneficial) in children is troubling because response to psychotropics in youth may be altered by developmental factors that may modify drug response (biological variability, pharmacodynamics, and pharmacokinetics) and other potential vulnerabilities in children (Vitiello and Jensen, 1995).

Media reports of increasing exposure of children to psychotropics highlight the concerns regarding the gap between what is known about these agents and how they are actually used. Remarkably, these same concerns apply not just to psychotropics but to all medications used in children: thus, 80% of all medication use in children is estimated to be "off-label" (American Academy of Pediatrics Committee on Drugs, 1996).

To date, studies of rates of pediatric psychopharmacological prescribing have largely been confined to geographically circumscribed settings (reviewed by Gadow, 1993), institutional or clinic settings (reviewed by Singh et al., 1998), or national studies of stimulant treatments alone (e.g., Zito et al., 1997). Such studies cannot be used

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to estimate the national rates of overall psychotropic use in the United States and are limited by their nonrepresentative nature (Kaplan and Busner, 1998; Kaplan et al., 1994; Safer, 1998; Zito et al., 1994).

Our review of the literature revealed that 2 studies have examined national data concerning psychotropic prescribing patterns in youth. Kelleher et al. (1989) used the 1985 National Ambulatory Medical Care Survey (NAMCS) to estimate national psychotropic use in patients younger than 18 years of age. They found that 1.5% of all office visits involved prescription of a psychotropic. Stimulants were, by far, the most frequently prescribed psychotropic medication. Prescription rates per pediatric office visit for psychotropic agents of all types were highest for psychiatrists by many orders of magnitude, followed by family physicians, pediatricians, and internists. (The absolute order among the nonpsychiatrist specialties varied somewhat, depending on the psychotropic agent). Because of the evidence for substantially increased pediatric prescribing in recent years (Safer et al., 1996), this study cannot be used to inform knowledge of current rates of pediatric psychotropic medication prescribing.

More recently, Safer and associates (1996) examined time-trend findings from several regional and national databases (2 large population-based databases, 3 pharmaceutical databases, and 1 physician audit) to estimate the prevalence of methylphenidate treatment in youth with attention-deficit hyperactivity disorder (ADHD) during the 1990s. They estimated that the number of U.S. children aged 5 to 18 receiving methylphenidate was 1.5 million in 1995. Of note, however, their report was restricted to methylphenidate only.

To address the gaps in our knowledge concerning current psychotropic medication prescribing practices for children and adolescents, we report below prescribing rate data drawing from 2 national surveys of office-based medical practices: the NAMCS and the National Disease and Therapeutic Index (NDTI). NAMCS is a large, national probability sample survey of patient visits to office-based practices, conducted annually by the National Center for Health Statistics. NAMCS is structured to collect data on office visits only. Prescription rates provided by NAMCS are not directly equivalent to the frequency of drug use per patient: because the unit of analysis is "visits" rather than patients, prescribing rates can be generalized to the frequency of medication prescription per office visit only. NDTI is a pharmaceutical marketing database available from IMS America Inc. (IMS America, 1995). In contrast to NAMCS, physicians in the NDTI survey report on all patient contacts (office or hospital; face-to-face or by phone). NDTI uses the term "mentions" to denote the times a drug is prescribed, refilled, recommended, or given to a patient as a sample.

Our analyses were conducted on NAMCS and NDTI data for the year 1995, specifically focusing on visits by children younger than 18 years to physicians for psychiatric reasons that also involved prescribing of a psychotropic medication.

METHOD

1995 NAMCS

A detailed description of the survey design, data collection procedures, and the estimation process is provided by Schappert (1994). The 1995 NAMCS had a multistage design, involving probability samples of primary sampling units, medical practices within primary sampling units, and patient visits within practices. For the 1995 survey, the data were obtained from a total of 36,875 patient record forms, provided by a national sample of 1,883 office-based physicians who participated in the survey (National Center for Health Statistics, 1997). The basic sampling unit was a patient visit to physicians engaged in office-based patient care and who were listed in master files maintained by the American Medical Association (AMA) and the American Osteopathic Association (AOA). Anesthesiologists, pathologists, radiologists, and federally employed physicians were excluded. The physician universe, so defined, was composed of 375,467 physicians in 1995. The 1995 NAMCS sample included 3,724 physicians. However, 1,137 physicians were excluded because they were retired or employed in teaching, research, or administration. Of the remaining 2,587 physicians, 73% (1,883) participated in the study.

Each record in the NAMCS data file represents 1 visit from the total sample of 36,875 visits. These data were weighted by an inflation factor ("the patient visit weight") on the 36,875 records, to produce national estimates of the annual frequencies of medication use and utilization of ambulatory medical care services. Calculations of annual visit rates were based on estimates of the population as of July 1, 1995, obtained from the U.S. Bureau of Census. An estimated total of 697,082,010 office visits made in the United States was obtained by this method. Physicians collected data by using 2 forms: the Patient Log and the Patient Record. Patient Logs sequentially listed patients seen in the offices during the assigned reporting weeks. During each visit, Patient Record forms were used to collect information on prescriptions and a limited number of patient variables (age, sex, reason for visit, *ICD-9* diagnoses, and concomitant drugs).

1995 NDTI

The 1995 NDTI was structured to collect data on patterns and treatment of disease in U.S. office-based medical practices. A 2-stage stratified, clustered, randomly drawn sampling design involving a precision estimation methodology was used. The basic sampling unit

was the physician workday. Physicians collected data on all patient contacts during 2 consecutive workdays every 3 months. The assignment of reporting days to physicians was randomized to ensure coverage of each workday. The physician universe consisted of specialties that primarily diagnose and treat disease (e.g., pathology and anesthesiology were excluded). For the 1995 survey, the sampling universe consisted of 333,621 physicians (IMS America, 1995). From these, the sample consisted of a panel of 2,940 office-based physicians, randomly recruited by phone from the AMA or AOA lists of nonsalaried physicians. After recruitment, physicians were mailed a case record book and were instructed to record all patient contacts (regardless of location) during the 2-day reporting period. Information reported by the physician included patient age, sex, location of contact, type of visit (initial or follow-up), *ICD-9* diagnosis, and drugs. The data were tabulated for each drug and therapeutic category. By convention, the term "mentions" is used to denote the times a drug is prescribed, refilled, recommended, or given to a patient as a sample. Data collected by representative physicians were then projected nationally.

Assessment of Psychotropic Use

Both databases were analyzed by 11 categories of psychotropics for patients younger than 18 years of age. Only the office visits made for psychiatric reasons (complaints, symptoms, or diagnoses), regardless of specialty, were included in the analysis. The category *stimulants* includes methylphenidate, pemoline, and amphetamine compounds. The *selective serotonin reuptake inhibitor* (SSRI) category includes fluoxetine, paroxetine, sertraline, and fluvoxamine. The *anticonvulsant mood stabilizer* category consists of carbamazepine and valproate, and the *central adrenergic agonist* category refers to clonidine and guanfacine. The *antidepressants* included in the nontricyclic antidepressant (non-TCA), non-SSRI category were venlafaxine, trazodone, and nefazodone. Bupropion was categorized separately because of its frequent use in treating ADHD.

TABLE 1
Number of Visits by Patients <18 Years Old for Psychiatric Diagnoses (1995 National Ambulatory Medical Care Survey)

Drug Category	*n*	Estimate	95% Confidence Interval
Stimulants	129	2,069,488	1,653,964–2,485,012
SSRIs	43	358,616	233,344–483,888
Central adrenergic agonists	26	202,032	24,444–279,820
Anticonvulsant mood stabilizers	25	318,971	89,769–548,173
TCAs	23	268,770	33,946–403,594
Benzodiazepines	15	218,523	25,920–411,126
Antipsychotics	9	71,863	6,871–136,855
Lithium	8	63,584	15,409–111,759
Bupropion	3	25,069	0–53,668
Non-TCA, non-SSRI antidepressants	3	15,345	0–33,690
Buspirone	2	10,692	0–25,510

Note: Estimates based on fewer than 30 records are considered unreliable. Data from National Center for Health Statistics (1997). SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

RESULTS

The estimated frequencies of the 11 groups of psychotropics are displayed in descending order in Tables 1 and 2. Table 1 displays the NAMCS data on the number of visits to office-based medical practices that involved prescription of a psychotropic for a psychiatric reason to youth by physicians of all types (specialist or primary care). This table projects the actual number of visits to yield national estimates of pediatric visits for psychotropics during 1995. Not surprisingly, the number of office visits resulting in a psychotropic prescription was the highest for stimulants, prescribed in nearly 2 million visits. SSRIs were the second most prescribed psychotropic, and the number of office visits associated with SSRI prescription was greater than those involving TCA prescriptions. Lithium and anticonvulsant mood stabilizers (valproate and carbamazepine prescribed for a psychiatric reason), central adrenergic agonists (clonidine and guanfacine), antipsychotics, and benzodiazepines were also prescribed during a substantial number of office visits. However, the number of visits for the remaining categories of psychotropics was too small for a reliable computation. For example, projection of *n* for non-SSRI, non-TCA antidepressants (trazodone, nefazodone, and venlafaxine) to the national estimates resulted in a 95% confidence interval of 0 to 33,690, indicating unreliability.

TABLE 2
Number of Drug Mentions (in Thousands) for Patients <18 Years Old With Psychiatric Diagnoses (1995 National Disease and Therapeutic Index)

Drug Category	*n*	Estimate in Thousands	95% Confidence Interval
Stimulants	1,410	5,971	4,501–6,895
SSRIs	316	1,083	776–1,390
TCAs	298	969	684–1,254
Central adrenergic agonists	132	431	167–598
Antipsychotics	108	355	204–506
Benzodiazepines	92	280	143–417
Anticonvulsant mood stabilizers	55	185	70–299
Lithium	51	175	67–283
Non-TCA, non-SSRI antidepressants	35	106	40–171
Buspirone	17	55	—
Bupropion	47	42	—

Note: Estimates less than 100,000 are considered unreliable. Data from IMS America (1995). SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

The 1995 NDTI data on the pediatric use of psychotropics are summarized in Table 2, which shows number of psychotropic mentions for a psychiatric reason by all types of office-based physicians. The greatest number of drug mentions occurred in the stimulant category, nearly 6 million during 1995. The number of mentions for SSRIs was about 1.08 million and that for TCAs was 0.97 million. Other noteworthy mentions included central adrenergic agonists, lithium, anticonvulsant mood stabilizers, antipsychotics, and benzodiazepines, but the *n*'s were smaller for these categories.

DISCUSSION

To our knowledge, this is the first study to document the extent of pediatric use of all types of psychotropics in the United States during the 1990s. Data from both surveys revealed that stimulants are the most frequently prescribed psychotropic agent in the United States during 1995, followed by the SSRIs. The concordance of results between NAMCS "visits" and the NDTI "mentions" lends greater credence and interpretability to our findings. Because NAMCS data are restricted to office visits and NDTI mentions are more inclusive of all types of physician–patient contacts, rates of NDTI psychotropic "mentions" are expectedly greater than those obtained from NAMCS "visits," generally 2-fold or more.

Examination of both databases indicates that the SSRIs are used more often than TCAs, suggesting a TCA-to-SSRI shift in youth during the 1990s as SSRIs came on the market (Safer, 1998). A similar shift is already well documented in adults (Olfson and Klerman, 1993). With the exception of stimulants and SSRIs, the *n*'s for the NAMCS database are too small for valid estimates (fewer than 30 records are considered unreliable for this survey). Nonetheless, NAMCS data tentatively suggest that central adrenergic agonists and TCAs were among the 5 most frequently prescribed psychotropics during pediatric office visits in 1995. This suggestion is strengthened by the support from the NDTI data, which found that TCAs were the third most frequently mentioned psychotropics and central adrenergic agonists ranked fourth in the frequency of mentions.

The NDTI data on anticonvulsant mood stabilizers do not correspond with that from NAMCS. Whereas these agents were ranked the fourth most frequently prescribed psychotropic class by NAMCS visits, they were ranked seventh by NDTI mentions. The likely low reliability of the mood stabilizer data was also suggested by comparisons of visits: mention ratios for commonly prescribed psychotropics. While the visits/mentions ratio is approximately 1:2 to 3 for stimulants, SSRIs, TCAs, and central adrenergic agonists, this ratio was reversed in favor of visits for anticonvulsants (1.7:1). Our anticonvulsant use results may have been confounded by difficulties discriminating their use as mood stabilizers versus their use for seizure disorders in one or both databases or by the need for more frequent office visits to monitor blood levels. We took great care to separate anticonvulsant use data for seizure disorders, but errors in physician coding of diagnostic and reasons for visit data cannot be excluded.

The visits/mention ratio for benzodiazepines is the lowest of all the ratios, 1:1.4, perhaps indicating that these medications are rarely prescribed or refilled without a specific office visit for that purpose, or possibly reflecting the unreliability of these estimates for infrequently prescribed medications. Yet taken together, the NAMCS and NDTI data suggest that antipsychotics and benzodiazepines are among the 7 most commonly used psychotropic classes, while other agents such as lithium, bupropion, buspirone, and new antidepressants are among the least prescribed psychotropic agents in children.

Our results should be interpreted with caution because these databases are limited in several ways. It is important to note that the sample size of children seen for psychiatric reasons was relatively small in both databases, resulting in lower reliability of estimates in youth than in adults (Zito and Safer, 1998). Reliability may be compromised by other factors as well. Thus, on the basis of comparisons of 1991 stimulant prescription activity from 3 databases, Safer et al. (1996) found that databases generally yielded differing estimates of drug prescription rates that varied with the source. While an examination of prescribing rate trends within a given database over the period of several years might increase confidence in overall prescribing patterns, space limitations precluded these analyses in this report.

These databases have other limitations as well. Derived estimates do not take into account the uncertain compliance of patients, nor other factors that are likely to affect prescribing practices (e.g., reliability of physician diagnoses, diagnostic indication, socioeconomic status, payer, etc.) (Olfson et al., 1998). Both databases do not provide information about the duration or dosage of the drug trials or treatment response, nor do they

TABLE 3
Scientific Knowledge in Pediatric Psychopharmacology Versus Frequency of Use: A Mismatch?

		Level of Supporting Data[a]				Estimated Frequency of Use	
Category	Indication	Short-Term Efficacy	Long-Term Efficacy	Short-Term Safety	Long-Term Safety	Rank in Descending Order (NAMCS)	Rank in Descending Order (NDTI)
Stimulants	ADHD	A	B	A	A	1	1
SSRIs	Major depression	B	C	A	C		
	OCD	A	C	A	C	2	2
	Anxiety disorders	C	C	C	C		
Central adrenergic agonists	Tourette's disorder	B	C	B	C	3	4
	ADHD	C	C	C	C		
Valproate and carbamazepine	Bipolar disorders	C	C	A[b]	A[b]	4	7
	Aggressive conduct	C	C	A	A[b]		
TCAs	Major depression	C	C	B	B	5	3
	ADHD	B	C	B	B		
Benzodiazepines	Anxiety disorders	C	C	C	C	6	6
Antipsychotics	Childhood schizophrenia & psychoses	B	C	C	B	7	5
	Tourette's disorder	A	C	B	B		
Lithium	Bipolar disorders	B	C	B	C	8	8
	Aggressive conduct	B	C	C	C		

Note: NAMCS = National Ambulatory Medical Care Survey; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; ADHD = attention-deficit hyperactivity disorder; OCD = obsessive-compulsive disorder.

[a] A = adequate data to inform prescribing practices; for efficacy and short-term safety: ≥2 randomized controlled trials (RCTs) in youth; for long-term safety: epidemiological evidence and/or minimal adverse incident report to the Food and Drug Administration. B = for efficacy and short-term safety: 1 RCT in youth or mixed results from ≥2 RCTS.

[b] Safety data based on studies of children with seizure disorder.

yield information on the prescribing patterns of physicians practicing outside of office-based settings.

The methodology of the 2 databases does not allow direct estimation of the number of children receiving psychotropic agents, thereby making it difficult to determine the public health impact of physicians' current prescribing practices. Nonetheless, in the absence of other national pediatric psychopharmacoepidemiological data, our results are informative of national patterns of pediatric psychotropic exposure. Patient-specific prescription and use rates would require confirmation with primary data collection sources directly from a national sample of children, rather than primarily relying on prescribing data provided by physicians.

Scientific Knowledge Versus Prescribing Practices: A Mismatch?

The implications of these findings for researchers and policymakers can be gleaned by examining our results in terms of current level of prescribing and safety/efficacy knowledge (Table 3). We divided the data into 3 levels (A, B, and C) based on the level of support for their use, as suggested by the International Psychopharmacology Algorithm Project (Jobson and Potter, 1995; Vitiello, 1997). Level A denotes support by 2 or more randomized controlled trials (RCTs), B-level data indicate support by at least one RCT, and C-level data are based only on informed clinical opinion, case reports, or open, uncontrolled trials. We adapted these levels for the

pediatric population by assigning level C to all adult-based controlled data in the absence of appropriate trials in children. Unlike Jobson and Potter, we also used these levels to inform the safety database; thus, the above definitions of levels A, B, and C were retained to depict the short-term safety database. However, because level A (2 or more RCTs) for long-term safety data may be neither ethical nor feasible, we relied here on the availability of pharmacoepidemiological evidence of safety with low incidence of adverse event reports to the Food and Drug Administration (FDA). The B-level data in the context of long-term safety implied that clinically significant adverse events were restricted to case reports and/or anecdotal reports, suggesting possible rare side effects, while level C referred to no data or minimal data supporting long-term adversity or safety.

These 3 levels depict our assessment of the currently available pediatric safety and efficacy data for 8 psychotropic groups, sorting groups by level of use. Inspection of Table 3 reveals a significant mismatch between the level of prescribing of nonstimulant psychotropics and the scientific knowledge regarding their use.

Safety

For psychotropics to be used in pediatric populations, a risk-benefit analysis that includes safety is crucial. The application of existing safety databases for most psychotropics to the pediatric population is limited, however. Despite the increasing emphasis on inclusion of special populations, premarketing RCTs do not generally include a sufficient number of children or adolescents. Consequently, their results are not generalizable to the pediatric populations that may be exposed to the drug after approval.

In addition, limitations inherent in RCT methodology diminish its value in determining safety of psychotropics in youth. First, premarketing RCTs are not typically large enough (n = 3,000–4,000) to detect a rare adverse drug event (ADE) even in adults (Lewis, 1981). Second, the duration of a typical RCT (less than a year) is too short for detection of long-term ADEs or those that have a long latency period. Third, exclusion of comorbid conditions and concomitant medication decreases the generalizability of safety results from RCTs. Finally, RCTs are usually used for the indications for which the efficacy is being studied, not for the actual evolving use of the medication. Within RCTs, the clinical condition may be narrowly defined and atypical cases excluded.

Given the limitations of the available safety data as well as the companion difficulties entailed in mounting sizable RCTs in children and adolescents, we suggest that knowledge of short-term safety data in pediatric psychopharmacology be based on evidence from a minimum of 300 youths exposed to the pharmacological agent during controlled clinical trials. However, this will only detect ADEs occurring more frequently than 1 in 100 exposed youth, and rare but serious ADEs (such as possible desipramine-related cardiac mortality) may be seldom noted (Biederman et al., 1995). Thus, RCT data in youth must be augmented by long-term pharmacoepidemiological studies in youth as well as experimental data from developing animals (Jensen et al., 1994; Zito and Riddle, 1995). Longitudinal pediatric data are especially needed, because most psychiatric disorders of childhood and adolescence tend to be chronic, frequently requiring long-term pharmacological treatment. In addition, long-term risks associated with psychotropics may be underrecognized, underreported, and understudied. While psychopharmacoepidemiological data are less rigorous than those from RCTs, such data may be more representative of the general pediatric population, hence more generalizable (Zito and Riddle, 1995).

In the absence of long-term safety data for most psychotropics in youth, the unique developmental effects of psychotropics in children and adolescents are not known. Thus, it must be determined whether long-term psychotropic treatments produce sustained improvement and positively impact the course of disorders (e.g., decreased kindling and reduced behavioral sensitization in bipolar children by mood stabilizers) or whether long-term use causes developmental (particularly neurodevelopmental) toxicity.

To some extent, the nonpsychiatric literature can be a useful, albeit limited source of safety data for psychotropics that are also used for nonpsychiatric reasons. For example, carbamazepine (CBZ) is used both as an anticonvulsant and as a mood stabilizer. A review of the pediatric epilepsy literature reveals that CBZ is generally well tolerated over the long-term and its use is associated with few cognitive problems. However, the neurological literature may not address the issues of CBZ-induced mania and possible differential effects of this agent in children with seizures versus those with bipolar disorder. Whereas the epilepsy literature suggests that CBZ use is associated with few behavioral or cognitive side effects

(Herranz et al., 1988), there are at least 4 case reports of CBZ-induced mania in the child psychiatric literature (Bhatara and Carrera, 1994; Myers and Carrera, 1989; Pleak et al., 1988; Reiss and O'Donnell, 1984), as well as an open study in persons with mental retardation suggesting that the "pure" psychiatric use of CBZ is more frequently ($p < .05$) associated with adverse behavioral effects than the use of CBZ as an anticonvulsant (Friedman et al., 1992).

Relatedly, the authors of a controlled study of CBZ in children with aggressive behavior reported the frequency of side effects was higher with CBZ than with lithium in similar populations (Cueva et al., 1996). The possibility that CBZ may cause behavioral side effects more frequently in youth with bipolar disorders than those with seizure disorders can only be tested by including data from children and adolescents with bipolar disorders. Such considerations suggest important constraints on the generalizability and excessive reliance on nonpsychiatric patient studies for inferences about pediatric psychiatric populations.

Specific Gaps in Safety Data. There appears to be increasing interest in and use of the SSRIs and novel antipsychotics in the 1990s, as evidenced by the reported TCA-to-SSRI shift during the 1990s (Safer, 1998). But because these agents have been introduced only during the past decade, much still needs to be learned about their safety, particularly the effects of their long-term administration in youth. Long-term safety data for both of these new psychotropic categories in youth are still sparse, further highlighting the need for systematic efforts to address these knowledge gaps.

Another major area of deficiency of safety knowledge concerns the increasing use of combined therapies (polypharmacy) in the face of almost no data on drug-drug interactions in children. For example, several fatalities allegedly caused by clonidine-methylphenidate interactions were reported to the FDA in 1995 (Popper, 1996; Swanson et al., 1996). Yet even today, systematic data on the combined use of clonidine and methylphenidate remain sparse. Similarly, although SSRIs are known to have potential for several drug-drug interactions in adults, interactions of SSRIs with various drugs used in pediatric patients remain poorly studied.

Efficacy

Ideally, not only should the efficacy of psychotropics be supported by a A-level data (>2 RCTs), but evidence for the long-term efficacy of agents should also be available. This point is illustrated by reviewing the research evidence for pediatric use of 2 most frequently used classes: stimulants and SSRIs. A-level data are available for short-term efficacy and safety of stimulants. Although the data on long-term efficacy of stimulants are limited, outcomes from 4 longer-term trials are just now becoming available (e.g., Arnold et al., 1997; Gillberg et al., 1997; Hechtman and Abikoff, 1995; Horn et al., 1991).

The efficacy of SSRIs in depressed youth is supported by one RCT (level B), but the use of SSRIs in obsessive-compulsive disorder (OCD) is supported by A-level data. By contrast, there are no controlled data supporting the use of SSRIs in pediatric anxiety disorders other than OCD. Thus, additional short- and long-term efficacy data are needed for SSRIs, because the disorders for which SSRIs are used tend to be chronic or recurrent (e.g., depression and anxiety disorders).

Specific Gaps in Efficacy Data. Given the inadequacy of efficacy data for most nonstimulant psychotropics, studies are needed for the majority of agents. However, efficacy data appear to be most urgently needed for SSRIs, mood stabilizers, and novel antipsychotics, as the level of use of these psychotropics appears to be highest in the growing list of psychotropics used in youth. In contrast to adult psychopharmacology that is focusing on differential efficacy and speed of onset of these categories of psychotropics, pediatric psychopharmacology needs basic studies of the efficacy of these agents.

Conclusion

While the pharmaceutical industry is showing increased interest in conducting psychotropic medication trials in children and adolescents, the rate of progress is likely to be slow without sustained federal leadership and support. To address these difficulties, the FDA has made, in recent years, a comprehensive effort to increase the number of new drugs with clinically significant use in pediatrics that carry adequate labeling for pediatric use. In 1994, the FDA requested the pharmaceutical industry to survey the available data on the efficacy and safety of marketed medications in children for the purpose of determining whether those data are sufficient to support additional pediatric use information in the labeling (FDA, 1994). More recently, the FDA has proposed new regulations requiring manufacturers that develop new chemical entities for therapeutic indications to submit data relevant to the efficacy and safety of

these compounds in pediatric populations (FDA, 1997). These data will have to be provided before the approval of the drug to enter the market or soon after its approval. On a case-by-case basis, these data will not be required for compounds that are unlikely to be used in children. If approved, these regulations will significantly increase the authority of the FDA to mandate research in children for future drugs. Based on current regulations, the FDA already has the authority to require manufacturers of marketed drugs to provide safety and efficacy data in children in certain circumstances.

Several institutes of the National Institutes of Health (NIH) are also actively addressing the problems of lack of information. Thus, the National Institute of Mental Health and the National Institute of Child Health and Human Development of the NIH have developed pediatric pharmacology research networks, each consisting of 7 or more regional research units focused on safety and efficacy of medications in children. Also, the NIH has recently implemented new guidelines that *presume the inclusion of children in all studies of human subjects* (including clinical trials), *if* the condition or disorder under study is found in children and *if* there are no overriding ethical, regulatory, or safety issues barring the inclusion of children in the study.

Despite signs of progress, it will be important that industry, NIH institutes, pharmacology investigators, and families work closely together to address these knowledge gaps. We offer several straightforward, though possibly controversial recommendations:

First, whenever possible, practitioners and professional associations should encourage the enrollment of children in responsibly conducted rigorous clinical trials, rather than simply provide the medications in the absence of supporting evidence. This may help address the difficulties in recruiting sufficient subjects for clinical trials, as well as mitigate the ongoing prescriptions of medications that may be neither safe nor effective.

Second, the NIH institutes should strategically target the development of short-term safety and efficacy studies where knowledge gaps are the greatest (e.g., SSRIs, mood stabilizers), levels of prescribing are the highest (e.g., SSRIs), and/or potential for toxicities with long-term exposure most prominent (e.g., novel antipsychotics, SSRIs).

Third, the FDA should continue its efforts to introduce the recently proposed new regulations mandating pediatric studies for new pharmacological entities and pursue the full implementation of its regulatory authority to encourage the development of clinical trials in children and adolescents. For example, for agents that appear likely to be used in children and adolescents who have psychiatric illnesses comparable with those in adults, the pharmaceutical company might be asked to start the necessary pharmacokinetic, dose-ranging, and short-term efficacy studies in pediatric patients before FDA approval is given for the medication indication in adults.

Fourth, for companies that voluntarily develop medications and indications for children and adolescents, extension of patent life may help offset the costs of such studies and the potential liability the company may bear.

Fifth, long-term safety and efficacy will not likely be supported by industry on a voluntary basis; thus, responsible agencies within the federal government (FDA, NIH) should ensure that issues related to long-term safety and efficacy of psychotropic agents are systematically examined. The FDA's MedWatch system (Kessler, 1993), which allows physicians to report adverse events on a voluntary basis, may be insufficient to track fairly common behavioral adverse events that easily may be confused with the manifestations of the psychiatric disorder itself. Thus, more comprehensive assessment and monitoring data are needed, perhaps similar to tumor registries or ongoing efforts in pediatric and family practice research networks.

Finally, longitudinal, naturalistically gathered clinical data alone will be insufficient to fully address the possibility of drug toxicities, particularly behavioral side effects. Thus, experimental data constitute crucial evidence. Strategic studies with animal species may be required to specifically examine the effects of psychotropic agents on brain maturation during critical periods of neurodevelopment.

While simply gathering safety data may seem pedestrian from a narrow scientific perspective, it is a public health imperative, and this responsibility must be shared by NIH, FDA, scientists, and informed consumer groups. The lack of safety and efficacy data for psychotropic medications is of general concern, not just for parents of children with mental illness and their physicians, but for all with a stake in the future of the nation's children. These initiatives, if appropriately pursued, should allow us cautious optimism for pediatric psychopharmacology, and more importantly, for the futures of children with mental illness.

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