Services and Prevention: Pharmacoepidemiology of Antidepressant Use

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Between 1988 and 1994, data from 3 large sites revealed a 3–5 fold increase in the prevalence of antidepressant (ATD) treatment for U.S. youths aged 2–19 years. In 1994, the ATD prevalence for youths of this age ranged from 13 per 1000 (in the HMO) to 18 per 1000 (in 2 state Medicaid systems). Males predominated in the 10–14-year-olds treated with ATDs, whereas females predominated among 15–19-year-olds. Caucasians were more than twice as likely to receive ATD therapy than their African-American counterparts. Primary care providers were the major source of ATD prescriptions for youths. The leading diagnoses in primary care were ADHD followed by depression, whereas the diagnostic order was reversed for youths who received psychiatric services. This review provides details concerning these patterns and trends in ATD treatment of youths from community-based clinical data sources. In addition, the role of these data in an expanded, comprehensive psychotropic knowledge base is discussed. Finally, the implications of an expanded knowledge base for ATD treatments are discussed in regard to generating research questions on effectiveness and safety and to improve treatment consensus within a public-health perspective. Biol Psychiatry 2001;49: 1121–1127 © *2001 Society of Biological Psychiatry*

Key Words: Pharmacoepidemiology, child and adolescent psychopharmacology, consensus development, mental health services, antidepressants

Introduction

This paper reviews findings from a pharmacoepidemiologic analysis of antidepressant (ATD) utilization data and attempts to expand the current knowledge base for antidepressant use among children and adolescents. In addition, the paper discusses the ways in which an expanded theoretical model will give a more complete evaluation of pediatric psychopharmacologic medications by emphasizing the post-marketing phase of drug development. Part 1 provides a review of our study findings on ATD medication trends. The goal of this review is to illustrate pharmacoepidemiologic analysis by showing the changes in ATD utilization among U.S. youths for a 7-year period from 1988–1994 and the sociodemographic and clinical factors associated with ADT use. Part 2 proposes to expand the psychopharmacologic medication knowledge base. In part 3, the implications of the ATD utilization findings are discussed in terms of the proposed model and how such data may influence the building of a consensus in the following areas: 1) identifying psychopharmacologic patterns requiring new research on effectiveness including off-label use; 2) identifying effective treatment strategies in community-based practice settings; 3) raising questions about the safety of multiple medications, potential developmental consequences of long-term treatment, and the occurrence of rare adverse events.

I. Antidepressants among Children and Adolescents

Information sources for community-based estimates of pediatric psychopharmacology are quite limited (Zito and Safer 1997). Limitations include the fact that: 1) data sources are proprietary, consequently expensive, and primarily of interest for marketing purposes; 2) counts are usually based on prescription sales rather than youths receiving treatment; and 3) federally sponsored (public access) treatment surveys are not designed to sample an adequate number of youths. Research efforts to correct this paucity of data include efforts by our pharmacoepidemiology group to describe psychotropic medication patterns from 3 community-based sites. Two sites provided information based on Medicaid reimbursement claims data for medication and services. The third site is a group model HMO with computerized medication and service records. The computerized files, representing more than 800,000 youths eligible for services per year, were used to construct a data base covering a 10-year period for youths less than 20 years old, so as to permit analysis of the sociodemographic and clinical correlates of psychopharmacologic medication (Zito et al 1999). The following section briefly reviews data on antidepressant utilization, which is the

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The present discussion has the following objectives: 1) To show the changes in ATD utilization for U.S. youths for a 7-year period from 1988–1994; 2) To characterize the prevalence of ATD use in terms of age, gender, and ethnicity of youths aged 2–19 years old; 3) To characterize ATD utilization in terms of health service system factors, specifically, physician specialty (primary care versus psychiatry) and the relationship of physician specialty to the diagnoses associated with ATD utilization. These data illustrate the role of descriptive epidemiologic data in characterizing medication use in community settings and will be used in part 3 of this paper to show how such data expand the knowledge base for pediatric psychopharmacology.

Method

Three large data sets were assembled from 2 types of health care systems. The first 2 are outpatient data sets from 2 geographically distinct Medicaid populations, 1 in a midwestern state and 1 in a mid-Atlantic state. The third set of data comes from a group-model health maintenance organization (HMO) serving a predominantly employed population in the Northwest region of the United States. Their total enrollment for ages 2 through 19 in 1988 and 1994, respectively, was as follows: Midwestern Medicaid (MWM), 542,431 and 578,401; mid-Atlantic Medicaid (MAM) 147,372 and 200,566; and group-model HMO (HMO) 110,900 and 121,332. These populations included both continuous and noncontinuous enrollees for each study year. Nonwhites were over-represented in the Medicaid populations and were under-represented among HMO enrollees according to general statistical profiles of the settings (Zito et al 1998b).

Study Measures

Data for the study were obtained based on the occurrence of a computerized prescription record for a psychopharmacologic medication during 7 one-year intervals from 1988 through 1994. Antidepressants (ATD) were categorized into 3 sub-classes: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and "Other antidepressants" (Other ATDs). The measures assessed were: 1) Total ATD prevalence (defined as the frequency of persons with 1 or more HMO pharmacy records or Medicaid prescription claims for an ATD medication per 1000 enrolled youths). 2) ATD sub-class prevalence (TCAs, SSRIs, Other ATDs). 3) Time trends using data from 7 cross-sectional annual datasets from 1988 through 1994. 4) Age-specific ATD prevalence for the 4 age strata according to US census categories (aged 2–4, 5–9, 10–14 and 15–19). 5) Gender-specific ATD prevalence is reported in terms of the male:female prevalence ratios. 6) Ethnicity data (available only for the Medicaid population) is reported in terms of the Caucasian:African-American medication prevalence ratios. 7) Clinical diagnoses and provider specialties associated with ATD utilization are reported for the 2 state Medicaid populations. The International Classification of Disease 9th edition (ICD-9) diagnosis codes, which are consistent with those of DSM-IV, were grouped into 5 of the most common diagnostic categories: Attention deficit hyperactivity disorder (ADHD), depression, anxiety, conduct and adjustment disorders. Based on their service use history from the claims data file, youths were then categorized by provider specialty into four mutually exclusive groups: any psychiatry service, only a primary care service (i.e., no psychiatry), other specialty service (i.e., neither psychiatry nor primary care), or missing. Those with any psychiatric services included youths receiving *solely* psychiatric services and those receiving psychiatric in addition to primary care or other specialty services. Comparisons were made between youths seen in primary care only and those seen in psychiatric services in terms of their use of ATD medications (total and sub-class). 8) The major diagnostic correlates of ATD use. Statistical analysis consisted of the population-based prevalence and 95% confidence intervals for total and sub-class ATD use according to health care site.

Results and Interpretation

ANTIDEPRESSANT PREVALENCE TRENDS: TOTAL AND SUBCLASS. There was a 2.9-fold increase from a total ATD prevalence among youths 2–19 years old during the 7-year period from 1988 through 1994 (from 6.7 per 1000 in 1988 to 19.1 per 1000) for MWM and a 4.6-fold increase for MAM (from 3.9 per 1000 to 17.8 per 1000) (Table 1). The HMO population, however, had a rate similar to MAM in 1988 but was 28% lower than the Medicaid population by 1994. Lower psychopharmacologic utilization is typical among non-Medicaid youths because Medicaid youths include those with disabilities (Supplemental Security Income status) and those from foster care settings, factors that have been shown to account for higher psychopharmacologic utilization rates (dosReis et al in press).

ATD subclass prevalence was then examined according to health care site. Despite widespread promotion of SSRIs, 1994 data reveal that over half of ATD use was attributable to the TCA subclass. Across the 7-year period, SSRIs demonstrated a very steep increase (19-fold), an order of magnitude greater than that of the leading subclass, TCAs. This increase in use could be anticipated for a recently marketed medication with a new mechanism

Table 1. Proportional Utilization of Antidepressants in MWM Youths in 1994 According to the 5 Leading Psychiatric Diagnoses for Antidepressant-treated Youths with Primary Care Services Compared with Those with Psychiatric Services

Psychiatric Diagnosis	Primary care (n=3354)								Psychiatric services (n=2622)							
	Any ATD		TCAs		SSRIs		Other ATD		Any ATD		TCAs		SSRIs		Other ATD	
	n	col%*	n	row%*	n	row%	n	row%	n	col%	n	row%	n	row%	n	row%
ADHD	1448	43.2	1274	88.0	207	14.3	91	6.3	823	31.4	603	73.3	262	31.8	126	15.3
Depression	1178	35.1	541	45.9	708	60.1	176	14.9	1452	55.4	573	39.5	1021	70.3	339	23.3
Anxiety disorder	451	13.4	195	43.2	273	60.5	78	17.3	519	19.8	201	38.7	375	72.3	145	27.9
Conduct disorder	365	10.9	255	69.9	124	34.0	43	11.8	454	17.3	255	56.2	237	52.2	98	21.6
Adjustment disorder	291	8.7	160	55.0	127	43.6	58	19.9	774	29.5	359	46.4	471	60.9	171	22.1

* Column and row percents exceed 100% because youths may have had more than 1 diagnosis (col) or more than 1 ATD sub-class (row).

of drug action and promising a markedly improved side effect profile relative to the standard treatment (TCAs). Most of the increased utilization occurred between 1991 and 1994.

SOCIODEMOGRAPHIC CORRELATES: AGE-, GENDER- AND ETHNICITY-SPECIFIC PREVALENCE. ATD prevalence trends were analyzed according to age group among youths from MWM and MAM. ATD prevalence correlated with increasing age in MWM, whereas in MAM, 10–14-year-olds were the most common utilizers. Preschool age youths (2–4 years old) had a 1.3- to 2.2-fold increase from 1991 to 1995, a finding that generated considerable interest when reported last year (Zito et al 2000). MWM data from 1994 showed that ATD subclass use varied in relation to the age group of the youths: SSRI use increased with age while TCA use decreased with age. Sharp differences in the gender ratios were observed across the current study period (1988–1994) when age was factored into the analysis. Males predominated among 10–14-year-olds in all 3 health care settings in 1988 with slight increases for MAM and MWM in 1994. For 15–19-year-olds, females predominated among MWM and HMO youths and the gender ratio was about equal in MAM. The influence of ethnicity on ATD prevalence in 1994 was measured in terms of Caucasian to African-American prevalence ratios, which ranged from 2.3 for MAM to 2.6 for MWM among 2–19-year-olds. This excess use among Caucasians is consistent with our earlier findings for the leading psychotropic medications among 5–14-year-old Medicaid youths (Zito et al 1998a).

CLINICAL CORRELATES: DIAGNOSIS AND PHYSICIAN SPECIALTY. To characterize the health system factors associated with ATD use for 1994, we identified service claims with psychiatric diagnosis and provider specialty codes for 5,976 of the 9,647 MWM youths with ATD medication records. Of the 5,976, 72.1% received primary care services and 27.9% received psychiatric services. Among youths with a psychiatric diagnosis, 54.9% had only 1 diagnosis coded during the study year, 26.8% had 2 and the remainder had 3–10 diagnoses. Overall, the proportion seen by primary care was 1.8 times greater than the proportion with psychiatric services.

When ATD use was related to provider specialty, a state by specialty interaction was observed: whereas in MWM ATD use was attributable to youths solely with primary care services (72%), in MAM the bulk of ATD use occured in those with psychiatric services (58%). Table 1 shows the relative pattern of the most common psychiatric diagnoses associated with total and sub-class ATD use according to whether youths had primary care services or had psychiatric services alone or in combination with primary care or other specialty services. Whereas the leading diagnosis associated with the use of an ATD among those with primary care services was ADHD followed by depression, the leading diagnosis associated with an ATD among those with psychiatric services was depression followed by ADHD. Regardless of specialty, depression and anxiety were highest among SSRI users while ADHD and conduct disorder were highest among TCA users. Collectively, the subclass patterns show that SSRIs were predominant for depression without ADHD, whereas TCAs were dominant for the other diagnostic categories assessed. Interestingly, TCAs were associated with a diagnosis of nocturnal enuresis in less than 1% of the diagnosed youths in 1994. Overall, these findings show a substantial expansion in use of ATDs for youths, which is not explained by the modest clinical trial findings among prepubescent youths (Zito and Safer 2001). The present findings should be considered in light of the knowledge base of psychopharmacology, but first the knowledge base itself is discussed below.

II. Expanding the Knowledge Base

Textbooks of pharmacology offer the clinical reader a framework for the drug development process, a process of systematic studies to evaluate medication efficacy and

safety in humans (Nies and Spielberg 1996). Typically after animal studies, 3 phases of drug development are mandated by Food and Drug Administration (FDA) regulations (Anonymous 1995). Studies are conducted in very small samples of volunteers (phase 1) or individuals with a disorder (phase 2) for initial effectiveness, safety and dose finding. Phase 3 studies mandate randomized double blind controlled clinical trials, typically in 500–3,000 individuals, from which information is derived to establish both efficacy[1] and safety. Marketing generally follows phase 3 studies if the assigned FDA advisory panel recommends approval of the labeling information for the indication for which the study was undertaken. A fourth phase, post-marketing surveillance, has been discussed, debated and partially implemented during the past 3 decades (Zito and Riddle 1995). Phase 4 surveillance of effectiveness and long-term safety produces limited knowledge in contrast to the body of information that is generated from Phase 3 clinical trials. With respect to certain areas of methodology and infrastructure, it is currently inadequate to achieve its goals (Nelson 2000).

Pharmacologic treatment evaluation for pediatrics has received attention in the past few years partly because so much medication use in children (75%) represents off-label usage [Committee on Drugs 1996; Laughren 1996; Vitiello and Jensen 1997]. Researchers have criticized the current model (Jensen et al 1994) as too narrow a research database to encompass information on effectiveness. As a consequence of this concern, major federal initiatives have been undertaken to develop pediatric labeling information for medications (Anonymous 1994) and for clinical trials in pediatric psychopharmacology (Anonymous 1997) including partnering between the pharmaceutical industry and the National Institute of Mental Health (NIMH). These efforts will, no doubt, expand the clinical trial database on psychopharmacologicals in children and adolescents. However, further expansion of phase 3 information on efficacy and safety from short-term, parallel group clinical trials falls short of a complete knowledge base for pediatric psychopharmacologic drug evaluation (Vitiello in press).

A comprehensive knowledge base for psychopharmacology requires data from studies that utilize a variety of research study designs and are derived from usual practice settings that are specially equipped with the necessary infrastructure. This infrastructure will permit collaborative teams of drug development specialists, epidemiologists, psychopharmacologists and mental health specialists to assess short and long-term outcomes of both a beneficial and an adverse nature. These assessments should have a public health orientation, i.e., establish long-term effectiveness and safety of medications, monitor the quality of medications and other mental health treatment services and evaluate preventive intervention strategies. This approach is most consistent with an underlying psychobiological model of the etiology and treatment of mental and behavioral disorders (Engel 1977), a model that serves primary care and psychiatric treatment settings equally well while welcoming the service and prevention specialists to incorporate their unique contributions to the model. The inverted triangle (see Figure 1) illustrates the expanding knowledge base for a psychopharmacologic agent as its time on the market increases, showing the broadening exposure to additional individuals, many of whom would have been ineligible for the phase 3 trials, and reflecting expansion to off-label use. The increase in the size of the treated population in the usual practice setting gives the opportunity for 1) descriptive data on duration of treatment, medication combinations, dosage, and reasons for treatment; 2) analytic studies of effectiveness in cohorts on long-term therapy and comparisons between new and standard treatments; 3) case control or historical cohort studies of safety related to rare occurrences (less than 1 per 10,000 exposed individuals), e.g., pemoline and associated hepatic toxicity (Safer et al 2001); 4) adverse events related to child development, e.g., effects on cognitive and social development; 5) satisfaction with treatment according to the family and the patient; 6) opportunities for ad hoc research studies (e.g., outcome studies, surveys and randomized trials) as suggested by descriptive studies which identify treatment patterns in need of further assessment; 7) analysis of mental health treatment studies that integrate non-pharmacologic treatment interventions from community settings with the details of medication treatment from these settings; and 8) drug registry systems to

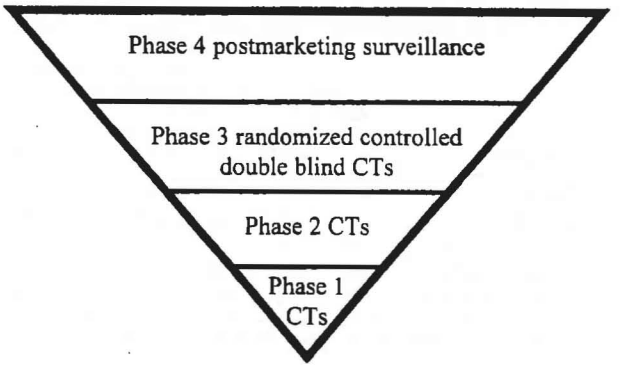

Figure 1. Model of a comprehensive psychotropic medication knowledge base with a public-health perspective.

[1]The term efficacy generally refers to evaluation of a medication effect under the ideal conditions of the randomized clinical trial for maximum internal validity. The term effectiveness is used to refer to how well the medication produces its effect under non-ideal, real world conditions, i.e., typical of the usual practice setting, to maximize representativeness, i.e., external validity.

assess high risk protocols among small numbers of treatment-resistant individuals (Vitiello in press).

III. An Expanded Knowledge Base for Building a Treatment Consensus

The implications of the ATD utilization findings are now discussed. The goal of this discussion is to show how such data could influence the building of a consensus in the following areas: 1) identifying psychopharmacologic patterns requiring new research on effectiveness including off-label use; 2) identifying effective treatment strategies in community-based practice settings; 3) raising questions about the safety of multiple medications, potential developmental consequences of long-term treatment, and the occurrence of rare adverse events. Each of these areas will be addressed below.

Identifying Psychopharmacologic Treatment Patterns

Identifying community treatment patterns is the goal of descriptive pharmacoepidemiology. The present data from 3 large community sites reflect practice among individuals enrolled in 2 systems—HMO for youths with employed parents and Medicaid for poor youths or youths in special circumstances (disabled or foster care youths). Several limitations apply: First, they do not represent the universe of community treatment settings; notably excluded are treated youths with commercial insurance, e.g., IPA or PPO coverage. Therefore, while very large and showing good overall consistency, the data are insufficient to generalize to the nation. Second, the geographic, income and ethnic disparities are not comparable across the 3 sites and this precludes more refined analyses in which it is necessary to account for all 3 crucial factors in modeling social factors related to medication patterns. Finally, these data are derived from an ad hoc research study and more recent data and analysis are not available without explicit funding—a situation not likely to be remedied by the current research agenda.

Several questions that consensus building should include come from monitoring psychopharmacologic treatment patterns. Among these are the following:

1) What benchmarks should be used to assess the extent of treatment, i.e., prevalence rates? While the need for regular psychopharmacologic reporting of information to better characterize mental health services is beginning to be recognized (Zito in press), the field lacks adequate infrastructure.
2) What is the relationship between descriptive data and appropriateness? Some researchers view the increased use of SSRIs in primary care settings with alarm (Rushton and Whitmire 2001). However, inferring inappropriate use from claims data should be viewed with caution. In some clinical areas inappropriate use is clear: low immunization rates clearly deserve attention whereas rising psychopharmacologic rates warrant further study to establish time in treatment, reasons for treatment, satisfaction with treatment and functional improvements. This spectrum of outcome studies will help to characterize regional and national variations in long-term benefits and problems not assessed in the phase 3 clinical trials. As currently constructed, prevalence data are oversimplified by arguments that imply that similar rates in a region imply appropriateness or that low rates imply appropriateness.
3) What is implied by a large increase in medication utilization within a short time period? For policy analysts, large increases in utilization may suggest that individuals have increased access, availability, and acceptability whereas for clinicians they may suggest increased case identification, broadened clinical criteria (e.g., ADHD criteria from DSM-IV compared with the narrower criteria of DSM III) or increased off-label use.

The prominent use of ATDs among youths with a diagnosis of ADHD in the cohorts should be further investigated. These findings are hypothesis-generating and can be used to justify studies with prospective designs, which are addressed in the next section. Similarly, multiple medication use can be characterized by analyzing large cohorts using administrative data and the results are useful to suggest prospective studies on the effectiveness and safety of, as well as satisfaction with, these combinations.

The 2.2-fold greater prevalence of an ATD for Caucasians relative to African-American youths shown in this study invites questions concerning the clinical significance of the variation. Specifically, does the ratio reveal over-utilization by Caucasian youths or under-utilization by African-American youths or are they reflective of culture-based differences in problem identification and treatment intervention? Interestingly, when research leaders were asked to guess the likely psychopharmacologic medication prevalence disparity between Caucasian and African-American youths, most guessed incorrectly, i.e., that African-Americans were more likely to receive medication. Their response demonstrates the importance of an empirical basis for assessing population-based trends rather than surmising these trends from tertiary care referral settings where highly selective patient experience can skew researchers' impressions. Health disparities have become the focus of national concern recently, e.g., the Surgeon General's initiative on health disparities (Department of Health and Human Services 2000). The challenge

of such broad campaigns is to derive a research agenda suitable for the specific health questions (e.g., behavioral or emotional) and for each population (e.g., preschoolers).

Identifying Effective Strategies for Community Settings

When descriptive epidemiology is used to generate hypotheses for additional study, the question now turns to the mechanisms available for further study. One approach is to extend randomized clinical trials into community treatment settings. These study findings would capture outcomes for populations previously excluded from efficacy studies. However, they will not be able to address equally compelling questions that relate to long-term effectiveness and long-term safety. Such questions require a mix of study designs that may loosely be termed outcomes research. Typically they are observational studies (non-experimental) embodying a case-control or cohort study design. Cohort designs will require time, training, and funding—in short, an infrastructure—so as to characterize effectiveness in the usual practice setting. But other designs will also be valuable: ad hoc survey designs would be valuable to understand what African-American youths relative to Caucasian youths are experiencing in terms of case referral, acceptability of treatment and outcomes of both non-pharmacologic and pharmacologic treatments. Ideally, this study would be conducted in collaboration with the community-based school system. Such collaborations have produced valuable information regarding racial disparities in the utilization of methylphenidate for the treatment of ADHD (LeFever et al 1999; Safer and Malever 2000) but could be further developed for outcomes assessment.

Monitoring for Medication Safety

Long-term safety questions are rarely answerable by means of randomized trials for ethical and methodological reasons. Thus, routine active surveillance is necessary and population-based epidemiologic methods can provide rigorously developed evidence for the causal association of a medication exposure with an adverse event in humans. Current methods for monitoring drug safety in the US are based on a voluntary, (passive surveillance) signal-detection system and are far less developed than systems in other countries with full enumeration of the populace and national health insurance systems (Nelson 2000). As an alternative to the existing system, a demonstration project of a national reporting system that monitored usage from specially organized community settings could address child safety questions in a variety of ways. First, if a safety question is answerable with variables that exist in administrative claims data then, for relatively little money and time, questions could be assessed in a case control or historical cohort model. Examples include: 1) whether high dose desipramine was associated with sudden unexpected death among youths treated for ADHD [a study that takes vastly more resources and time with traditional case control methods (Walsh 1999)] and 2) how long a time period would be required to find an association between pemoline and liver transplants? Finally, safety monitoring could require special mechanisms for controversial treatment protocols. For example, the continuing use of pemoline in the face of widespread public health concerns and requirements for informed consent could be justified by intense surveillance provided by a case registry to monitor outcomes. Concerns about complex multidrug regimens consisting of, for example, 3 or more psychopharmacologics to manage behavior are suitable for N-of-1 study designs in which individuals are randomized to treatment periods of combinations under double blind conditions (Guyatt et al 1986). Other high risk protocols could be identified from the descriptive epidemiology provided by national monitoring or from clinical literature reports. Finally, long-term monitoring of cohorts permits the study of developmental changes that might be suspected, e.g., examining the influence of prophylactic phenobarbital on the cognitive functioning of toddlers (Farwell et al 1990).

Conclusion

Building a consensus around the necessary variables and methods for monitoring mental health services so as to be able to address the unmet needs of youths with depressive disorders is a challenging public health task. This paper emphasizes the value of including medication utilization data from reliable community-based sources. Doing so will augment the clinical trial database in terms of effectiveness research and long-term safety monitoring. Ultimately, the challenge is to integrate findings from community-based and clinical trial assessments of medication and non-pharmacologic treatment outcomes within a psychobiological model for a balanced and more complete psychopharmacologic knowledge base.

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