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Pediatric Psychotropic Polypharmacy

ABSTRACT

Study Objective: This study was a literature review designed to assess the rates of psychotropic "polypharmacy" in the pediatric population. Psychotropic polypharmacy was defined as the practice of prescribing two or more medications (e.g. concomitant psychotropic medications) for one or more diagnosed psychiatric conditions and/or behavioral symptoms.

Methods: A literature review of relevant articles pertaining to polypharmacy was completed using the Pub Med database from 1994 through April 2004 for pediatric populations under 18 years old.

Results: Studies were reviewed from various pediatric settings. While the extent of polypharmacy varied from the different populations, all the studies comparing these rates across time showed an increase in this practice. The use of stimulants with another psychotropic medication was the most frequent combination.

Conclusions: There is limited information about the actual rates of psychotropic polypharmacy in the pediatric population. However, the data that are available demonstrate that this practice is on the rise. This is of specific concern due to the increase of adverse events with polypharmacy. The implications of polypharmacy, including efficacy and side effects, are generally unknown and may vary by specific combination. Therefore, these prescribing practices should be conducted with caution, and systematic research is needed.

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INTRODUCTION

The need for research in pediatric psychopharmacology in order to develop a body of evidence-based medicine treatments has been well addressed.[1,2] A recent study reported the continuing increase in psychotropic medication prescriptions over 10 years (1987–1996), representing a two- to three-fold increase with a prevalence of six percent of youth (under 20 years of age) on psychotropic medications in 1996.[3] However, efficacy of "off label" use, cotreatment from multiple health care providers, and prescription of Food and Drug Administration (FDA)-approved drugs with adult indications in children are a few of the many areas for which there is a paucity of systematic or epidemiological data. Recent articles have emphasized the need to collect long-term safety data of psychotropics in children[4] to develop systematic ways to define and track adverse events[5] and to have full access to all available information on psychotropic clinical trials in pediatrics, particularly with the current bias of not publishing negative data.[6] All of these issues regarding the need for safety and efficacy data, coupled with the dramatic rise in prescribing psychotropics in youth, make the rising use of polypharmacy, or the use of concomitant psychotropic medications, one of the most critical issues that must be studied.[7]

It is important to clearly define the actual terms used for simultaneous psychotropic prescription. *Copharmacy* describes the pharmacologic treatment of different disorders with two or more medications. *Combined pharmacotherapy* is the use of more than one medication to treat one disorder.[8] *Concomitant psychotropic medication* is the use of two or more medications for either the same or different psychiatric symptoms or disorders.[7] Since all the studies referenced do not distinguish between the definitions, all terms will be considered under the domain of *polypharmacy* in this review.

In the face of limited evidence-based medicine, little is known about polypharmacy in the context of pediatric psychiatric illness. In adult psychiatry, the rate of polypharmacy has been shown to be increasing. Some factors possibly contributing to this phenomenon include the availability of more drugs and the use of drug augmentation as a treatment strategy.[9] The concomitant use of multiple psychotropic medications in children is also on the rise. However, there are no systematic studies of medication augmentation treatment trials in children, which leaves a vacuum of evidence-based treatments for using multiple medications for a pediatric psychiatric disorder.

There have been few studies that address the rationale, specific rates, benefits, and risks associated with combining medications. Even when polypharmacy is endorsed, it is done with caution, citing the need to carefully review the case and consult an experienced colleague, and then subsequently monitor efficacy and drug-drug interactions.[10] This issue has been addressed by the American Academy of Child and Adolescent Psychiatry (AACAP) in the following policy statement: "Anecdotally the prescribing of multiple psychoactive medications…in the pediatric population seems on the increase. Little data exists to support advantageous efficacy for drug combinations… keeping such use to clearly justifiable [clinical] circumstances."[11] In order to address the paucity of data surrounding pediatric polypharmacy, this paper will summarize studies describing the rates of concomitant psychotropic prescription. The impetus to determine the level of evidence for polypharmacy prescribing rates is based upon the concern that there are few practice parameter-based guidelines for this, as well as the increasing risk of adverse reactions with polypharmacy, within the context of limited efficacy and safety information even for monotherapy of psychotropics in youth.

METHODS

A literature review of PubMed from 1994 to spring of 2004 was conducted using different combinations of the search criteria: polytherapy, polypharmacy, psychopharmacology, psychotropic medication, and child psychiatry. Additional studies were selected from bibliographies of review articles. Searches were limited to children 0 through 18 years old, with papers written in English. Papers were used if they were from US populations and if they discussed concomitant psychotropic medication use and/or if they addressed the issues pertaining to polypharmacy.

RESULTS

Psychotropic polypharmacy in the general population—national studies. While few studies specifically reviewed prescription rates of polypharmacy, some investigations have included data of this practice in specific populations. Olfson and colleagues assessed the frequency of polypharmacy in the national general pediatric population.[12] Data from two national surveys representing US civilian, noninstitutionalized populations 18 years old or younger was analyzed. The surveys were based on queried medical events from the parents or adult guardians of the children studied, and the results were verified with medical providers. They found that among the general population, the co-prescription of psychotropic medications increased from 0.03 in 1987 to 0.23 in 1996 (p=0.0002), representing a nearly eight-fold increase, as seen in Table 1. In the latter year, 33.7 percent of children using antidepressants used another class of medications, the most common being stimulants. Additionally, 19.4 percent of pediatric patients using stimulants used another class, the most common being antidepressants. In patients who received one medication, the rate of having a second medication added increased 25 times over that nearly 10-year interval, documenting the increase in polypharmacy.

TABLE 1. A summary of the rates of concomitant psychotropic medication in the United States pediatric population

AUTHORS	STUDY DESIGN	POPULATION SAMPLE	COHORT	DATES	RATES	MOST FREQUENT COMBINATIONS
Martin, et al., 2003	Pharmacy claims data	Medicaid patients in Connecticut	200,000	July 1998 to June 1999	0.7%	• Antidepressant and antipsychotic 22% • Stimulant and antidepressant 15%
Olfson, et al., 2002	Data from the 1987 National Medical Expenditure Survey (NMES) and the 1997 Medical Expenditure Panel Survey (MEPS)	U.S. civilian, noninstitutionalized population	• 10,389 • 6,490	• 1987 • 1996	3% 23%	• Antidepressant and antipsychotic 22% • Stimulant and antidepressant 15%
Rappley, et al., 2002	Pharmacy claims data (< 3 yrs age)	ADHD patients with Medicaid in Michigan office-based practices	127	1995–1996	35%	Methylphenidate and clonidine
Bhatara, et al., 2002	Data was analyzed from consecutive National Ambulatory Medical Care Surveys	Office-based physician practices in the US	• 231 • 228 • 203 [# prescribed stimulants]	• 1993–1994 • 1995–1996 • 1997–1998	• 4.78 • 10.79 • 24.70 (% of visits with concomitant psychotropic prescription)	Clonidine and various antidepressants
Safer, 1997	Outpatient and inpatient chart review	Maryland community health centers	• 86 (outpatient) 75 (inpatient) • 158 (outpatient) 59 (inpatient)	• 1998–1992 • 1994	• 9% (outpatients); 26% (inpatients) • 21% (outpatients); 42% (inpatients)	Rates not specifically analyzed
Kaplan, et al., 1994	A questionnaire examining prescribing practices was completed based on chart reviews	Psychiatric outpatients in New York (NY) and Ohio (OH)	• 46 (*n*=800) • 100 (*n*=622)	• 1990 (NY) • 1989 (OH)	11% 22%	Rates not specifically analyzed

One study using data from the National Ambulatory Medical Care Survey (NAMCS) examined national trends in combined pharmacotherapy with stimulants for children under 18 years old.[13] Among pediatric office visits between 1993 and 1994 where stimulants were prescribed, 4.78 percent included prescription of a concomitant psychotropic drug. This percentage increased to 24.7 percent between 1997 and 1998, over a five-fold increase.

Psychotropic polypharmacy in a state Medicaid population. Another study examined the use of psychotropic agents in a Connecticut statewide sample of Medicaid patients.[14] Psychotropic medication pharmacy claims were reviewed for almost 200,000 children through 18 years of age between July 1, 1998 and June 3, 1999. Multiple psychotropic pharmacotherapy was defined by prescription of two or more different psychotropic drug classes during a seven-day interval. The polypharmacy rate in the entire population was 0.7 percent, representing 13.6 percent of those receiving at least one psychotropic medication. The most common combinations of medications in this polypharmacy population included antidepressant and antipsychotic (22%), stimulant and antidepressant (15%), and stimulant and alpha 2 agonist (13.5%). This suggests that a significant amount of children taking psychotropic medications are on at least two concomitantly.

Polypharmacy in healthcare facilities. In examining patient populations, one study reviewed the records of youths seen in four separate community health centers in Maryland for two time periods: 1988 to 1992, and 1994.[15] Records from 1988 through 1992 showed a polypharmacy rate of nine percent for outpatients and 26 percent for inpatients. Records from 1994 showed an increase to 21 percent for

outpatients and 42 percent for inpatients, suggesting polypharmacy is on the rise. A similar study reviewed outpatient charts of patients from two university-affiliated psychiatric outpatient clinics in New York and Ohio.[16] Out of those patients receiving medication, the rate of multiple concurrent psychotropics prescribed to children was 11 percent (n=5) in New York and 22 percent (n=22) in Ohio. Out of these 27 occurrences, 10 had stimulants as one of the classes of drugs. Although the absolute rates differ geographically for these two studies, both demonstrate a universal increase in rates of concomitant polypharmacy.

Polypharmacy with stimulants and young children. Another investigation of office-based practices in a Michigan cohort examined records of 223 consecutive children ≤3 years old with ADHD.[17] Fifty-seven percent (127 of 223) were on psychotropic medication, and of these greater than one-third (35%, n=44) were being treated with more than one drug, either solely for ADHD or for an additional comorbid psychiatric diagnosis. This included 60 occurrences of 2 to 4 medication combinations. There were 30 different medication combinations, 22 of which were only used once. Medication monitoring with follow-up visits was variable with 19 percent having intervals greater than every six months between visits or no follow-up. Among the authors' concerns were the "erratic and inconsistent" prescribing practices, especially pertaining to polypharmacy. Despite these limits, it is clear that there has been a dramatic increase in psychotropic prescriptions in youth and in the use of polypharmacy.

DISCUSSION

The rates of reported polypharmacy differ among various settings. Psychiatric inpatient facilities have higher rates of polypharmacy than outpatient facilities and pediatric offices, which would be expected. In all populations, however, a stimulant co-prescribed with other drugs appears to be the most frequent form of polypharmacy. There has been an increase in the rates of prescribing atypical antipsychotics, which would be expected due to their availability over the last 10 years. In addition, there has clearly been a universal increase in the frequency of prescribing concomitant medications or stimulants with other medications.

This paper only focused on populations within the United States. Other healthcare systems are unique with different issues regarding access and tracking of prescription records. Once rates in the United States are more clearly defined, further studies may attempt to compare cross-cultural polypharmacy, both within and outside the United States.

Further research is warranted in order to describe the following: trends in the demographics of the diagnosed psychiatric conditions and comorbid medical conditions; the classes, dosages, and schedules of medications used; documentation regarding the rational for polypharmacy; and the prescribing physicians (child psychiatrists, pediatricians, family practitioners, neurologists) and the settings (inpatient, outpatient, residential, juvenile correctional facilities) surrounding psychotropic polypharmacy. Additionally, further study is indicated to help determine whether specific populations (e.g., preschoolers, children in foster care, and Medicaid and lower socioeconomic status versus fee for service) are at greater risk for receiving polypharmacy, particularly without concomitant psychosocial treatments or adequate assessments and follow-up.[17,18] Furthermore, the implications of polypharmacy regarding the risks and benefits of each psychotropic agent separately and cumulatively and the associated medicolegal liability to the treating physician should be carefully investigated.

The most significant concern is that there is an increased risk of adverse events with polypharmacy.[19] There are numerous examples of drug-drug interactions, which are receiving increasing attention and concern. For example, there was a sudden death of a child on methylpenidate and clonidine, which raised the issue of the safety of combining those two agents.[20] There was a death of a nine-year old on fluoxetine, promethazine, methylphenidate, and clonidine.[21] Serotonin syndrome, a serious and potentially fatal illness, can result when a youth receives two medications with serotonergic properties.[22,23] There are limits to the data on adverse events on a single medication, which becomes even more problematic with combinations of medications. The safety of some

monotherapy has been called into question, with the recent FDA Public Health Advisory of a possible association between use of antidepressants in children and the development of suicidal ideation.[24] This issue of the development of activation and/or suicidal ideation has been the subject of many recent reviews,[25,26] and if there is so much concern for monotherapy, it certainly raises the uncertainty when polypharmacy is added in. Determining actual rates of concomitant psychotropic medications is very difficult due to limitations in how data is collected and maintained across healthcare systems and providers. There is no accurate

method to access prescriptions and their actual uses across different samples. Since most of these investigations are limited to study specific definitions of prescribing practices, actual rates of polypharmacy may still be unclear due to discontinuation of medications and noncompliance. Also, cotreatment by different providers is not adequately assessed in order to determine frequencies of concomitant pharmacotherapy. In addition, since the patient groups were different, it is difficult to accurately compare rates of polypharmacy. Finally, patient populations were mostly limited, unless otherwise specified, to outpatient facilities or the general population. There are little data showing the rate of polypharmacy in other settings (e.g., inpatient facilities, residential, juvenile justice settings) as well as the diagnoses (or symptoms) for which the medications were targeting.

While the accurate rates of psychotropic polypharmacy in pediatric populations is not known, it is clear that that this practice is on the rise. This increasing practice has resulted in the above-described policy statement from the AACAP and additional political and media attention. In patients with multiple diagnoses or one diagnosis refractory to monotherapy, polypharmacy may be warranted. It is important to identify and study the role of a medication as either an augmenting or adjunctive agent. Clearly, a systematic study of the rates, safety, and efficacy of concomitant medication prescription is required. Until then, caution must be taken when initiating these prescribing practices.

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