PREDICTORS OF POLYPHARMACY AND OFF-LABEL PRESCRIBING OF PSYCHOTROPIC MEDICATIONS: A NATIONAL SURVEY OF CHILD PSYCHIATRISTS

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The undersigned, appointed by the dean of the Graduate School, have examined the thesis entitled

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DEDICATION

I dedicate this thesis to my parents, Dale and Ana Lorena Kearns, and to Dan Copp.

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ABSTRACT

In the current study we used a national survey of child psychiatrists to examine typical prescribing practices for children with anxiety, depression, and disruptive behavior disorders from a social judgment theory perspective. We examined the extent to which polypharmacy and off-label prescribing occur in routine practice and the degree to which child characteristics, child psychiatrist characteristics, and medication availability may influence these prescribing practices. We found that child psychiatrists most often prescribed medications that were FDA approved for both age and problem type, and were progressively less likely to choose medications without approval for either age or problem type, and without approval for both age and problem type. We also found that prescribing multiple concomitant medications was the norm. We employed best subsets regression to determine the best subset of theoretically relevant predictors to explain polypharmacy and off-label prescribing. The single best-fitting, theoretically sound model predicting polypharmacy and off-label prescribing of medications included just one predictor variable: total number of diagnoses. These findings suggest that comorbidity is an important issue in the pharmacotherapy of children with mental health disorders that must be addressed in future clinical trials.

INTRODUCTION

There has been a marked increase in the prescription of psychotropic medications with children since the 1990's (Safer, 1997). The increase in prescribing however, has not been matched by a solid understanding of the safety and efficacy of these psychotropic medications for children (Vitiello, Bhatara, & Jensen, 1999) and there is concern within the psychiatric community that prescribing practices may have outpaced available safety and efficacy research (Choonora & Conroy, 2002; Jensen et. al, 1998; Lowe-Ponsford & Baldwin, 2000; Vitiello et al., 1999). This concern has primarily involved two types of prescribing practices: (a) the prescription of multiple, concurrent psychotropic medications with youths (i.e., polypharmacy) and (b) the prescription of medications that do not have FDA approval and the requisite safety and efficacy data for the specific population to whom they are being prescribed (i.e., off-label prescribing; Weisz & Jensen, 1999).

Researchers have expressed concerns about the widespread practices of polypharmacy and off-label prescribing with youths because of the limited evidence on the efficacy and safety involved in both practices (Safer, Zito, & dosReis, 2003; Weisz & Jensen, 2001). Both polypharmacy (Safer, et al., 2003) and off-label prescribing have been widely reported with children (American Academy of Pediatrics Committee on Drugs, 1996; Choonara & Conroy, 2002; Jensen et al., 1999; Lowe-Ponsford & Baldwin, 2000), with some estimates as high as 80% of medications prescribed to children being off-label (American Academy of Pediatrics Committee on Drugs, 1996) and estimates of polypharmacy being upwards of 52.4% (Russell, George, & Mammen, 2006).

Although polypharmacy and the off-label use of medication may involve prescribing a medication with a limited evidence base, they do not inherently represent "bad" practices or practices based on no evidence (Zito et al., 2008). Banning either practice could instead create a barrier to quality care (American Academy of Child and Adolescent Psychiatry, 2009). Instead, the American Academy of Child and Adolescent Psychiatry recommends that, in addition to reading the FDA approved medication label, prescribers should also consult the results from randomized controlled trials, consensus guidelines, and practice parameters in order to most effectively practice evidence-based psychopharmacology (American Academy of Child and Adolescent Psychiatry, 2009). If the recommendation to make prescribing decisions based on research evidence, were widely followed, polypharmacy and off-label prescribing could represent cutting edge, research-supported practice consistent with the standard of care (American Academy of Child and Adolescent Psychiatry, 2009). Research has found, however, that these prescribing practices often lack solid scientific evidence (Radley, Finkelstein, & Stafford, 2006) and can thus be risky in practice.

Off-label prescriptions, in particular, may reflect a lack of formal approval based on available evidence regarding a medication's efficacy with (a) a specific age, (b) a psychiatric disorder or problem, or (c) both age and disorder. The risks associated with the off-label use of medications rest largely with their unknown safety and efficacy. Although all medications carry some risk of side effects or adverse events, this risk may be more pronounced when a medication is prescribed off-label with respect to age, especially when a medication is not approved for any pediatric use. For example, when a medication that is approved for treating depression in adults is prescribed to an eight year

old with depression, there is an unknown, and possibly much greater, potential for harm to the eight year old than exists for an adult. There are important developmental influences on children's responses to medications that can affect the way a medication is absorbed, distributed, metabolized, and excreted (Kearns et al., 2003). For example, psychotropic medications that are safe with adults can have toxic effects in younger children due to the immaturity of the neuroendocrine system and blood–brain barrier, lowered activity levels of detoxifying enzymes, and changes in the neural circuitry and neurotransmitter systems (Kearns, et al., 2003). Indeed, serious side effects such as extreme weight gain, elevated prolactin levels, and abnormal electrocardiograms have been found following off-label use of medications in children (Pappadopulos et al., 2002). Side effects, and sometimes serious adverse events, can be a risk even when medications are used as approved. With off-label prescribing, however, those adverse events may be completely unforeseen by both parents and prescribers—a possibility that has led some researchers to describe the off-label use of medications with children as a serious public health concern (Vitiello, et al., 1999).

In addition to safety concerns with off-label prescribing, there are also concerns regarding efficacy. Even when a medication may be safe for use in pediatric populations, it still may not be efficacious. Off-label prescribing with respect to problem or disorder may thus mean that an individual is receiving a medication that is not demonstrated efficacious, or perhaps even demonstrated ineffective, for his or her problem (Radley, et al., 2006; Walton et al., 2008). For example, if a 12 year old child with Attention-Deficit/Hyperactivity Disorder (ADHD) is prescribed a medication approved for those 10 and up with Obsessive Compulsive Disorder (i.e., off-label for problem) instead of a

medication approved and demonstrated to be efficacious for ADHD, that child may be much less likely to improve. Indeed, early onset mental disorders that are left untreated or are improperly treated, are linked to academic failure, childbearing in adolescence, unsteady employment, premature and unstable marriages, and violent behavior (Wang et al., 2005), as well as increasingly severe disability and comorbidity that becomes progressively more difficult to treat (Kessler et al., 2005).

Medical Decision Making and Social Judgment Theory

Prescribing practices, like other medical decisions, can be influenced by a variety of client, physician, and contextual characteristics (Ghodse & Khan, 1988). Although the variables most relevant to off-label prescribing of psychotropic medications in children are not clear, several medical decision-making models have been proposed to help explain the processes by which physicians decide to prescribe a particular medication (Smith & Gilhooly, 2006). Social judgment theory is one such theory; it describes how judgments or decisions are made under uncertainty (Brehmer & Joyce, 1988). According to social judgment theory, individuals perceive and differentially weigh, or attend to, various cues in their environment in order to make a decision in uncertain situations (Cooksey, 1996). Given that medical decisions must be made without total certainty of the outcome, this theory may be a helpful framework for understanding and investigating medical decision making (Galanter & Patel, 2005; Patel, Kaufman, & Arocha, 2002). Ideally, physicians use all relevant empirical and clinical knowledge available to them, including the severity of the problem and the presence of alternative treatments, in an attempt to balance the risks and potential benefits of a particular treatment choice for each individual patient (Kratochvil et al., 2006). As physicians attend to various

informational cues, they may place more or less importance on one or another feature as they make treatment decisions (Wigton, 1996). Some have proposed that physicians are, in a sense, implicitly multiplying each informational cue by its perceived relevance and then summing the weighted cues to arrive at a treatment decision (Wigton, 1988).

Social judgment theory incorporates several key ideas. First, social judgment theory argues that the outcomes of decisions are probabilistic because there is variability between individuals in how they perceive the cues and because the environmental cues themselves can be unreliable and/or differ across contexts (Wigton, 2008). This idea helps explain the variability in the informational cues most relevant to a given clinician and the variability in the decisions made by individual clinicians across various contexts (Wigton, 2008). Second, and following from the previous idea, the relationship between the individual decision and the environmental cues can be modeled using correlation statistics such as multiple regression (Harries & Harries, 2001). Third, social judgment theory stresses the importance of representative design, meaning that decision making studies must closely approximate real life decision making contexts in order to provide valid information (Harries & Harries, 2001; Wigton, 2008).

A few studies using social judgment theory have examined the impact of client variables on physicians' prescribing decisions. For example, in a study of lipid lowering medication prescriptions to patients with hypercholesterolaemia, coronary heart disease and cholesterol level were the two biggest predictors of medication prescribing (Backlund, Danielsson, Bring, & Strender, 2000). This makes good sense given that medical guidelines suggest lipid lowering medication for patients with coronary heart disease (Backlund, et al., 2000). Even so, for 25% of the doctors in the sample, the

presence of coronary heart disease was not a significant cue (Backlund, et al., 2000). In a second study, this one examining antidepressant medication prescriptions to patients with depression, investigators found that patient sleep disturbance, thoughts of suicide, duration of symptoms, and patient preference for medication were the biggest predictors of medication prescribing, and that physicians were tending to overprescribe in relation to the guidelines by about 40% (Smith, Gilhooly, & Walker, 2003). These studies highlight the utility of using a social judgment theory framework in identifying and explaining variability amongst physicians in their prescribing decisions. The existing research on medical decision making is limited, however, in that researchers to date have only examined the impact of client characteristics on prescribing practices. Characteristics of the decision makers themselves, or of the decision itself, may also be important cues to consider in the decision making process.

Although not based on social judgment theory, previous surveys and charts review studies suggest several additional patient, medication, and physician characteristics that may also be important informational cues in child psychiatrists' prescription decision making. Previous surveys and chart reviews have examined predictors of (a) the prescription of multiple, concurrent psychotropic medications (i.e., polypharmacy), (b) the prescription of second generation antipsychotic (SGAs) medications, and (c) the prescription of psychotropic medications to preschoolers. . Research on the prescription of SGAs is important to the issue because researchers have suggested that the widespread use of second generation antipsychotics has largely been off-label (Connor, Ozbayrak, Harrison, & Melloni Jr, 1998; Kaplan, Simms, & Busner, 1994). Although most of the research identifying predictors of the prescription of SGAs

has not explicitly examined whether or not the medications were prescribed off-label, it is included in the review because it, like more general off-label prescribing, is an example of a prescribing practice that has outpaced its evidence base (Cooper et al., 2006). Finally, the prescription of psychotropic medications to preschoolers is relevant because the prescription of medications to children in this age group is largely off-label since so few psychotropic medications have approval in the preschool range (Zito et al., 2000).

Informational Cues Relevant to Prescribing Decisions

Availability of FDA Approved Medications

The availability of the treatment of choice (i.e., FDA approved medication) may be an important informational cue in the prescribing decision. Only 20-30 % of FDA approved medications have approval for pediatric use (Meadows, 2003). This limitation in availability of approved medications for children may be due to industry incentives. Before 1997, there were no incentives, and big disincentives (e.g., ethical, practical, and financial limitations to doing clinical trials with children), for studying psychotropic medications in children (Meadows, 2003). As a result, there was almost no research on the safety and effectiveness of psychotropic medications with children during this time. This changed in 1997 and 1998, following the FDA's passing of two initiatives meant to encourage pharmaceutical companies to extend clinical trials to pediatric populations (Meadows, 2003). The 1997 Pediatric Exclusivity Provision of the Food and Drug Administration Modernization Act (FDAMA) provided companies with the incentive of an additional six months of exclusivity before other companies can begin selling generic versions (Meadows, 2003). The 1998 FDA's Pediatric Rule went beyond incentivizing pediatric research and began *requiring* pediatric studies for a new medication application

whenever the FDA determined (a) the product was likely to be used in a substantial number of pediatric patients, or (b) the product could provide a meaningful benefit to the pediatric population over existing treatments (Meadows, 2003). Even with these new incentives and requirements, gathering the evidence necessary for FDA approval is costly and takes time. In the meantime, psychiatrists are left with the difficult task of deciding what treatments to administer given the limited evidence.

The availability of medications with favorable pharmacological profiles has been speculated to be a reason for the recent increase in the prescription of a variety of newer pharmacological agents to children (Olfson et al., 1998; Pincus et al., 1998). Researchers have argued that the dramatic increase in the number of antidepressants prescribed to children beginning in the 1990's is due to the availability of newer medications such as fluoxetine, sertraline, and paroxetine that have been found (in adults) to be safer and to show a more favorable adverse effect profile than older antidepressants (Olfson, et al., 1998; Pincus, et al., 1998). Researchers documented a similar trend with respect to the prescription of second generation antipsychotics (SGAs). In a study examining predictors of new prescriptions of SGAs with 6803 children using a state-funded health insurance database, the researchers attributed the 2.5 fold increase in SGAs prescribed to children with ADHD or Conduct Disorder (over a 6 year period), as being due in part to the availability of newer atypical pharmacological agents that had fewer associated adverse effects than their older counterparts (Cooper, Hickson, Fuchs, Arbogast, & Ray, 2004). In both of these examples, the increase in use of these medications with children has preceded FDA approval for use in pediatric populations. For example, in the case of the two SSRI's that have pediatric approval (Fluoxetine and Sertraline), Fluoxetine did

not become approved for pediatric use until 2003 and Sertraline did not gain pediatric approval until 2005—several years after the increase in prescriptions of these medications in children had been documented (Olfson, et al., 1998; Pincus, et al., 1998).

These examples point to changes in prescribing patterns following the availability of newer and safer medications on the market, even without FDA approval for pediatric use. In the absence of better alternatives, psychiatrists seem willing to prescribe new medications that seem safe for children even if the data are just based on adults. Prescribing single medications that do have pediatric approval would provide an even safer alternative. Medication availability may be an important informational cue that influences prescribing practices. Given these findings one would expect that medication availability would be negatively related to polypharmacy and/or off-label prescribing practices.

Demographics and Problem Presentation of the Child Patient

Age. Previous research has found patient age to influence psychiatric prescribing practices in children. In a chart review study covering 1292 active cases between the ages of 1 and 18 years at 8 outpatient treatment locations in central New York, Staller, Wade and Baker (2005) found that children in the 10-14 year old age range compared to those in the 5-9 year age range were more likely to be prescribed an antipsychotic and more likely to be prescribed multiple medications. Similarly, among 9,447 children who received at least one psychotropic medication in a Medicaid managed care database, Martin and colleagues (2003) older children (11.5 vs. 10.4) were more likely to be prescribed multiple medications. Given these findings, we might expect that psychiatrists

are more likely to make off-label and polypharmacy prescribing decisions with their older child and adolescent cases.

Sex. Another patient variable that has been found to influence prescribing practices in children, and may thus be another important informational cue is the sex of the child. In the Staller and colleagues' (2005) study described above, and in another comparison of prescribing patterns of primary care providers and psychiatrists caring for children with mental illness, using claims from 5485 children who initiated a new episode of treatment from a MarketScan© national private health insurance database, researchers found that males were more likely to be prescribed a SGA medication than females (Harpaz-Rotem & Rosenheck, 2006; Staller, et al., 2005). In a study examining trends in SGA medication prescription trends for children using data from the National Ambulatory Medical Care Survey (NAMCS), a large national survey of office-based medical practices, Olfson and colleagues (2006) concurred that male patients were more likely to receive a prescription for a SGA medication than females. Being a male has been found to predict polypharmacy as well (Martin, et al., 2003; Staller, et al., 2005).

Some evidence indicates that male preschoolers are also more likely to receive psychotropic prescriptions than female preschoolers. In a study examining the prevalence of the use of psychotherapeutic medications in 274,518 preschoolers ages 2-5 using a Medicaid insurance claims database, researchers found that boys were 2.4 times more likely to receive a medication than girls (Zito et al., 2007). Since boys have higher rates of externalizing disorders than girls (American Psychiatric Association, 2000), however, it is not clear whether differences in prescribing practices can be explained by sex alone or may also relate to the presence of an externalizing disorder. Thus, in

keeping with the previous findings, we would expect boys to be more likely to receive polypharmacy and/or an off-label prescription when they also have a disruptive behavior problem.

Race. Race has also been found to influence prescribing practices, and may thus be another important informational cue to examine. In their aforementioned study, Olfson and colleagues (2006) found that white patients were more likely to receive a prescription for a SGA medication than minority patients. Similarly, Martin and colleagues (2003) found that white patients were more likely to receive polypharmacy than racial or ethnic minorities. Majority race has also been linked to increased rates of psychotropic prescriptions to very young children. In their study of preschoolers , Zito and her colleagues found that white preschoolers were 4 times more likely to receive a medication than black preschoolers (2007). Although race may play an important role in prescribing decisions, the pre-existing dataset used in the current study does not provide case level information on race or ethnicity.

Problem type. Another patient characteristic that has been found to influence prescribing practices with children is the patient's problem type or diagnosis. In their chart review study, Staller and colleagues (2005) found that those with an externalizing disorder were more likely to hold a SGA prescription than those without. Another chart review study of 83 children in residential treatment found that antipsychotics were frequently prescribed off-label for aggressiveness (Connor, et al., 1998). Aggression was also associated with polypharmacy in this study (Connor, et al., 1998). As such, we might expect psychiatrists to be more likely to prescribe multiple concomitant

medications and/or medications off-label to children presenting with externalizing disorders.

Comorbidity. Another patient factor that has been found to influence prescribing practices in children is the presence of comorbidity, or multiple co-occurring psychiatric diagnoses. Patients with comorbid diagnoses have been found to be more likely to receive a prescription for a SGA medication than patients with a single diagnosis (Olfson, et al., 2006). Comorbidity has also been linked to polypharmacy. A study using cross-sectional data on 392 child and adolescent patients aged 2–17 years from the 1997 and 1999 American Psychiatric Practice Research Network Study of Psychiatric Patients, found that comorbidity predicted polypharmacy even after controlling for the presence of specific diagnoses (ADHD, Schizophrenia, Bipolar Disorder, depression, and anxiety), other patient clinical characteristics, demographic characteristics, health plan characteristics, and clinician characteristics (Duffy et al., 2005). Comorbidity has also been found to be related to the prescription of psychotropic medications to very young children. A study using a Medicaid insurance claim database, found that in the 223 children between the ages of 1 and 3 identified as having ADHD, having a comorbid mental or physical illness predicted significantly greater likelihood of prescribing a psychotropic medication to children (Rappley et al., 2002). Given its association with other riskier prescribing practices, one would predict that comorbidity would be positively related to polypharmacy and/or off-label prescribing practices.

Severity. Severity, the degree or level of a problem/disturbance or the extent to which the problem interferes, or causes distress or disability, has also been found to predict prescribing practices. Polypharmacy in children has been found to be associated

with prior hospitalization and being in an inpatient treatment setting, both of which are markers of illness severity (Duffy, et al., 2005). Severity has also been found to be related to the prescription of psychotropic medications to very young children. In a study of psychotropic prescribing practices with preschoolers between the ages of 3-5, using parent interviews and psychiatric evaluations of 267 children recruited from primary care and daycare centers, researchers found that those who were prescribed psychiatric medications were more likely to have higher levels of impairment and were 11 times more likely to be rated as severe than those who were not prescribed a psychotropic medication (Luby, Stalets, & Belden, 2007). Severity seems to not only affect the likelihood of prescribing a medication, but also psychiatrists' willingness to go beyond the available evidence in their prescription. Coyle (2000) reports that in an unpublished survey of 35 members of the editorial board of the *Journal of Child and Adolescent Psychopharmacology,* 80% reported either no or extremely rare prescription of stimulants, clonidine, antidepressants, or antipsychotics for 2- to 4-year-old children (all of which would be off-label for age). Those who responded in the affirmative said they had only done so in the most severe, difficult cases such as children with severe self-injurious behavior (Coyle, 2000). Although severity may be important to consider, the pre-existing dataset used in the current study does not provide information on patient severity and is therefore not examined in the current study.

Physician Knowledge, Attitudes and Work-Related Behaviors

Child psychiatrists' knowledge, attitudes, and work related behaviors may be important predictors in their prescribing decisions. If psychiatrists' decision to engage in polypharmacy or prescribe off-label is indeed an informed decision, examining research

on the sources of information that they most use and value may be important to understanding off-label prescribing and polypharmacy. The American Academy of Child and Adolescent Psychiatry (AACAP) has published over 30 practice parameters which are supposed to guide child psychiatrists' prescribing practices by providing recommendations based on the best available empirical knowledge and clinical consensus (American Academy of Child and Adolescent Psychiatry). A survey of 635 psychiatrists from the AACAP guild examined child psychiatrists' awareness, knowledge, agreement with, utilization of, and satisfaction with the AACAP practice parameters, and found that discussions with colleagues, reading about parameters in the AACAP journal, continuing medical education, and receiving in-service training were significantly related to both familiarity with, and utilization of, practice parameters (Rosof-Williams, Bickman, & Bernet, 2001). Of these variables, discussion with colleagues explained the most variance in both familiarity and utilization of practice parameters, followed by reading research journals (Rosof-Williams, et al., 2001). In contrast, child psychiatrist's age, years of experience, overall patient volume, board certification, conference attendance and affiliation with a medical school were not significant predictors of familiarity with and utilization of practice parameters (Rosof-Williams, et al., 2001).

In contrast with Rosof-Williams and colleagues (2001), another study using interviews with 100 German psychiatrists to examine the influence of patient and child psychiatrist characteristics on psychiatrists' choice of antipsychotic medications for adult patients with schizophrenia, found that physician age was a significant predictor of off-guideline prescribing (Hamann, Langer, Leucht, Busch, & Kissling, 2004). Specifically, older psychiatrists were five times more likely than younger psychiatrists to prescribe

first generation antipsychotic medications despite the existence of several practice guidelines recommending the use of second generation antipsychotic medications as the first-line of treatment (Hamann, et al., 2004). The investigators speculated that this finding may have been due to differences in training. Because older psychiatrists' training presumably predated the emergence of second generation antipsychotics, they were more likely to use the medications with which they had become familiar during training--first generation antipsychotics (Hamann, et al., 2004). While potential differences in the training programs in Germany, or the prescribing practices of German psychiatrists, may limit this study's applicability to U.S. psychiatrists, the interpretation of the findings suggests that age or training may be a potential predictor of prescribing practices. Given these findings, one would expect that board certification, experience, and size of caseload would be unrelated to polypharmacy and/or off-label prescribing practices and that percentage of child specific training received, attitudes toward empirical evidence, the extent to which the psychiatrist regularly reads scientific journals, and the extent to which the psychiatrist regularly talks to colleagues about new practices, would be positively related to polypharmacy and/or off-label prescribing practices.

Summary

The existing empirical literature suggests that characteristics of the child, the physician, and the availability of approved medications for the specific child age and problem type may all be important informational cues used by child psychiatrists as they make prescribing decisions. Child characteristics that may predict a greater likelihood of being prescribed a medication off-label, or being prescribed multiple concomitant medications, include being male, older, white, and having externalizing behavioral

symptoms, more comorbid diagnoses, and more severe problems. Physician characteristics such as percentage of child specific training received, attitudes toward empirical evidence, the extent to which they regularly read scientific journals, and the extent to which they regularly talk to colleagues about new practices may also influence their likelihood of engaging in polypharmacy and off-label prescribing. Finally, characteristics of the medication itself, such as the availability of an FDA approved medication for a particular child case may also influence off-label prescribing practices. Taken together, the research suggests several child, medication, and physician variables that may be important predictors in gaining a better understanding of the choice to prescribe an off-label medication or to prescribe multiple medications at once.

Study Aims

Drawing from social judgment theory, the aims of the current study are to (a) examine the frequency of off-label prescribing with children and (b) identify the personal and case characteristics most strongly predictive of prescribing decisions made by child psychiatrists. In order to serve as a replication test for prior examinations of polypharmacy, we will also (c) examine the frequency of polypharmacy and (d) investigate predictors of polypharmacy. Using data from a national survey of mental health providers serving children and adolescents with anxiety, depression, and/or disruptive behavior disorders (Hawley, 2007), the proposed study will examine the extent to which child characteristics, the availability of an FDA approved medication for that child's age and problem type, and characteristics of the prescriber him or herself, influence prescribing practices of child psychiatrists working within routine clinical service settings. This information may help identify gaps in available treatment

resources, identify common medication practices in need of further investigation, and ultimately help to facilitate child psychiatrists' use of best practices.

As noted above, from a social judgment theory perspective, a child psychiatrist's prescription decision can be viewed as the outcome of a risk-benefit analysis in which he or she is presented with a variety of pieces information and must combine and weigh each piece to arrive at a decision. In the case of off-label prescribing, the various outcomes of that decision (i.e., prescribing a medication on-label, prescribing a medication that has pediatric approval but not for the age group or problem for which it is being used, and prescribing a medication off-label by both age and problem type) can be seen as having a natural ordering based on the potential safety risk and efficacy benefit that each decision involves. Specifically, prescribing on-label should convey the least amount of risk and the greatest potential benefit, because the safety and efficacy of that medication for a child of that particular age group and problem type is established and formally recognized by the FDA. Prescribing off-label for problem type or age (a medication with pediatric approval but not for the age or problem for which it is being used) has a slightly higher risk because, while there is some evidence for safety with respect to age, solid efficacy evidence (needed for FDA approval) is lacking. Prescribing off-label for both age and problem type can be seen as the riskiest decision because there is the least amount of evidence for the safety and efficacy of that medication for a child with that problem.

METHOD

As part of a larger national survey of 5000 mental health providers (Hawley, 2007), 1000 psychiatrists were randomly selected from the American Academy of Child and Adolescent Psychiatry (AACAP) membership list. Each was mailed a 5 page questionnaire developed using the Tailored Design Method, a survey methodology that has been shown to increase response rate (Dillman, 2000). The questionnaire covered demographic characteristics, work attitudes and setting, caseload characteristics, as well as assessment and treatment strategies used in their practice. Clinicians were randomly sent 1 of 3 versions of the survey that asked about a recent, representative child treated for a primary presenting problem of (a) anxiety, (b) depression, or (c) disruptive behavior. Clinicians were also asked to provide the age, sex, primary problem or diagnosis, and secondary problems or diagnoses of that recent case. They were also asked, "Did this child receive psychotherapy? Did this child receive medication? If so, what medications were prescribed? Did you use a treatment manual?" Further details of the survey design and administration can be found elsewhere (Jensen-Doss & Hawley, 2010).

Measures

Defining Off-label

Because there is no comprehensive and definitive source describing all psychotropic medications that have pediatric approval (FDA, Division of Drug Information, Center for Drug Evaluation and Research, personal communication, October 28, 2010), we created a chart with this information to use for coding in the current study.

As a starting point, we went through a standard psychopharmacological textbook to gather a list of psychiatric medications available in the U.S. (Perry, Alexander, Liskow, & DeVane, 2007). We then looked for the medication label for each medication listed in the 2007 Physician's Desk Reference (2007) and recorded the general indication of the medication, the ages for which it was approved, and the indication of the medication for pediatric use specifically (which sometimes varied from its adult indication). If the label was not available in the Physician's Desk Reference (2007), we looked up the label on the FDA's website at FDA.gov (Haynes, 1995). If a medication's label was not available on the FDA website and/or the label was not clear with respect to whether or not a medication had pediatric approval, we contacted the FDA directly via email and/or telephone. When the FDA was unable or unwilling to provide the answer or to supply a copy of the label directly, we searched for labels on the following website suggested by the FDA: http://dailymed.nlm.nih.gov/dailymed/about.cfm (FDA, Division of Drug Information, Center for Drug Evaluation and Research, personal communication, October 28, 2010). For any discrepancies across sources, the FDA was used as the final authority. Using recommendations provided by the FDA (FDA, Division of Drug Information, Center for Drug Evaluation and Research, personal communication, October 27, 2010), in order to be considered approved for pediatric use, pediatric approval had to be specifically listed under the section titled, "Indications and Usage" of the FDA label; to be considered an approved problem type or disorder indication, the indication had to be listed in that section as well.

After compiling the chart of approved medications, we then went to the medical database Epocrates Online © ("Epocrates Online,") and searched by disorder for

recommended medications. If this website indicated a new medication or indication, we went back and verified it by looking at the FDA labels. We repeated the process using the electronic Physician's Desk Reference © ("PDR Online") and FDA labels from 2010. We then looked at a registry on the FDA website of pediatric labeling changes between 1998-2010 (Food and Drug Administration).

Finally, we sent the medication coding chart we had compiled to a practicing child psychiatrist and member of the Academy of Child and Adolescent Psychiatry to suggest additional medications that we may have missed. At the end of the process, we had two coding charts, one for 2007 and one for 2010, each of which listed the names of the medications that have pediatric approval for specific psychiatric disorders and the ages for which they are approved (see Appendices A and B). The medications in the charts are grouped by disorder for ease of use.

Off-label Medication Risk

A coding manual was developed using this chart to code FDA approval of each medication the respondent reported prescribing to his or her recent, representative case (see Appendix C). Specifically, each medication was coded as having (a) FDA approval or not for the age of the child presented (approval for age), (b) FDA approval or not for any of the child's problems or diagnoses (approval for problem type). Two undergraduate research assistants and one master's level graduate student served as coders. A randomly selected sample of 20% of responses was selected to assess interrater reliability. The interrater reliability for the raters was found to range between Kappa = 0.90 to 0.97 ($p < 0.001$).

A set of variables that captured risk with respect to off-label prescribing for each medication along an ordered continuum was then created from the coded information. If a medication had been used "on label" it received a 1, off-label for either age or problem type a 2, and off-label for both age and problem type a 3. Because most child psychiatrists prescribed more than one medication, and using multiple medications itself conveys some additional risk, a summary variable, Total Risk, was created that captured the cumulative risk each psychiatrist took in his or her prescribing decision across medications. For example, if a psychiatrist described using three medications with a child: the first on-label (1), the second off-label for problem type (2), and the third off-label for both age and problem type (3), the risk for each medication was summed 1+2+3 = 6 to capture the total risk for that child.

In order to examine how changes in labeling and approval status may have impacted the findings, this entire coding process was completed twice: once according to the FDA drug labels that were available at the time of the data collection (i.e., approved on or before June 2008 since surveys were mailed and returned late 2007-early 2008) and another with the current labels available at the time of data analysis (approved on or before December 2010). Because, as noted above, clinical trials are necessarily completed in advance of the receipt of formal FDA approval status, the later approval date (2010) allowed the examination of research supported practices that may have simply outpaced FDA's formal approval. Variables representing total risk with respect to off-label prescribing for each of the time periods were used as dependent variables in the study. The coded medication risk based on 2007 FDA approvals was Total Risk =2.734

(SD=1.918). The coded medication risk based on 2010 FDA approvals was Total Risk =2.473 (SD=1.713).

Availability of FDA Approved Medications

In order to calculate how many medications were available for a child of a specific age and problem type, we counted how many medications were available for a child of a specific age with a specific disorder in 2007 and in 2010. For the sake of simplicity, we counted medications that come in a variety of formulations (e.g. extended release, short acting, sublingual, chewable vs. tablet, etc.) as a single medication. We then entered the 2007 and 2010 medication counts as separate variables for each disorder that represented the number of medications approved for a child that age with that disorder. We then summed the variables across each disorder for each child (once for 2007, once for 2010). For example, a psychiatrist treating a 10 year old child with OCD, Depression, and Tourette's would have 4 medications approved for OCD, 2 medications approved for Tourette's, and 1 medication approved for Depression for a total of 7 FDA approved medications from which to choose for that case presentation. The average number of FDA approved medications for the treated child was 8.654 (SD=6.764) based on 2007 approvals and 9.216 (SD=7.316) based on 2010 approvals.

Explanatory Variables

Based on social judgment theory and the available empirical literature, we examined 13 variables as possible explanatory variables in the model. The following variables were categorical and coded as follows: child sex (0 = Male, 1 =Female); child age (1 =4-6, 2=7-10, 3 = 11-13, 4 =14-16); presence of a disruptive behavior disorder (0 = No, 1 =Yes); a sex X behavior disorder interaction term; and board certification (0 =

No, 1 =Yes). The remaining variables were continuous: the patient's total number of diagnoses (mean=3.045, sd=1.339); size of caseload (mean=153.323, sd=175.539); years since completion of training (mean=21.564, sd=11.664); the percentage of child specific training(mean=60.13, sd=20.379); attitudes toward empirical evidence(mean=4.178, sd=0.684); the extent to which the psychiatrist reads scientific journals(mean=4.1115, sd=0.778); the extent to which the psychiatrist talks to colleagues about new practices(mean=3.929, sd=0.877); and the number of approved medications for a child with that age and problem type (mean=8.654, SD=6.764 based on 2007 approvals and mean=9.216, SD=7.316 based on 2010; described above). Attitudes toward empirically supported practices ("I like to try new types of practices that have been supported by research."), the extent to which the psychiatrist reads scientific journals ("I regularly read professional journals or books relevant to my work") and the extent to which the psychiatrist talks to colleagues about new practices ("I regularly talk to colleagues about new practices relevant to my work") items were each self-reported by psychiatrists using a 5 point Likert-type scale ranging from 1=Strongly Disagree to 5= Strongly Agree (See Table 1).

Planned Analysis

Using available variables that previous research suggests may be important predictors of psychiatrists' prescribing decisions, we conducted 3 best subset regression analyses (Hocking, 1976), via SAS version 9.2's (SAS Institute, Cary, NC), "select the best" algorithm. The first regression used total number of medications prescribed as the dependent variable and case characteristics (child sex, presence of a disruptive behavior problem, child sex X disruptive behavior, total number of diagnoses), availability of a

medication with FDA approval for the child's age and problem type (using either 2007 or 2010 information to fit with the dependent variable), and psychiatrists' personal and work characteristics (caseload size, board certification, years since completion of training, % of child-specific training, use of journal articles, talking to colleagues, and attitudes toward empirical evidence) as the independent variables. This analysis was designed as a replication test of findings from previous research on the predictors of polypharmacy.

The next two regressions used total risk as the dependent variable (one regression for 2007 and one for 2010) and case characteristics (child sex, presence of a disruptive behavior problem, child sex X disruptive behavior, total number of diagnoses), availability of a medication with FDA approval for the child's age and problem type for that year, and psychiatrists' personal and work characteristics (caseload, board certification, years since completion of training, % of child-specific training, use of journal articles, talking to colleagues, and attitudes toward empirically based practices) as the independent variables. These analyses were designed to extend the previous research by including a dependent variable that contained information about both the number of medications given and the additional risk involved in prescribing a medication off-label.

Best subset regression models are helpful for identifying the subset of variables that best fit a multiple linear regression model, from among a larger set of theoretically meaningful independent variables (Hocking, 1976). Use of these models is especially helpful when many of the potential predictor variables are significantly correlated (Hocking, 1976), as we had here. In this analysis, we used a SAS algorithm to examine all possible combinations of our larger pool of predictors in order to select 5 regression models using Mallow's C_p as the selection criterion (Hocking & Leslie, 1967). In other

words, with the assistance of the algorithm we identified the subset of variables that produced the lowest model values of Mallow's C_p (Hocking & Leslie, 1967). We then inspected each of these 5 regression models to identify the predictors identified most consistently across subsets. We then ran each model individually, examined the adjusted R^2 values and parameter estimates for each, and chose the best fitting model that we believed made the most theoretical sense.

Hypotheses

1. Psychiatrists will be most likely to choose a medication that is FDA approved for both age and problem type, and progressively less likely to choose medications without approval for either age or problem type, and without approval for both.

2. The following child characteristics will be positively associated with both off-label prescribing and polypharmacy: total number of diagnoses, male sex, and presence of a disruptive behavior disorder.

3. The following child psychiatrist characteristics will be positively associated with both off-label prescribing and polypharmacy: percentage of child specific training received, attitudes toward empirical evidence, the extent to which he or she regularly reads scientific journals, and the extent to which he or she regularly talks to colleagues about new practices.

4. The following child psychiatrist characteristics will be unrelated to both off-label prescribing practices and polypharmacy: board certification, experience, and size of caseload.

5. Number of available FDA approved medications will be negatively related to both polypharmacy and off-label prescribing.

6. Labeling changes between 2007 and 2010 will not change the results with respect to predictors of off-label prescribing and polypharmacy. However, use of 2010 approval information may result in lower frequency of off-label prescriptions if physicians are prescribing based on evidence, but ahead of formal FDA approval, with respect to some of their prescription choices.

RESULTS

Response Rate

Of the 1,000 psychiatrists who were mailed a survey, 81 had undeliverable addresses. Of the 919 psychiatrists presumably reached via mail, 408 (44.3%) responded to the survey, a rate comparable to the 24-49% response rates seen in previous surveys of child psychiatrists (Rosof-Williams, et al., 2001; Weersing, Weisz, & Donenberg, 2002). Among those who responded, 103 indicated they did not provide services to youths so we did not make further use of their responses for the present study. Of the 305 psychiatrists who indicated they do work with children, 226 provided sufficient information about the medication(s) prescribed to a recent, representative case to permit coding and inclusion in the final sample.

Characteristics of the Child Psychiatrists

The average age for respondents was 50.28 (SD = 11.095) with 55.6% of the sample being male (see Table 2). They were predominantly Caucasian (77.8%) followed by smaller representations from Asian/Pacific Islanders (12%), Hispanic/Latinos (5.3%), African Americans (3.1%) and other (2.2%). They had an average of 21.6 (SD = 11.095) years of experience, with 42.2% indicating that they work in private or group practice and the remainder indicating they work in community mental health centers (33.8%), higher

educational settings (20.9%), inpatient clinics (19.6%), residential treatment/group homes (8.4%), day treatment facilities (4.4%), school settings (2.7%), HMO, PPO, Managed Care Organizations (1.8%), or Other (11.6%).

On average, psychiatrists indicated they work 43.23 (SD=14.36) hours a week and spend about ½ of their time prescribing medication (51.07%), and the rest of their time conducting therapy (15.34%), doing case preparation (12.58%), supervision (7.35%), reading professional journals or books (4.4 %), and attending trainings or seminars (2.76 %). Psychiatrists indicated that they have an average of 152 active child cases and work with mostly elementary (21.32 %), middle/junior high (21.41 %), and high school youths (27.56 %), as well as adults 18-64 years old (19.73 %), and smaller amounts of time working with preschool/kindergarten aged children (8.2 %), and senior citizens (2.03%).

Characteristics of a Recent, Representative Case

66.2% the children psychiatrists described in their treatment of a recent representative case were male. Almost half were in the older age range of 14 to 17 (42.4%), over a third were in the 7 to 10 year old range (35.9%), and smaller percentages were in the 11 to 13 year old range (18.9%) and 3 to 6 year old range (2.8%). The five most frequent diagnoses were anxiety disorders (64.6%), depression (58.4%), disruptive behavior problems (53.5%), ADHD (48.7%), and a history of abuse or trauma (24.8%) (see Table 3 for a breakdown of all disorders treated). On average, these children had 3.04 diagnoses and were prescribed 1.52 medications. The medications most commonly prescribed off-label for both age and problem type were, Escitalopram Oxalate (19.8%), Quetiapine (18.6%), and Clonidine (11.6%).

Frequency and Predictors of Polypharmacy

When describing their treatment of a recent representative case, 60.6% of psychiatrists reported prescribing only one medication while close to 39.4% reported prescribing multiple medications.

Using the best subset regression procedures containing the number of available medications variable for both 2007 and 2010 separately, with total number of medications prescribed as the dependent variable, we identified the following five models posted below containing the best subset of predictors according to Mallow's C_p criterion. Because models containing either the 2007 or 2010 medication availability variable selected identical variable subsets, only the models for 2007 are reported here.

1. Total number of medications = child sex X behavior problem interaction (x_1) + total number of diagnoses (x_2)

$F(2, 225)=17.92$, $p<.001$, $R^2= 0.13$, $B_1 = 0.036$, $p = 0.309$, $B_2 =0.211$, $p <.001$

2. Total number of medications = total number of diagnoses (x_1)

$F(1, 225)=34.79$, $p<.001$, $R^2= 0.13$, $B_1 = 0.205$, $p < .001$

3. Total number of medications = % of child training received (x_1) + child sex X behavior problem interaction (x_2) + total number of diagnoses (x_3)

$F(3, 218)=12.14$, $p<.001$, $R^2= 0.133$, $B_1 = 0.002$, $p = 0.445$, $B_2 =0.037$, $p=0.304$, $B_3 = 0.22$, $p<.001$

4. Total number of medications = number of available medications in 2007 (x_1) + child sex X behavior problem interaction (x_2) + total number of diagnoses (x_3)

$F(3, 225)$ 14.46, $p<.001$, $R^2= 0.152$, $B_1 = 0.021$, $p =0.01$, $B_2 =0.04$, $p=0.298$, $B_3 =0.154$, $p<0.001$,

5. Total number of medications = child sex X behavior problem interaction (x_1) + attitudes toward research supported practices (x_2) + number of diagnoses (x_3) $F(3, 225)$ 12.24, $p<.001$, $R^2= 0.13$, $B_1 = 0.04$, $p = 0.268$, $B_2= 0.08$, $p=0.255$, $B_3 =0.212$, $p<.001$.

Across these models, total number of diagnoses was the most consistent predictor, appearing in all 5 models. In our final model containing only total number of diagnoses as a predictor, total number of diagnoses significantly predicted total number of medications $F(1, 225)$ 34.79, $p<.001$, $R^2= 0.13$, $B_1 = 0.205$, $p < .001$, (95% CL : 0.137-0.274), $\beta = 0.37$.

Frequency and Predictors of Off-Label Prescribing

Across providers in 2007, 45% of all medications were prescribed completely on-label, 30% of all medications were prescribed off-label for either age or problem type and 25% of all medications were prescribed off-label for both age and problem type. When examined using the 2010 standards, psychiatrists prescribed 50% of all medications completely on-label, 35% of all medications off-label for either age or problem type and 15% of all medications off-label for both age and problem type. These results confirm the first hypothesis that psychiatrists would be most likely to choose a medication that is FDA approved for both age and problem type, and progressively less likely to choose medications without approval for either age or problem type, and without approval for both. The change in percentages across categories between the two time periods reflects the fact that some medications that were considered off-label in 2007 had gained pediatric approval and were no longer considered off-label in 2010.

In order to identify predictors of off-label prescribing, we then conducted a best subset analysis using the 2007 medication risk variable as the dependent variable. Using the best subset regression procedure, we identified the following five models containing the best subset of predictors according to Mallow's C_p criterion:

1. Total risk 2007 = total number of diagnoses (x_1)

$F(1, 225) = 13.47$, $p<.001$, $R^2= 0.0525$, $B_1 = 0.341$, $p<.001$

2. Total risk 2007 = number of available medications in 2007 (x_1) + total number of diagnoses (x_2)

$F(2, 225)= 6.71$, $p= .002$, $R^2= 0.048$, $B_1 = -0.002$, $p = 0.93$, $B_2 = 0.346$, $p =0.002$

3. Total risk 2007 = caseload (x_1) + total number of diagnoses (x_2)

$F(2, 180)= 7.45$, $p<.001$, $R^2= 0.067$, $B_1 = -0.001$, $p = 0.22.$, $B_2 = 0.361$, $p<.001$

4. Total risk 2007 = talking to colleagues (x_1) + total number of diagnoses (x_2)

$F(2, 225)= 7.43$, $p<.001$, $R^2=. 054$, $B_1 = 0.168$, $p = 0.241.$, $B_2 =0.329$, $p<.001$

5. Total risk 2007 = number of available medications in 2007 (x_1)+ caseload (x_2) + total number of diagnoses (x_3)

$F(3, 180)= 5.36$, $p=.002$, $R^2= 0.067$, $B_1 = -0.028$, $p=0.282$, $B_2 =-0.001$, $p=0.197$, $B_3 =-0.442$, $p<0.001$

Within these models, total number of diagnoses was the most consistent predictor, appearing in all 5 models and the only independent variable that significantly predicted total risk in 2007. In the final model containing only total number of diagnoses as a predictor, total number of diagnoses significantly predicted total risk in 2007 $F(1, 225)$ 13.47, $p<.001$, $R^2= 0.0525$, $B = 0.341$, $p<.001$, (95% CL: 0.158-0.524), $\beta = 0.238$.

We repeated the best subset analysis with the 2010 medication risk variable as the dependent variable (i.e., replacing the number of available medications in 2007 with those available in 2010). We identified the following five models containing the best subset of predictors according to Mallow's C_p criterion:

1. Total risk 2010 = total number of diagnoses (x_1)

$F(1, 225)= 10.31$, $p=.002$, $R^2= 0.0397$, $B_1 = 0.268$, $p=.002$

2. Total risk 2010 = caseload (x_1) + total number of diagnoses (x_2)

$F(2, 180)= 5.66$, $p=.004$, $R^2= 0.049$, $B_1 =- 0.0008$, $p = 0.2733$, $B_2 =0.281$, $p=0.004$

3. Total risk 2010 = child's sex (x_1) + total number of diagnoses (x_2)

$F(2, 220)= 5.43$, $p=.005$, $R^2= 0.039$, $B_1 =- 0.116$, $p = 0.63$, $B_2 =0.292$, $p=0.001$

4. Total risk 2010 = number of available medications in 2010 (x_1) + total number of diagnoses (x_2)

$F(2, 225)= 5.34$, $p=.005$, $R^2= 0.037$, $B_1 = 0.012$, $p = 0.524$ $B_2 =0.233$, $p=0.02$.

5. Total risk 2010 = talking to colleagues (x_1) + total number of diagnoses (x_2)

$F(2, 225)= 5.69$, $p=.004$, $R^2= 0.04$, $B_1 = 0.132$, $p = 0.304$, $B_2 =0.259$, $p=0.002$

Four out of five of these models were identical to those using the 2007 medication risk variable. The only difference came in model 3, which suggested including child sex, a nonsignificant predictor in that model. Across these models, total number of diagnoses was again the most consistent predictor, appearing in all 5 models and again the only independent variable that significantly predicted total risk in 2010. As such, our final model contained only total number of diagnoses as a predictor. Total number of diagnoses significantly predicted total risk in 2010 $F (1, 225)$ 10.31, $p<.001$, $R^2= 0.04$, $B= 0.268$, $p=.002$, (95% CL : 0.104 -0.433), $\beta = 0.21$.

DISCUSSION

We used a national survey of child psychiatrists to examine typical prescribing practices for children with anxiety, depression, and disruptive behavior disorders from a social judgment theory perspective. We examined the frequency with which child psychiatrists prescribe medications on-label, medications that have pediatric approval but not for the age or problem type for which they are prescribed, or medications that do not have pediatric approval at all, and the frequency of polypharmacy. We also looked at the degree to which child characteristics, child psychiatrist characteristics, and medication availability may influence off-label prescribing practices, as well as the practice of polypharmacy.

We found high rates of polypharmacy and off-label prescribing consistent with past research (American Academy of Pediatrics Committee on Drugs, 1996; Choonara & Conroy, 2002; Jensen, et al., 1999; Lowe-Ponsford & Baldwin, 2000; Safer, et al., 2003). Specifically, we found that 39.4% of cases were prescribed more than one psychotropic medication, and 55 % of the psychotropic medications prescribed to children in our survey were off-label in at least one category. Consistent with our first hypothesis, psychiatrists were prescribing higher rates of on-label medications and progressively lower rates of medications without approval for either age or problem type, and without approval for both. This rank ordering of prescription rates was consistent with our conceptualization of risk and did not change across time periods. Between the two time periods, however, changes in the percentages across time periods reflected the fact that many of the medications that were considered off-label during the data collection period

had gained approval by 2010. For example, the two medications that were most frequently prescribed off-label for both age and problem type during 2007 period, Escitalopram Oxalate and Quietapine, had gained pediatric approval for use in pediatric populations by 2010. This pattern suggests that psychiatrists may have been aware of pending approval status of the medications or of the research findings necessary for FDA approval when they prescribed them. Such instances of off-label prescribing would in fact reflect evidence-based pharmacotherapy that was ahead of FDA approval.

We also found that the single best fitting, theoretically sound model predicting both polypharmacy and the off-label prescription of medications included just one predictor variable: total number of diagnoses. This finding was consistent across the two study periods (2007 and 2010). It suggests that child comorbidity better predicts prescribing practices than other child characteristics, psychiatrist characteristics, and even the availability of FDA approved medications for the child's age and presenting problem(s). Indeed, the other child characteristics, medication availability, and psychiatrists' characteristics suggested in previous research did not independently predict polypharmacy or off-label prescribing when examined together.

From a practical standpoint, it is not difficult to imagine why total number of diagnoses may significantly predict off-label medication use and polypharmacy. A child with multiple co-occurring diagnoses will potentially have symptoms that are not easily treated with a single on-label medication. Most medications are designed to treat a single disorder and, while some medications may be indicated for more than one disorder (e.g., OCD and Depression), those indications may not fit the child's presentation (e.g., ADHD and Anxiety). Comorbidity appears to be the rule rather than the exception in routine

clinical practice settings (Newman, Moffitt, Caspi, & Silva, 1998). In this study as well, children had on average 3 separate diagnoses and 90% of psychiatrists indicated that their recent, representative case had two or more disorders. If the treating psychiatrist aims to treat each disorder with a separate medication, this will result in polypharmacy. Each additional medication prescribed may also result in a greater likelihood that at least one of those medications will be off-label. Furthermore, because comorbidity is often associated with greater symptom severity (Kessler, et al., 2005), children with comorbid diagnoses may be more difficult to treat and thus may not be adequately treated by available on-label medications or a single medication.

The finding of child comorbidity as the single significant predictor of both polypharmacy and off-label prescribing highlights the gap between research and practice. In order to provide the highest level of care, child psychiatrists must have empirical information about optimal treatment practices for children with comorbid disorders. However, most clinical trials are conducted with children who have single diagnoses (NAMHC Workgroup on Mental Disorders Prevention Research, 2005). Empirical evidence on how to treat children with more complex case presentations is seriously lacking. Although there are a few clinical trials that address issues of comorbidity (e.g.Abikoff et al., 2005; Spencer et al., 2008) more are needed to ensure that psychiatrists have a solid evidence base on which to base their decisions.

Related to this issue of ensuring that child psychiatrists have the most up to date scientific information on which to base their decisions, is the matter of where psychiatrists obtain the information that helps guide prescribing practices. The finding that the most frequently prescribed off-label medications gained FDA approval shortly

after the data collection period suggests that psychiatrists' had some advanced knowledge about the safety and efficacy of the medications that had outpaced FDA approval. Unfortunately, the available survey data does not reveal exactly how they obtained this information. They may have found it in published clinical trials, by attending conferences or otherwise keeping up with the professional literature, but we did not find attitudes toward empirical evidence, reading journal articles, or talking to other psychiatrists to be significant influences on their prescribing practices. It is possible that such information comes from pharmaceutical company representatives, but we are unfortunately unable to examine this with our current data.

Many instances of off-label prescribing remained even after accounting for up to a 3 year delay (from 2007 to 2010) in official approval. Ambiguity in the way the FDA label is written may also contribute to many instances of off-label prescribing. For example, our research team found that the label for Clonidine, the third most prescribed medication with no approval for pediatric use, was written in a way that made it ambiguous as to whether or not it had pediatric approval in 2007. Specifically, under the heading for "Pediatric Use" the label for the oral form of the medicine from 2007 stated "Safety and effectiveness in pediatric patients below the age of twelve have not been established" but did not explicitly say under the "Indications and Usage" heading that it was approved for children. In 2010, however, the label stated "Safety and effectiveness in pediatric patients have not been established in adequate and well-controlled trials." The difference in the labels left us wondering whether (a) Clonidine had pediatric indication for use in children ages 12 and above in 2007 but then lost its pediatric indication, or (b) Clonidine never had pediatric approval. To address the confusion, we

initially contacted a pharmacist who worked at the drug manufacturer, Boehringer Ingelheim Pharmaceuticals, Inc. and were informed that, to the best of his knowledge, he thought it meant that Clonidine had been approved for use in pediatric populations in 2007 according to the standards that existed at the time, but a later review by the FDA determined that based on the current standards of evidence required for approval (which had changed) it no longer met criteria necessary for FDA approval (Boehringer Ingelheim Pharmaceuticals, Inc., personal communication, October, 2010). Our research team then called a pharmacist at the FDA and were informed that Clonidine had in fact never been approved for pediatric use. In 2007 it may have been considered "not contraindicated" but not officially indicated. After reviewing the evidence in 2009, however, the FDA decided that the label needed to be rewritten to reflect its lack of approval. This single anecdote is provided to reflect the ambiguity in trying to interpret many FDA approval labels (indeed, the correct interpretation of a label may be challenging for even the employees of the medication manufacturer).

Strengths

Overall, this study had several strengths. We used a nationally representative sample of child psychiatrists and extended the existing literature by examining both polypharmacy and a dependent variable that contained information about both the number of medications given and the additional risk involved in prescribing a medication off-label. We also introduced a novel way of conceptualizing off-label prescribing as the result of a decision making process that involves the weighing of safety and efficacy risks of a prescription decision along an ordered continuum. We had a response rate of (44.3%), comparable to the high end of the 24-49% response rates found in previous

surveys of psychiatrists (Rosof-Williams, et al., 2001; Weersing, et al., 2002). Finally, we produced a comprehensive chart containing information about the on-label medications that are approved to treat children with mental health issues grouped by disorder.

Limitations

Despite its many strengths, the study also had several limitations. First, we only examined practices in child and adolescent psychiatrists rather than all providers of psychotropic medications to children and adolescents. Most children with mental health problems are treated by pediatricians and family practice doctors (Goodwin, Gould, Blanco, & Olfson, 2001). We focused on child psychiatrists because, in comparison to general practitioners, psychiatrists should have a greater familiarity with the scientific evidence base, be more likely to read the scientific literature in specialty journals, and be more familiar with cutting edge technological advances for the pharmacological treatment of mental disorders (Pincus, et al., 1998). By examining the prescribing practices of those physicians who have the most specialized training in children's mental health, we were able to get an estimate of the upper bound of quality care one could expect in routine clinical practice.

We also restricted to guild members, who may not be representative of the entire population of child psychiatrists. They may, in fact, be the most compliant among child psychiatrists and the most up-to-date on research by virtue of keeping active membership and getting the scientific journal as part of their membership dues. The findings from this study may therefore not be generalizable to non-guild members or general providers who may be more or less compliant with FDA guidelines.

Another limitation of the study was that it used an archival data set. The questions that could be asked and the variables that could be examined in relation to prescribing practices are limited to those available in the dataset. Other important variables that may be related to prescribing practices could unfortunately not be examined. For example, the dataset did not have information on previous treatments attempted or medication allergies that may have precluded the use of a medication that had FDA approval. It is certainly possible that some of the cases described in the survey had already been prescribed on-label medications for their problems from their pediatricians or general practitioners, but had found them to be ineffective or insufficiently helpful. The survey also does not contain information on the role of parents or the pharmaceutical industry that may be important variables in influencing prescribing practices. There is also lack of specificity regarding dosage information and titration that might have provided additional information with respect to the appropriateness of prescribing practices. It does not provide information about the race and severity of the child being treated, or the organizational setting in which treatment took place. The archival nature of the data set also precluded full use of the social judgment theory methodology with multiple observations for each participant and individual analysis (Doherty & Kurz, 1996).

One final caveat is that we only looked specifically at predictors of polypharmacy and off-label prescribing and not at evidence-based or rational prescribing more generally. Prescribing only a single, FDA approved medication would be the most clear-cut way to ensure safety and efficacy of a medication. However, given that formal approval often lags behind the completion of the clinical trials on which approval is

based, a strict adherence to FDA guidelines, could in fact present a barrier to providing the highest quality of care (American Academy of Child and Adolescent Psychiatry, 2009). As noted earlier, although polypharmacy and off-label prescribing are associated with a more limited evidence-base, they are not inherently bad practices. Indeed, if decisions to engage in polypharmacy or to prescribe off-label were made based on the most up to date scientific information, they could represent a cutting edge, research-supported practices that could provide the highest quality care (American Academy of Child and Adolescent Psychiatry, 2009). Research, however, has found that this is often not the case in practice (Radley, et al., 2006). Both practices thus warrant further investigation because of the controversy that often surrounds them, the concerns raised by psychiatric researchers about the practice and the potential risks associated with prescribing a medication with a limited evidence base (e.g.Vitiello, et al., 1999).

Future Directions

Despite the limitations, the study revealed a potentially important factor that must be considered in the dissemination of empirical findings—the issue of comorbidity. A better understanding of the extent to which comorbidity influences psychiatrists' prescribing decisions may reveal potential targets for intervention and thus deserves additional research. Given the findings it seems clear that we need more clinical trials focused on best practices for medications for common co-occurring disorders.

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Table 1
Variables Used in Analysis

Child Characteristics	
% (N) Male	66.2 %
Age	
3 to 6 years old	2.8%
7 to 10 years old	35.9%
11 to 13 years old	18.9%
14 to 17 years old	42.4%
Presence of a Behavior Disorder	53.5%
Total Number of Diagnoses M(SD)	3.045 disorders (1.339)
Medication Availability	
Medication Availability 2007 M(SD)	8.654 medications (6.764)
Medication Availability 2010 M(SD)	9.216 medications (7.316)
Psychiatrist Characteristics	
Caseload M(SD)	152 active cases (175.539)
Board Certification	36.2%
Experience M(SD)	21.6 years (11.095)
% of Child Specific Training	60.13% of Total Training
Use of journal articles M(SD)	4.112 (0.778)
Talking to colleagues M(SD)	3.929 (0.877)
Attitudes toward empirically based practices M(SD)	4.178 (0.684)

Table 2

Provider Characteristics

Demographic Characteristics	
% Male	55.6 %
M (SD) Age	50.28 years (11.095)
Ethnicity	
White/Caucasian (non-Hispanic)	77.8%
Hispanic/Latino	5.3%
Black/African American	3.1%
Asian/Pacific Islander	12%
Mixed/Other	2.2%
Work Setting	
Elementary, Middle, or High School	2.7%
Higher Education Setting	20.9%
Outpatient Clinic	33.8%
Private Practice	42.2%
Day Treatment Facility	4.4%
Residential Facility or Group Home	8.4%
Inpatient Hospital or Medical Clinic	19.6%
Managed Care Organization	1.8%
Other	11.6%
Professional Characteristics	
Experience	21.6 years (11.095)
Hours Worked	43.23 hours (14.36)
Caseload	152 active cases (175.539)

Table 3

Characteristics of the Recent Representative Case

Demographic Characteristics	
% (N) Male	55.6 %
Age	
3 to 6 years old	2.8%
7 to 10 years old	35.9%
11 to 13 years old	18.9%
14 to 17 years old	42.4%
Diagnoses	
Total Number of Diagnoses M(SD)	3.04 diagnoses (1.339)
Anxiety	64.6%
Depression	58.4%
Disruptive Behavior Problems	53.5%
Autism	2.7%
Learning Disorder	20.8%
Eating Disorder	2.2%
History of Abuse/Trauma	24.8%
ADHD	48.7%
Tourette's Syndrome	0.4%
Bipolar Disorder	2.7%
Enuresis	0.4%
OCD	10.6%
Mental Retardation	4.9%
Substance Abuse Disorder	9.3%
Schizophrenia	0.4%
Medications	
Total Number Received (M)	1.52 medications (0.75)
Top 3 Off-Label (Both)	Escitalopram Oxalate (19.8%)
	Quetiapine (18.6%)
	Clonidine (11.6%)

PSYCHOTROPIC MEDICATIONS APPROVED FOR CHILDREN ACCORDING TO 2007 FDA DRUG LABEL

Trade Name	Generic Name	Approved Indication	Age
Ritalin	Methylphenidate	ADHD	6+
Strattera	Atomoxetine	ADHD	6+
Methylin	Methylphenidate	ADHD	6+
Concerta	Methylphenidate	ADHD	6+
Adderall	Amphetamines, Mixed Salts	ADHD	6+
Focalin	Dexmethylphenidate	ADHD	6+
Daytrana	Methylphenidate	ADHD	6+
Vyvanse	Lisdexamfetamine	ADHD	6+
Desoxyn	Methamphetamine	ADHD	12+
Dexedrine	Dextroamphetamine Sulfate	ADHD	6+
Dextrostat	Dextroamphetamine	ADHD	6+
Metadate CD	Methylphenidate Hcl	ADHD	6+
Risperdal	Risperidone	Autism (irritability)	5+
Thorazine	Chlorpromazine	Behavioral problems	1 to 12
Haldol	Haloperidol	Behavioral problems	3 to 12

Trade Name	Generic Name	Approved Indication	Age
Abilify	Aripiprazole	Bipolar (Mania)	10+
Risperdal	Risperidone	Bipolar (Mania)	10+
Desmopressin Acetate	Desmopressin Acetate	Enuresis	6+
Tofranil	Imipramine	Enuresis	6+
Haldol	Haloperidol	Hyperactivity	3 to 12
Prozac	Fluoxetine	Major Depressive Disorder	7+
Zoloft	Sertraline	OCD	6+
Prozac	Fluoxetine	OCD	8+
Luvox	Fluvoxamine	OCD	8+
Anafranil	Clomipramine	OCD	10+
Abilify	Aripiprazole	Schizophrenia	13+
Risperdal	Risperidone	Schizophrenia	13+
Orap	Pimozide	Tourette's Syndrome	12+
Haldol	Haloperidol	Tourette's Syndrome	3 to 12

PSYCHOTROPIC MEDICATIONS APPROVED FOR CHILDREN

ACCORDING TO 2010 FDA DRUG LABEL

Trade Name	**Generic Name**	**Approved Indication**	**Age**
Ritalin	Methylphenidate	ADHD	6+
Strattera	Atomoxetine	ADHD	6+
Methylin	Methylphenidate	ADHD	6+
Concerta	Methylphenidate	ADHD	6+
Adderall	Amphetamines, Mixed Salts	ADHD	6+
Focalin	Dexmethylphenidate	ADHD	6+
Daytrana	Methylphenidate	ADHD	6+
Vyvanse	Lisdexamfetamine	ADHD	6+
Intuniv	Guanfacine	ADHD	6+
Desoxyn	Methamphetamine	ADHD	12+
Dexedrine	Dextroamphetamine Sulfate	ADHD	6+
Dextrostat	Dextroamphetamine	ADHD	6+
Metadate CD	Methylphenidate Hcl,	ADHD	6+
Risperdal	Risperidone	Autism (Irritability)	5+
Abilify	Aripiprazole	Autism (Irritability)	6+
Thorazine	Chlorpromazine	Behavioral Problems	1 to 12

Trade Name	Generic Name	Approved Indication	Age
Haldol	Haloperidol	Behavioral Problems	3 to 12
Abilify	Aripiprazole	Bipolar (Mania)	10+
Zyprexa	Olanzapine	Bipolar (Mania)	13+
Risperdal	Risperidone	Bipolar (Mania)	10+
Seroquel	Quetiapine	Bipolar (Mania)	10+
Desmopressin Acetate	Desmopressin Acetate	Enuresis	6+
Tofranil	Imipramine	Enuresis	6+
Haldol	Haloperidol	Hyperactivity	3 to 12
Prozac	Fluoxetine	Major Depressive Disorder	7+
Lexapro	Escitalopram	Major Depressive Disorder	12+
Zoloft	Sertraline	OCD	6+
Prozac	Fluoxetine	OCD	8+
Luvox	Fluvoxamine	OCD	8+
Anafranil	Clomipramine	OCD	10+
Abilify	Aripiprazole	Schizophrenia	13+
Risperdal	Risperidone	Schizophrenia	13+
Seroquel	Quetiapine	Schizophrenia	13+
Zyprexa	Olanzapine	Schizophrenia	13+
Orap	Pimozide	Tourette's Syndrome	12+
Haldol	Haloperidol	Tourette's Syndrome	3 to 12

MEDICATION CODING MANUAL

1. Variables: Each medication listed should be coded for the following:
    A. Approval for Age: **Med_#_Age**
    B. Approval for Problem Type in Children: **Med_#_Child_Prob**

*# corresponds to whether the medication is the 1st, 2nd, 3rd, 4th, or 5th listed.

2. Approval for Age:
    A. Definition: whether or not the medication is approved for a child of a particular age
    B. Coding Instructions: find the medication on the medication chart, determine whether it is approved for a child of that particular age and enter a 0 or 1. If there are several ages listed in the medication chart, ***code for the youngest age allowed***.
    C. Codes:
    0 = No
    1 = Yes

3. Approval for Problem Type in Children:
    A. Definition: whether or not the medication is approved for a particular problem in individuals younger than 18 years old
    B. Coding Instructions: find the medication on the medication chart, determine whether it is approved for a particular problem type and enter a 0 or 1. A medication should receive a code of 1 if it is approved for any of the conditions listed or indicated.
    C. Codes:
    0 = No
    1 = Yes

Special Situations:

Missing Data:

*If information such as child's age or problem type is missing and prevents the assignment of a code for one of the variables, enter a -9 in place of a code to indicate that it is missing.

*Codes of -7 indicate missing by design.

How to Code When Child's Age Is Missing:

When child's age is missing, please code as follows:

For the variable **Med_#_Age:**

- *If the medication is approved for a child of age **1+, code Med_#_Age as 1** (since a medication approved for a child of age 1+ would have age-based approval for all of the children in our sample).
- *If the medication is approved for a child **2+ or older, code Med_#_Age as -9** missing (since we do not know if the medication would have had age-based approval for the child in question).

Asperger's Disorder and Pervasive Developmental Disorder:
Asperger's Disorder and Pervasive Developmental Disorder are considered to be types of Autism. As such, if a medication is approved for use in children with Autism, it should also be considered approved for children with Asperger's or PDD.

Anxiety Disorders
Because some anxiety disorders such as social anxiety, separation anxiety, and generalized anxiety disorder are difficult to differentiate, if a medication is approved for use in one of those disorders, it should be considered to be approved for use in any of the other disorders as well.

Dysthymia
Please code Dysthymia or Dysthymic Disorder as you would for Depression. If a medication is approved for Depression, please consider it approved for these other disorders as well.

Adjustment Disorder with Anxiety and Adjustment Disorder with Depression:
If a medication is approved for use in anxiety, it should also be considered approved for Adjustment Disorder with Anxiety. If a medication is approved for use in Depression, it should also be considered approved for Adjustment Disorder with Depression.

Acronyms for Disorders/Problem Type:
MDD = Major Depressive Disorder
GAD = Generalized Anxiety Disorder
OCD = Obsessive Compulsive Disorder
ADHD = Attention Deficit Hyperactivity Disorder
PTSD = Post Traumatic Stress Disorder
PMDD = Premenstrual Dysphoric Disorder
NOS = Not Otherwise Specified
ODD = Oppositional Defiant Disorder
PDD = Pervasive Developmental Disorder
RAD= Reactive Attachment Disorder