Risk Factors for Discontinuing Drug Therapy Among Children with ADHD †

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Abstract

Compliance with drug therapy is of major concern to clinicians as well as policy makers since uncontrolled symptoms due to noncompliance present health risks for patients and may lead to social costs. Noncompliance comes in the form of skipped dosages as well as discontinuation well before a clinician deems it appropriate. The problem is especially severe in behavioral disorders among children where the symptoms can last well beyond adolescence. We use pharmacy dispensing and clinical diagnosis data on children diagnosed with attention-deficit hyperactivity disorder (ADHD) and who are on ADHD-related medications. The paper shows how the pharmacy refill data fit naturally into a discrete time hazard rate framework, and then compares estimates from alternative definitions of discontinuation. We use a long follow-up period (up to six years), allow for a flexible duration dependence and account for unobserved heterogeneity. The expected duration is about 18 months with significant differences across race, gender, copays, medication switching, and seasonality. We find that African-American, Hispanic and, Asian children are about 39% more likely, on average, to quit therapy in a given month than white children. Similarly, compared to a child that initiates drug therapy at age nine, a child that starts therapy at age ten is 26.4% more likely to discontinue at any given time. Earlier literature using the hazard approach reports smaller associations between these covariates and durations. We show that this could be because of ignored unobserved heterogeneity, use of a relatively short follow-up study design and monotonic duration dependence. Finally, our results are of particular relevance to clinicians as well as to policy makers given recent changes in federal and state policies that may make early detection and diagnosis of ADHD among children less likely.

Key words: ADHD, drug therapy, compliance, duration, hazard models, adherence

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1. INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder associated with significant impairments which commonly continue into adulthood, including earlier exit from school, more frequent firing from jobs, poorer driving performance, and greater substance abuse (Mannuzza et al., 1997, Barkley et al., 2006, Biederman et al., 1995, Barkley et al., 1996). Many studies have shown that both behavioral and medication treatments can improve symptoms and functioning in those with ADHD in the short term (MTA Cooperative Group et al., 1999, Greenhill et al., 2002). However, long term follow-up studies indicate that outcomes are poor when ADHD patients reach adulthood (Spencer et al., 1996, Mannuzza et al., 1997, Barkley et al., 2006). The cause for these poor outcomes is unclear, but one theory is that poor adherence to medication regimens and premature discontinuation of treatment may be major reasons (Charach et al., 2004, MTA Cooperative Group, 2004).

Treatment adherence is a major problem in ADHD management and in the treatment of pediatric disorders in general (Firestone, 1982, Sleator et al., 1982, La Greca, 1990, Shope, 1981). Adherence to prescribed stimulant medication regimens for ADHD has been poor, with estimates ranging from 44% to 87% (Firestone, 1982, Sleator et al., 1982, Corkum et al., 1999, Hack and Chow, 2001, Thiruchelvam et al., 2001). Several studies have documented a number of factors that are associated with poor adherence to ADHD medication regimens. These include the daily frequency of medication prescribed, frequency of provider follow-up, rigorous monitoring of medications, structure of drug formularies as well as parental fears about side-effects, and the age and race/ethnicity of the patient (Shope, 1981, Greenberg, 1984, La Greca, 1990, Finney et al., 1993, Jensen et al., 2001, Swanson, 2003, Huskamp et al., 2005, Monastra, 2005). Additionally, it appears that physicians are often unaware of the degree of adherence itself and are poor predictors of patient adherence to medical regimens (Firestone, 1982, Finney et al., 1993).

Recent literature on compliance of drug therapy has often relied on constructed measures of correspondence of the actual dosing history with the prescribed drug regimen. This is done by computing a measure of compliance from the elapsed time between a refill pick-up date and the number of days for which medication was supplied at the previous prescription fill date (Perwien et al., 2004, Sanchez et al., 2005, Kemner and Lage, 2006). For instance, following Rizzo and Simon's (1997) methodology, Perwien et al. (2004) define a medication possession ratio (MPR) as the number of days supplied in a prescription divided by the number of days until the next prescription was filled, and define a patient to be "compliant" if this ratio is greater than 0.8. A common theme among these studies is to tabulate proportions of compliant patients by stratified sub-samples based on

gender, race, age, comorbidities and initial type of drug prescribed. These studies have been informative about the characteristics of patients (and drugs – Immediate Release (IR) versus Extended Release (ER)) that are compliant *while they are on drug therapy*. However, these studies do not tell us much about who is likely to stay on medication therapy.

To look at longer term patterns and the probability of staying on medication therapy, Thiruchelvam et al. (2001) follow a sample of 63 children over three years (after attrition) on ADHD medication and report that older children, those with fewer teacher-rated ADHD symptoms, and those with oppositional defiance disorder (ODD) were less likely to continue to take stimulant medication for three consecutive years. By contrast, Marcus et al. (2005) use a large sample, control for child characteristics (age, race, gender, comorbidities) and analyze the impact of the initial methylphenidate drug prescribed (IR-MPH or ER-MPH) on the duration of drug treatment and find that ER-MPH treatment was correlated with longer mean duration times (140.3 vs. 103.4 days with ER-MPH having 37% longer durations).

In this study, we answer a related question: Given that a child initiates drug therapy, what factors predict the likelihood that s/he will discontinue therapy at any given time? Specifically, using several alternative definitions of discontinuation, we estimate the impact of child age at the start of medication therapy, demographics (gender, race), income, coinsurance, measures of comorbidity, and the number of times a child switches the main drug on the probability of discontinuation of drug treatment.

Related literature that analyzes the duration patterns via multivariate regression analysis (or descriptive analysis) is ill suited to inform about the risk factors for discontinuing therapy (Kemner and Lage, 2006, Lage and Hwang, 2004, Miller and McGrail, 2004). First, these methods cannot adequately account for the impact of time-varying covariates (for instance, changes over time in comorbidities, copay or the number of times a child switches drugs). Additionally, they cannot differentiate the impact of *child age at drug initiation* from that of *child aging* (or duration dependence). Second, these methods are limited in their ability to utilize the information provided by censored therapy spells (right-censored observations), or require some strong assumptions about the data generating process to overcome censoring bias. The limitations are exacerbated in studies where the data are truncated at shorter durations.

By contrast standard hazard rate models make efficient use of the information provided by children with incomplete therapy spells, can readily accommodate time-varying factors (which reduces the potential for bias from omitted variables or censoring) and, can allow for duration dependence in a flexible way. Further the hazard rate estimates can be used to back-out the association of a

covariate on the duration itself, i.e., report expected durations by selected subgroups such as by gender or other demographic variables of interest. Marcus et al. (2005) also use a (continuous time) hazard rate approach on data truncated at 12 months of follow-up and impose a monotonic duration dependence. Unlike their study, we estimate discrete time hazards on data truncated at up to 72 months of follow-up, allow for a flexible duration dependence pattern as well as unobserved heterogeneity. As a result our estimates of the impact of several covariates on the probability of discontinuing therapy and on the duration are larger than those reported by Marcus et al. (2005). Our estimates show that the duration dependence is indeed nonmonotonic (decreasing till month seven and then increasing again after month 48) with an average duration for a male child of about 18 months.

With respect to the covariates we find that: (1) older children have shorter duration times and, even after controlling for confounding factors, are more likely to discontinue drug therapy – a child who is 9 years old is 26.4% more likely to discontinue therapy if s/he was one year older at the start of medication therapy; (2) females are 10.06% more likely to discontinue therapy; (3) African-American, Hispanic and children of Asian decent are more likely to discontinue drug therapy than white children (42.2%,48% and 26.9% respectively); (4) those with no copay are significantly less likely to quit drug therapy compared to those who pay $1-$9.99 copay (12.7% less likely); (5) while the unadjusted duration times are longer for children with two or more comorbidities, when we adjust for other factors, they are neither more nor less likely to discontinue drug therapy compared to children with one or no comorbidities, and (6) children are more likely to discontinue drug therapy during summer months. Note that this last result already takes into account that the child may be on the so-called 'drug-holiday', i.e. children are more likely to go off drug therapy during the months of June, July and August but do not return to therapy within any reasonable time even after the summer ends.

The rest of the paper is organized as follows. The next section describes the setting, study population and our definition of discontinued drug therapy. Section 3 describes the data in detail and provides descriptive statistics. In section 4, we present our methodology and report on the impact of a number of factors (including time varying covariates) on the risk of discontinuing drug therapy. The last section discusses our results in comparison to results based on alternative methods used in the existing literature and outlines the policy implications of some of our findings.

2. Data Description

2.1. **Setting & Study Population.** The data are drawn from children enrolled in Kaiser Permanente (KP) of Northern California (KPNC), which is a nonprofit, integrated health care delivery

system providing care in 23 counties to over 3 million members of whom about 700,000 are under 18 years of age. Our objective was to analyze the duration of ADHD-related drug therapy from the time that a child first starts therapy. Using KPNC electronic databases, we extracted all fills for ADHD-related medication (psychostimulants or atomoxetine) from KPNC outpatient pharmacies between January 1, 1996 and December 31, 2005. For each individual receiving a fill, we identified the first fill between January 1, 2000 and December 31, 2004 that was not preceded by any other fill for ADHD medications in the previous four years. The date of this first fill was used as the start data of medication therapy. Only children between 5 and 15 years of age on their start date, and who were continuous members of KPNC for at least four years prior to their index date (and thus could be expected to fill prescriptions at KPNC pharmacies), were included in the analyses (N=7,467). We also required that all children in the sample be born in a KPNC hospital (N=4,386), so as to capture race, which is recorded in the KP hospitalization database but is otherwise unknown. Missing values on some of the covariates resulted in a final data set consisting of 4,091 children.[1]

2.2. **Covariates.** Several covariates are recorded for each person. These include gender, race, income, pharmacy copay, psychiatric comorbidities (listed below), and the number of times a child's ADHD drug was switched while they were on drug therapy (e.g. from long-acting to short-acting form, or from methylphenidate to mixed amphetamine salts). The last three covariates are time-varying variables. Familys' estimated median income is based on census block group according to 2000 US Census data. Using outpatient visit diagnosis codes, we identified (in each year since 1996) whether the child was seen for any of the following mental health disorders (MHDs): substance abuse disorder, psychoses, unipolar mood disorders, bipolar mood disorders, pervasive developmental disorders, anxiety disorders, obsessive-compulsive disorders, tic or Tourette syndrome, post-traumatic stress disorder, conduct disorder, oppositional or defiant disorder, or learning disorders (excluding speech and language problems). From these MHDs, we constructed the comorbidity variable which takes values of (i) zero, (ii) one, or (iii) two or more MHDs. Similarly, the drug switching variable is also coded to values of (i) zero, (ii) one, or (iii) two or more switches.

2.3. **Definition of Discontinuation.** Children may go on and off drug therapy several times during their life, and as such the underlying problem is one of multiple spells. Our focus, however, is on the *first time a child discontinues drug therapy* (henceforth called an exit), where it is either the first time that the drug therapy has been initiated, or it has been re-initiated after a significantly long period. It is primarily for this reason that we work with a sample of children who have been continuously enrolled in KPNC for at least four years with no pharmacy fills related to any ADHD

[1]Due to concerns about sample selection, we checked if restricting the sample to those born in a KP hospital changed our results. It did not. The 4,091 number changes slightly across alternative data sets that we constructed for robustness checks.

medications prior to obtaining an ADHD-related pharmacy fill. We identify exits based on time elapsed between refill dates while accounting for the number of day's supply dispensed. We start by defining a discrete 30-days period (loosely called a month) for every child. The calender date of the first pick up marks the beginning of the first 30-days period for a child. If the pick up was for a 100-days supply then periods one, two and three are defined to have a 30-days supply available in each of those periods, and period four has a 10-days supply available in it. If at any time before the end of period four, there is another pick up then days-supply is adjusted accordingly. For instance, if during period four another 100-days supply of the same drug was dispensed, then periods four through six are marked as having a 30-days supply available to them and period seven is marked with a 20-days supply available in it. This carry-over counting of days-supply is reset to zero if the pick up was for a different class of drugs. For example, if a child's medication was switched from a short-acting to a long-acting form (say Ritalin to Ritalin SR or Concerta) or when the main active ingredient was changed (methylphenidate (Ritalin) to a mixed amphetamine salt (Adderall)) then the days-supply is reset to zero.

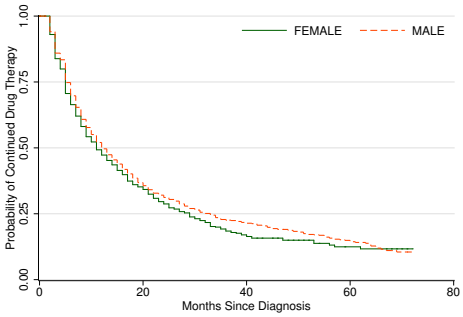
Our definition of an exit is based on a sequence of 30-day periods and the days' supply available in each of these periods. The baseline definition of an exit is three consecutive periods with ten-days or less supply available in each period. When such a combination is observed, a child is considered to have exited the sample sometime during the first 30-days interval. Alternative definitions that we use are (a) two consecutive periods with 10-days or less supply in each period, (b) four consecutive periods with 10-days or less supply in each period, and (c) three consecutive periods with 0-days supply available in each period.[2] Since some children may choose to 'suspend' drug therapy during summer breaks without necessarily exiting drug treatment, a two and four month definition is especially useful in checking the robustness of our results. Similarly, our definitions also allow for mini-breaks. For instance, if a prescription was filled for a 100-days supply (which was the most commonly observed days supply in our data) and the child was not administered any drug over the weekends, then the prescription would have actually lasted 140 days or, equivalently one additional month plus 10 days.

3. Descriptive Statistics

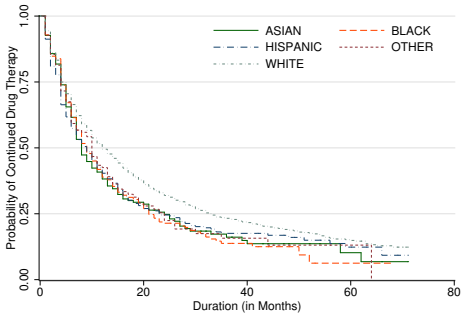
Our sample (based on the 3-months 10-days supply definition) consists of 4,091 children of which 3,203 discontinued drug therapy (exited) while the remaining 888 did not discontinue (henceforth

[2]In addition to these definitions, we also estimated the hazard function with several other definitions of discontinuation. These were (d) one period with 10-days, (e) three periods with 1-day, three periods with 9-days (f) five periods with 10 days. Results from these alternative definitions are not reported since they were similar to those that are reported in the paper.

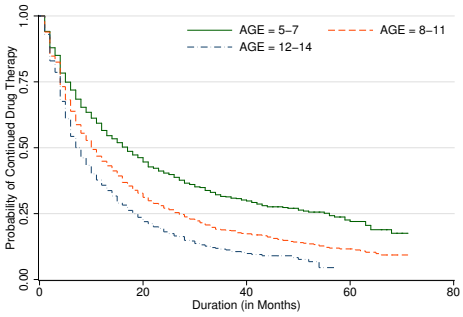
called censored) by the end of the six-year observational window. These 4,091 children provide a total of 56,692 person-months.[3]



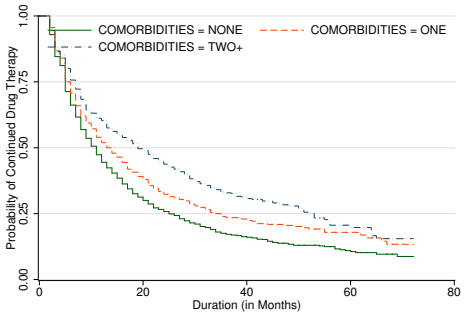
(a) Survivor Functions By Gender



(b) Survivor Functions By Race



(c) Survivor Functions By Age at Start of Drug Therapy



(d) Survivor Functions By Co-morbidities

FIGURE 1. Survivor Functions by Selected Covariates

3.1. **Variation in Duration Times (by child characteristics).** Among those with completed therapy spells, the mean and median time on drug therapy is 10.1 and 7 months respectively. However, there is considerable variation in duration times across sub-groups (the standard deviation is 9.5 months). Mean duration times differ by gender and race: compared to the 2,377 boys, the 826 girls in the sample have 0.83 months shorter mean duration times, while compared to white children (2,284), African-Americans (266) have roughly 2 months shorter therapy durations (with a less stark contrast among African-American, Hispanic, Asian and Other races). See Table 1 and Figures 1(a) and 1(b).

There are also large differences in mean duration time by age at start date of drug therapy (henceforth initiation date) and comorbidities (see Table 1 and Figures 1(c) and 1(d)). Among the 929 children who are less than eight years old on initiation date, the mean duration of the therapy spell

[3]The person-months are not equal to $4091 \times 12 \times 6 = 294,552$ because (1) children enter the risk set at different points in calender time, and (2) once children exit we remove them from the observational set.

TABLE 1. Duration of Therapy (Exit Sample) by Covariates

	Mean	Median	Stdev	Min	Max	N
Overall	10.054	7	9.494	1	69	3203
Age at Diagnosis (<8)	11.484	8	10.972	1	69	929
Age at Diagnosis (8-11)	9.873	7	9.127	1	67	1600
Age at Diagnosis (12-14)	8.515	6	7.723	2	55	674
Gender (Male)	10.268	7	9.819	1	69	2377
Gender (Female)	9.439	7	8.463	1	62	826
Race (White)	10.594	7	9.990	1	69	2284
Race (Black)	8.560	7	7.229	2	52	266
Race (Hispanic)	8.460	6	8.032	1	67	385
Race (Asian)	9.084	7	7.670	1	41	167
Race (Other)	9.475	6	9.973	2	65	101
Income (1st Quintile)	10.079	7	10.103	1	65	390
Income (2nd Quintile)	9.991	7	9.067	1	65	553
Income (3rd Quintile)	9.908	7	9.149	1	58	641
Income (4th Quintile)	10.185	8	9.163	1	69	703
Income (5th Quintile)	10.084	6.5	9.972	1	67	916
Copay‡ ($0)	11.013	7	10.267	1	69	390
Copay‡ ($1-$9)	8.371	6	7.592	1	60	1084
Copay‡ (≥$10)	10.894	7	10.221	1	67	1729
Drug Switches‡ (Zero)	7.158	5	6.312	1	53	2203
Drug Switches‡ (One)	13.495	11	10.053	3	69	662
Drug Switches‡ (2 or more)	22.192	19	13.115	4	67	338
Comorbidities‡ (Zero)	9.410	7	8.581	1	69	2010
Comorbidities‡ (One)	10.365	7	9.474	1	67	712
Comorbidities‡ (2 or more)	12.287	8	12.380	1	65	481

Note: ‡For the time-varying covariates, stratification is based on their value in the last month observed.

is 11.5 months. By comparison, the 650 children above or at the age of 12 at the initiation date have almost 3 months shorter duration times. We classify comorbidities into three groups (0, 1 or 2 or more). Based on comorbidities in the period of discontinuation, the mean length of the therapy spell for children with zero comorbidities is 9.4 months and is shorter than those with some comorbidities (10.4 and 12.3 respectively). The differences in therapy duration by other child and family characteristics are summarized in Table 1.

3.2. **Variation in Child Characteristics (by drug therapy status).** The average age of a child at the beginning of the therapy in our sample is 9.5 years (standard deviation is 2.5 years and median 9.2 years) but for those children that discontinue the therapy it is 9.7 years, while among those that do not discontinue it is 8.9 years (see Table 2). Males represent 74.7% of our main sample. Among those that discontinue, males represent 74.2% while among those that do not discontinue, the fraction of male children is 76.5%. White children represent 72.4% of the sample, African-American 7.9%, Hispanic 11.6%, and 5.1% and 3% are Asian and Other (non-white) children respectively. Again, there are small differences across children that discontinue (i.e. exit) versus those that do not (i.e. are censored). For instance, while the share of white children is 72.4% overall in the sample, it is lower among those that discontinue the drug therapy compared

to those who stay on the drug therapy (71.3% vs. 76.4%) and the difference is larger among other groups (8.3% vs 6.5% for African-American children and 12% vs. 10% for Hispanic children).

TABLE 2. Descriptive Statistics and Regression Coefficents

	Means (StdDev)			Regression Coefficients (StdErr)		
	Overall	Not Censored	Censored	Ln(MPR) (OLS)	Ln(Dur) (OLS)	Ln(Dur) (Gen. Tobit)
Age at Diagnosis	9.512 (2.485)	9.688 (2.487)	8.879 (2.373)	-0.010^a (0.002)	-0.032^a (0.006)	-0.080^a (0.007)
Gender (Male)	0.747 (0.435)	0.742 (0.438)	0.765 (0.424)	0.008 (0.009)	0.072^b (0.033)	0.104^b (0.040)
Gender (Female)	0.253 (0.435)	0.258 (0.438)	0.235 (0.424)			
Race (Black)	0.079 (0.270)	0.083 (0.276)	0.065 (0.247)	-0.030^b (0.015)	-0.174^a (0.055)	-0.287^a (0.068)
Race (Hispanic)	0.116 (0.320)	0.120 (0.325)	0.100 (0.300)	-0.052^a (0.012)	-0.228^a (0.045)	-0.341^a (0.056)
Race (Asian)	0.051 (0.219)	0.052 (0.222)	0.045 (0.208)	-0.049^a (0.017)	-0.110^c (0.065)	-0.215^a (0.081)
Race (Other)	0.030 (0.171)	0.032 (0.175)	0.026 (0.159)	-0.007 (0.022)	-0.103 (0.083)	-0.219^b (0.103)
Race (White)	0.724 (0.447)	0.713 (0.452)	0.764 (0.425)			
Income (1st Quintile)	0.120 (0.325)	0.122 (0.327)	0.115 (0.319)	0.002 (0.014)	0.032 (0.051)	0.010 (0.063)
Income (2nd Quintile)	0.171 (0.376)	0.173 (0.378)	0.163 (0.370)	0.010 (0.012)	0.026 (0.044)	0.027 (0.054)
Income (3rd Quintile)	0.206 (0.404)	0.200 (0.400)	0.226 (0.419)	0.018 (0.011)	0.016 (0.042)	0.059 (0.051)
Income (4th Quintile)	0.224 (0.417)	0.219 (0.414)	0.241 (0.428)	0.017 (0.011)	0.047 (0.041)	0.093^c (0.050)
Income (5th Quintile)	0.279 (0.449)	0.286 (0.452)	0.255 (0.436)			
Copay‡ ($0)	0.124 (0.329)	0.122 (0.327)	0.131 (0.337)	0.017 (0.013)	0.063 (0.048)	0.096 (0.059)
Copay‡ ($\geq$$10)	0.567 (0.496)	0.540 (0.498)	0.664 (0.472)	0.002 (0.008)	-0.069^b (0.031)	0.025 (0.038)
Copay‡ ($1-$9.99)	0.309 (0.462)	0.338 (0.473)	0.205 (0.404)			
Drug Switches‡ (Zero)	0.621 (0.485)	0.688 (0.463)	0.378 (0.485)			
Drug Switches‡ (One)	0.231 (0.422)	0.207 (0.405)	0.321 (0.467)			
Drug Switches‡ (2 or more)	0.148 (0.355)	0.106 (0.307)	0.301 (0.459)			
Comorbidities‡ (Zero)	0.603 (0.489)	0.628 (0.484)	0.515 (0.500)	0.035^a (0.012)	0.154^a (0.047)	0.038 (0.056)
Comorbidities‡ (One)	0.226 (0.418)	0.222 (0.416)	0.239 (0.427)	0.039^a (0.014)	0.145^a (0.054)	0.082 (0.065)
Comorbidities‡ (2 or more)	0.171 (0.377)	0.150 (0.357)	0.247 (0.431)			
Semester‡ (Spring)	0.311 (0.463)	0.391 (0.488)	0.021 (0.145)			
Semester‡ (Summer)	0.287 (0.453)	0.350 (0.477)	0.061 (0.239)	0.008 (0.010)	0.127^a (0.040)	0.179^a (0.048)
Semester‡ (Fall)	0.402 (0.490)	0.259 (0.438)	0.918 (0.275)	0.012 (0.008)	0.110^a (0.033)	0.146^a (0.040)
Time‡	13.858 (13.449)	10.054 (9.494)	27.577 (16.371)			
Constant				-0.257^a (0.023)	2.078^a (0.087)	2.939^a (0.105)
Persons	4091	3203	888	4091	3203	4091

Note 1: ‡ Regressions based on the first period values. However, the means and std deviations are reported for the last month observed.
Note 2: Except for time and age variables, the numbers are percentages.
Note 3: a, b, c are significance levels at 1,5 and 10% respectively, and standard errors in parenthesis.

Twelve percent of the children in our sample are in the lowest income group, while 17.1%, 20.6%, 22.4% and 27.9% are in the 2nd, 3rd, 4th and 5th income groups respectively. This distribution of persons in different income groups is relatively similar across those that discontinue drug therapy versus those that do not.

Among the time-varying covariates, in the month when the therapy is discontinued or the therapy spell is censored, 12.4% of the children have zero copay, 30.9% have a copay in the $1 to $9.99 range, while 56.7% have a copay of $10 or more. Similarly, by the last month observed, 62.1% had never switched their ADHD drug, 23.1% had switched it once and 14.8% switched it more than once. Also, 60.3% had no recorded comorbidities, 22.6% had one comorbidity and 17.1% had two or more comorbidities.

Correlation with MPRs: To see which of these child characteristics are correlated with the medication possession ratio (MPR), we estimated a simple OLS regression of log of MPR on child characteristics (and used the first period value for the time varying covariates). The MPR was constructed in a manner comparable to that used in the literature.[4] The results are given in column (4) of Table 2 and show, for instance, that a one year older age at initiation is associated with a 1% lower MPR. These results should be interpreted in the context of the MPR *while* the children are on drug therapy. Thus, for instance, African-American, Asian and Hispanic children have lower MPRs compared to the White American children by 3%, 5.2% and 4.9% respectively. There are no statistical differences by gender, income status, or copay. However, compared to children with two or more comorbidities, those with no comorbidities have 3.5% and 3.9% higher MPRs.

Correlations with Durations: Note that the distribution of copay, drug switching and comorbidities is quite different among those that eventually exit versus those that are censored. While these descriptive statistics are informative about the correlation of these covariates and the length of drug therapy, they do not control for confounding factors (or for the time varying nature of some of these variables). To get a sense of how these covariates are correlated with the length of drug therapy, we estimated an OLS regression of log duration for children with completed spells.[5] The results are reported in column (5) of Table 2 and the signs on the coefficients are generally consistent with duration times reported by subgroups in Table 1. For instance, the coefficient of .072 on males implies that, compared to females, males have 7.2% longer therapy durations. Similarly, African-American, Hispanic, Asian and Other children have 17.4%, 23%, 10.9% and 10.3% shorter therapy durations compared to white children.

Since these OLS estimates are based on children who have completed therapy spells (i.e. are not censored), these estimates would be, at best only inefficient if the censored and uncensored children have similar characteristics. However, as earlier pointed out, the characteristics across these two groups are quite different, especially in their distributions of copay and, comorbidities (and drug switching) variables. Thus, the association between covariates and the duration from the OLS estimates on uncensored children are likely to be very different if we also include the sample of children with censored observations. To check this, we re-estimated the log duration model on the full sample using a Generalized Tobit (right censoring with individual censoring times). Results are displayed in the last column of Table 2. The coefficients on age, gender and race variables all increase in magnitude. For instance, the coefficient on male implies that males have 10.4% longer

[4] Specifically, we constructed it by dividing the sum of the number of drug-days supply available in each period to the total number of days a child is observed in the study period.

[5] We set the time varying covariates to their first period value and did not include the variable on drug switches since in the first period everyone has the same value of zero for this variable.

durations than females (compare this to the OLS estimate of 7.2%) and African-Americans have 28.8% shorter durations compared to white children (compare this the OLS estimate of 17.4%). A comparison of coefficients across the two models shows that OLS coefficients are generally smaller in magnitude.

Neither of these regression based methods for analyzing durations provide any straight forward way to incorporate time-varying covariates. Using the first period value or last period (or some other combination) of the time-varying covariates is quite arbitrary, and will result in very different estimates. In fact we checked this by replacing the first period values with the last period values. All coefficients changed in magnitude and significance levels (but as before, the OLS coefficients were smaller in magnitude than the generalized Tobit estimates). Further, the regression on completed spells samples simply ignores information available from children with incomplete therapy spells. Expanding the analysis to full sample requires correcting for censored observations. However, standard correction procedures such as Tobit and Heckit, or generalized Tobit as implemented in column (5) of Table 2, impose strong distributional assumptions (particularly, Tobit assumes normality of the error terms and homoskedastic errors) and even then, do not account for time-varying covariates nor for a flexible duration dependence.

By contrast, the hazard framework provides a straight forward way to incorporate time-varying covariates, utilize information provided by incomplete therapy spells (common in observational and clinical data), and allows for duration dependence (parametrically and non-parametrically). Finally, while the hazard framework addresses a different question (i.e., what is the probability that an individual discontinues therapy conditional on not discontinuing until then?), the estimates of the hazard function can be used to back-out the association between a covariate and the expected duration length.

4. Empirical Methods and Results

4.1. **Statistical Specification.** We use discrete time hazard rate models to estimate the impact of age at start of medication therapy, demographics (gender, race), income, coinsurance, measures of comorbidity, and number of times a child switches the main drug for therapy on the timing of discontinuation of drug therapy.

In a continuous time model, let $\lambda_i(t)$ be the hazard or the instantaneous probability that a child discontinues drug therapy at time t, conditional on not having discontinued it until that point in time. Next, allow the hazard to have the proportional form given by

$$\lambda_i(t) = \lambda_o(t) exp(x_i(t)'\beta) \tag{1}$$

where $x_i(t)$ are the potentially time varying individual specific covariates that effect the hazard rate, and $\lambda_o(t)$ is the baseline hazard function that describes the risk for an individual with $x_i = 0$.

If $f_i(t)$ and $F_i(t)$ are the corresponding density and cumulative density functions, then it can be shown that the survivor function $S_i(t)$ is given by $S_i(t) = exp\{-\int_0^t \lambda_i(\tau)d\tau\}$ where the integral in the curly brackets in the last expression is the cumulative hazard of discontinuation. Since the data are observed at discrete time periods, we follow the grouping of continuous time proportional hazard rate models with grouping points at $t_j, j = 1, \ldots, J$ (where $J = 72$) to describe the discrete time proportional hazards model (see Meyer (1990), Prentice and Gloeckler (1978), Kalbfleisch and Prentice (2002), Cameron and Trivedi (2005)). Let the intervals be $[0, t_1), [t_1, t_2), \ldots, [t_j, \infty)$ then, assuming that the child specific covariates are constant during each interval (though the hazard itself is not constant during the interval), the expression $exp(x_i(t)'\beta)$ can be pulled out of the integral within a discrete interval. Hence the cumulative discontinuation probability by the end of period t is given by

$$F_i(t) = 1 - S_i(t) = 1 - exp\Big\{-\sum_{j=1}^{t} exp(x'_{ij}\beta + \lambda_j)\Big\}, \tag{2}$$

where $\lambda_j = ln(\int_{t_{j-1}}^{t_j} \lambda_o(\tau)d\tau)$ is the natural log of the integrated baseline hazard within an interval. If t_j is the first time period during which a child is observed to have discontinued the drug therapy, then $F_i(t_j) - F_i(t_{j-1})$ is the probability that the child discontinues during the period and $S_i(t_j) = 1 - F_i(t_j)$ is the probability that s/he does not. Then the discrete time hazard (λ_{ij}), i.e. the conditional probability that child i discontinued drug therapy in period $[t_{j-1}, t_j)$ and the likelihood function (L) are given by

$$\begin{aligned} \lambda_{ij} &= Pr[t_{j-1} \le T_i < t_j | T_i \ge t_{j-1}] = \frac{F_i(t_j) - F_i(t_{j-1})}{1 - F_i(t_j)} \\ &= 1 - exp\{-exp(x'_{ij}\beta + \lambda_j)\} \\ \text{and } L &= \prod_{i=1}^{N} \Big[F_i(t_j) - F_i(t_{j-1})\Big]^{c_i} \Big[1 - F_i(t_j)\Big]^{1-c_i}, \end{aligned} \tag{3}$$

where $c_i = 1$ is an indicator variable if the child discontinues drug therapy and 0 otherwise.

The hazard rate approach also allows for modelling unobserved heterogeneity. For instance, if it is assumed to take a multiplicative form then equation (1) becomes $\lambda_i(t) = \lambda_o(t)\theta_i exp(x_i(t)'\beta)$, where following Meyer (1990), the term θ_i is independent of x_{ij}. This changes the discrete time hazard in equation (3) to $\lambda_{ij} = 1 - exp\{-exp(x'_{ij}\beta + \lambda_j + \ln[\theta_i])\}$. Even without assuming any distribution of θ_i, the model parameters (β, λ_j) can be consistently estimated following Heckman and Singer (1984). However it is common (and convenient) to assume gamma distribution for θ_i with unit mean and constant variance (i.e., $E(\theta_i) = 1, var(\theta_i) = \sigma^2$), which retains a closed form expression

for the log-likelihood function. Finally, the limiting case of $\sigma^2 \to 0$ reduces the log-likelihood with unobserved heterogeneity to the one given in equation (3).

4.2. **Results.** Table 3 summarizes estimates from several alternative specifications. The first seven columns do not account for unobserved heterogeneity, whereas column (8) re-estimates the specification in column (3) while modelling unobserved heterogeneity with a gamma distribution.

The first column in Table 3 reports association between hazard and gender, race/ethnicity and age at start of drug therapy on the continuation hazard. The reference group is white female children. Column two adds income and copay to the specification and column three further extends the specification by including the drug switching and comorbidity variables. Each of these models also controls for a baseline exit pattern parametrically using a third order polynomial of time, as well as seasonality of drug discontinuation behavior via indicator variables for summer and fall.[6]

The results consistently show that the baseline discontinuation risk rises rapidly until month 7 and then declines after that until month 48 (based on the estimates from specification (1)). We also find that the risk that a child discontinues therapy is greater during summer than in spring.

Turning to individual predictors, the estimates confirm that the discontinuation hazard differs systematically by child demographics and age at which drug therapy is initiated (compare Figure 1). Specifically, the risk of discontinuing the therapy is significantly higher among minority children and children who get diagnosed later. For example, based on specification (1), African-American, Hispanic and, Asian children are at least 33% more likely, on average, to quit therapy in a given month than white children.[7] While African-American and Hispanic children show the highest rates of discontinuation, the differences to Asian and Other (non-white) children are not statistically significant. Noting that the average age of a child at start of drug therapy is approximately 9 years in our samples (see Table 2), specification (1) suggests that the risk of discontinuation is 20.3% greater for children who start drug therapy at age 10 compared to children who start drug therapy at age nine.[8] In addition, there is some evidence that boys are less likely to discontinue the therapy than girls.

As shown in specification (2), the association of the demographic characteristics and age at start of drug therapy with the exit risk changes little when we control for copay and income. While the discontinuation risk appears unrelated to the income quintile, there is some evidence that copay is

[6]Semi-parametric forms for λ_i were also estimated by including a series of dummy variables, one for each period, instead of the cubic polynomial in time. Results were similar to those reported in the table and are not presented here.

[7]We compute the difference in the exit probability for African-Americans as $100 \cdot (\exp(0.314) - 1) = 36.88$.

[8]From specification (1) in Table 3 we compute the difference in the exit probability as $100 \cdot (\exp(0.088 \cdot 10) - 1) - 100 \cdot (\exp(0.088 \cdot 9) - 1) = 20.309$.

TABLE 3. Hazard Rate Estimates for Risk of Discontinuing Drug Therapy

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
x_2 : Age (at Initiation Date)	0.088^a	0.088^a	0.090^a	0.103^a	0.102^a	0.081^a	0.109^a	0.101^a
	(0.007)	(0.007)	(0.007)	(0.009)	(0.008)	(0.007)	(0.008)	(0.011)
x_3 : Gender (Male)	-0.086^b	-0.087^b	-0.090^b	-0.063	-0.085^b	-0.100^a	-0.091^b	-0.106^b
	(0.041)	(0.041)	(0.041)	(0.050)	(0.042)	(0.039)	(0.043)	(0.048)
$x_{4.1}$: Race (Black)	0.314^a	0.316^a	0.314^a	0.330^a	0.301^a	0.296^a	0.252^a	0.352^a
	(0.065)	(0.067)	(0.067)	(0.081)	(0.069)	(0.064)	(0.071)	(0.080)
$x_{4.2}$: Race (Hispanic)	0.336^a	0.331^a	0.336^a	0.330^a	0.307^a	0.236^a	0.333^a	0.392^a
	(0.056)	(0.056)	(0.056)	(0.071)	(0.058)	(0.054)	(0.059)	(0.073)
$x_{4.3}$: Race (Asian)	0.212^a	0.208^a	0.205^b	0.201^b	0.269^a	0.155^b	0.292^a	0.238^b
	(0.080)	(0.080)	(0.080)	(0.102)	(0.082)	(0.077)	(0.083)	(0.095)
$x_{4.4}$: Race (Other)	0.256^b	0.252^b	0.239^b	0.253^b	0.200^c	0.144	0.212^b	0.260^b
	(0.102)	(0.102)	(0.102)	(0.122)	(0.105)	(0.100)	(0.108)	(0.118)
$x_{5.1}$: Income (1st Quintile)		0.032	0.032	0.042	0.040	0.032	0.041	0.018
		(0.063)	(0.063)	(0.078)	(0.065)	(0.061)	(0.067)	(0.073)
$x_{5.2}$: Income (2nd Quintile)		-0.012	-0.012	-0.037	-0.007	-0.037	0.038	-0.024
		(0.055)	(0.055)	(0.068)	(0.057)	(0.053)	(0.058)	(0.064)
$x_{5.3}$: Income (3rd Quintile)		-0.034	-0.037	-0.061	-0.043	-0.030	-0.012	-0.052
		(0.052)	(0.052)	(0.064)	(0.054)	(0.049)	(0.055)	(0.060)
$x_{5.4}$: Income (4th Quintile)		-0.074	-0.076	-0.121^c	-0.058	-0.105^b	-0.015	-0.098^c
		(0.050)	(0.050)	(0.063)	(0.052)	(0.048)	(0.053)	(0.060)
$x_{6.1}$: Copay ($0)		-0.111^c	-0.109^c	-0.095	-0.121^c	-0.091	-0.110^c	-0.136^c
		(0.060)	(0.060)	(0.075)	(0.062)	(0.058)	(0.063)	(0.069)
$x_{6.3}$: Copay ($\geq$$10)		-0.056	-0.054	-0.032	-0.072^c	-0.023	-0.073^c	-0.060
		(0.039)	(0.039)	(0.049)	(0.041)	(0.037)	(0.041)	(0.044)
$x_{7.1}$: Drug Switches (Zero)			0.141^a	0.139^b	0.135^a	0.151^a	0.101^b	0.156^a
			(0.048)	(0.059)	(0.048)	(0.047)	(0.050)	(0.053)
$x_{7.3}$: Drug Switches (2 or more)			0.104	0.140^c	0.144^b	0.124^c	0.143^b	0.096
			(0.069)	(0.084)	(0.067)	(0.071)	(0.069)	(0.075)
$x_{8.1}$: Comorbidities (Zero)			0.096^c	0.126^b	0.053	0.084^c	0.050	0.087
			(0.052)	(0.064)	(0.052)	(0.050)	(0.054)	(0.060)
$x_{8.2}$: Comorbidities (One)			0.029	0.039	-0.025	0.017	-0.017	0.020
			(0.060)	(0.074)	(0.060)	(0.058)	(0.062)	(0.067)
$x_{9.1}$: Semester (Summer)	0.416^a	0.414^a	0.413^a		0.401^a	0.493^a	0.308^a	0.425^a
	(0.041)	(0.041)	(0.041)		(0.043)	(0.040)	(0.043)	(0.042)
$x_{9.2}$: Semester (Fall)	-0.132^a	-0.135^a	-0.135^a	0.203^a	-0.159^a	-0.035	-0.322^a	-0.122^a
	(0.045)	(0.045)	(0.045)	(0.045)	(0.046)	(0.043)	(0.048)	(0.046)
$x_{10.1}$: Time	0.038^a	0.039^a	0.046^a	0.028^b	0.054^a	0.073^a	0.017^c	0.075^a
	(0.009)	(0.009)	(0.009)	(0.011)	(0.009)	(0.009)	(0.009)	(0.022)
$x_{10.2}$: Time Square	-0.003^a	-0.003^a	-0.004^a	-0.003^a	-0.004^a	-0.005^a	-0.002^a	-0.004^a
	(0.000)	(0.000)	(0.000)	(0.001)	(0.000)	(0.000)	(0.000)	(0.001)
$x_{10.3}$: Time Cubed	0.000^a	0.000^a	0.000^a	0.000^a	0.000^a	0.000^a	0.000^a	0.000^a
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
x_1 : Constant	-3.665^a	-3.607^a	-3.839^a	-4.065^a	-4.187^a	-3.566^a	-4.046^a	-3.984^a
	(0.093)	(0.101)	(0.124)	(0.152)	(0.128)	(0.119)	(0.130)	(0.165)
$ln(\sigma^2)$								-1.415^b
								(0.683)
Log Likelihood	-11,921.43	-11,917.62	-11,910.66	-8,161.69	-11,815.43	-11,902.14	-11,473.50	-11,909.36
Persons (Riskset)	4,091	4,091	4,091	2,970	4,080	4,101	4,076	4,091
Person-Months	56,692	56,692	56,692	45,494	65,137	45,723	67,018	56,692
Exits	3,203	3,203	3,203	2,082	3,002	3,502	2,875	3,203

Note 1: a, b, c are significance levels at 1,5 and 10% respectively, and standard errors in parenthesis.

Note 2: Specifications (1)-(4) and (8) use 3 months with 10 days or less of drug supply definition for an exit (discontinuation). Specifications (5)-(7) use 3 months 0 days, 2 months 10 days, and 4 months 10 days definitions respectively. Additionally, specification (4) excludes all children from the risk set that eventually exited during the summer months. Specification (8) is similar to specification (3) except that it also allows for multiplicative unobserved heterogeneity with gamma distribution.

a risk factor for discontinuing therapy. Children of parents who are not subject to a copay (copay of $0) are about 10.51% more likely to continue the therapy compared to their counterparts who face a copay of $1 to $9.99. However, the statistical significance level is at 10% and the result is not robust across specifications.

Comparing the coefficients in specifications (2) and (3), we find that the inclusion of the switching and comorbidity variables does not significantly alter the estimated coefficients of the other covariates. Inspection of column three reveals evidence of a u-shaped relationship between the number of changes in the drug and the discontinuation risk. Children who never switched drugs or who switched drugs more than once are 15.1% and 10.9% more likely to discontinue therapy. Lastly, we investigate the relationship of comorbidities on the discontinuation hazard. As shown in specification (3), children without comorbidities (about 60%, see Table 2) have a slightly greater discontinuation hazard than children with two or more conditions, but this difference is significant only at 10% and the statistical significance is not present in some of the other specifications, particularly, in specification (8) which accounts for unobserved heterogeneity or specifications (5) and (7) both of which are stronger criterion for what constitutes an exit.

Specifications (4) through (7) provide a series of robustness checks. Specification (4) excludes all children from the risk set who eventually discontinue therapy during the summer months. By focusing on the sample of children who do not exit during the summer months, we further investigate the potential role of the school year. As shown in Table 3, the coefficient of the covariates are fairly similar for this subsample, suggesting that the results in columns (1) through (3) are not driven by school year seasonality. Specifications (5) to (7) apply a different rule regarding the days of drug supply when classifying a discontinuation. Specifically, specifications (5) and (6) use a 3-months 0-days and a 2-months 10-days definitions (a slightly stronger and a weaker criteria for an exit, respectively). Specification (7) applies a 4-months 10-days rule which again is stronger criterion than the 3-months 10-days supply rule underlying specifications (1) through (3). The estimates in columns five to seven show that neither strengthening nor weakening the definition of what constitutes the end of the therapy meaningfully changes the coefficients and provide further evidence in support of the importance of the determinants of ADHD drug therapy that we identified in specifications (1) through (3).

The last column, column (8), uses the same definition of discontinuation and set of covariates as in column (3) but now allows for unobserved heterogeneity. The coefficients in column (8) are slightly larger in magnitude than those in column (3). This is consistent with unaccounted unobserved heterogeneity in column (3) which, if present, generally results in underestimating the coefficients. While the coefficients in the two specifications are not very different, nonetheless,

unobserved heterogeneity is causing attenuation in specification (3) (and hence we use estimates from specification (8), our preferred specification, in the discussion). The unobserved heterogeneity is further evidenced by the ratio of the size of the variance to its standard error (-1.415/.683 = -2.072), as well as a likelihood ratio test of specification (8) versus (3).[9]

4.3. **Expected Durations (Race and Gender).** To compare the estimates from our preferred specifiction, column (8) in Table 3, to those from the log-duration regression and the generalized Tobit discussed above (see Table 2), we calculate predicted therapy durations (in months) by sex and race/ethnicity.[10] Table 4 shows the predicted durations for the median child, i.e. aged 9.2 at initiation, a $10 or more copay, in the third income quintile and with no comorbidities and no drug switches. Therapy length in specification (8) is predicted for values of θ_i that correspond to the mean, median, 25th and 75th percentile values of the heterogeneity parameter ($\theta_i = 1, .920, .639, 1.274$) respectively.[11]

TABLE 4. Expected Durations by Race and Gender

	OLS Specification		Tobit Specification		Hazard Specification (8), $\theta_i = 1$	
	Male	Female	Male	Female	Male	Female
White	9.83	9.14	20.41	18.40	18.05	16.10
Black	8.26	7.69	15.31	13.80	12.19	10.77
Hispanic	7.83	7.28	14.51	13.08	11.63	10.28
Asian	8.80	8.19	16.47	14.84	13.89	12.30
Other	8.87	8.25	16.40	14.78	13.54	11.98

	Hazard Specification (8) with $ln(\sigma^2) = -1.415$					
	$\theta_i = 0.920$		$\theta_i = 0.639$		$\theta_i = 1.274$	
	Male	Female	Male	Female	Male	Female
White	19.68	17.61	27.68	25.24	13.82	12.23
Black	13.42	11.87	19.94	17.86	9.19	8.12
Hispanic	12.81	11.32	19.14	17.10	8.76	7.75
Asian	15.25	13.53	22.32	20.09	10.49	9.27
Other	14.88	13.19	21.84	19.64	10.22	9.03

Note 1: In all cases, durations computed for a child aged 9.2 at initiation and with $10 or more copay, in the third income quintile and with no co-morbidities and no drug switches.

Note 2: For specification (8), the θ_i values correspond to the mean, median, 25th and 75th percentile values ($\theta_i = 1, .920, .639, 1.274$) respectively when θ_i is gamma distributed with mean 1 and $ln(\sigma^2) = -1.415$.

[9]The $\chi^2_{(1)}$ statistic has a value of $2(lnL_8 - lnL_3) = 2.588$ with the associated p-value of .107 suggesting that the null of no unobserved heterogeneity can be rejected at the 10% level. Note that this likelihood ratio test is not strictly valid since specification (3) is not nested in specification (8) but rather that (8) reduces to (3) in the limit that $\text{var}(\theta_i) \to 0$.

[10]For the OLS and Tobit specifications, expected duration are computed via smearing, i.e. $E(Dur) = exp(\widehat{\beta}' x_o + \widehat{\sigma^2}/2)$. For details see Duan (1983). For the hazard rate models we computed expected durations numerically as $\int_0^\infty \widehat{S}(t_a|x_0)dt_a$ where $\widehat{S}(t_a|x_0) = \prod_{s=1}^{a-1} exp(-exp(\lambda_{0s} + \widehat{\beta}' x_o(t_{s-1}) + ln\theta_o))$ and where λ_{0s} is the polynomial in time.

[11]Recall from above that θ_i is assumed to be gamma distributed with mean 1 and a variance, σ^2, that is to be estimated. Based on our estimates in Table 3 $ln(\sigma^2) = -1.415$ implying a variance of the gamma distribution of .2429.

The results illustrate the magnitude of the estimated coefficients and the concerns with a simple log-duration regression and (arguably to a lesser extent) with the generalized Tobit approach. Not surprisingly, the durations predicted for the median child are substantially shorter in the simple log-duration model compared to the generalized Tobit and our discrete time hazard model with unobserved heterogeneity. While the predicted durations from the generalized Tobit model are much closer to the results from the discrete time hazard models (than they are to the OLS results) the generalized Tobit estimates are derived under strong distributional assumptions and ignore unobserved heterogeneity. The implication of these assumptions is seen most easily when we compare the differentials in durations by race or gender ignoring censoring (as in OLS), when we account for censoring (generalized Tobit) and, when we allow for a more flexible hazard and account for some unobserved heterogeneity (specification (8)).

For instance (see Table 4), the simple OLS duration model predicts a gap in therapy length of less than a month between boys and girls (top panel, columns 1 and 2), compared to a gap of approximately 1.5 to 2 months in specification (8) with $\theta_i = 1$ (top panel, columns 5 and 6). The OLS regression implies 6.97% shorter durations for females while the generalized Tobit predicts 9.86% shorter durations for females. By contrast, specification (8) predicts 11.25% or 11.42% shorter durations for females depending on if you are a female with mean or median value of unobserved factors. Similarly, compared to white children, OLS regression predicts 15.92% shorter durations for African-Americans and the Tobit predicts 24.98% shorter durations. However, once again specification (8) predicts larger differentials by race: 32.76% or 32.22% shorter durations for African-Americans depending on if we use the mean or the median value for the heterogeneity parameter.[12]

4.4. **Expected Durations (Age at Initiation).** The coefficient on age (per specification (8)) is 0.101 implying that the exit probability for a child that initiates therapy at age 10 is 26.4% higher than for a child starting therapy at age nine.[13] Equivalently, based on our simulations (for a white male child), the estimates predict 16.55 months long therapy duration for a 10 year old and 18.44 months duration for a 9 year old, i.e. 10.2% longer durations for the 9 year olds. Further, this difference becomes even larger and grows to about 50% longer duration for a child that initiates therapy at age nine compared to a child that initiates it at age fifteen.

[12]Note that while different values of the heterogeneity parameter predict different levels of expected durations, the differentials by race, gender and other covariates remain substantially higher than those from the Tobit model. For instance, even if we were to use the θ_i value corresponding to the 25th or the 75th percentile, the white-black differential would still be 28.5% or 33.5% respectively.

[13]This follows from $100 * (exp(.101(10)) - 1) - 100 * (exp(.101(9)) - 1) = 26.4\%$.

Our estimate is much larger than the one reported by Marcus et al. (2005) who report that compared to children who initiate therapy between the ages of 6-12, those that initiate it between ages of 13-17 have about 21% shorter durations (or rather a survival time ratio of .79). In their study on durations of ADHD drug therapy, Marcus et al. (2005) estimate a continuous time Weibul hazard model. They define an event (the discontinuation of drug therapy) using a 30 days gap between the days-supply provided at a refill time and the next time the prescription is filled. (Note that we use a 90 days gap or what we call a 3 month period to define an event). Further, they break the sample into two groups: children between the ages of 6-12 and those between the ages of 13-17 at the time of initiation of drug therapy. We investigated why the magnitude on age is so much smaller in their study. This was done in two steps.

First, we re-estimated our model making three main changes: (a) switch to no unobserved heterogeneity, (b) switch to a one-month definition of discontinuation (as opposed to the three month definition) and, (c) convert our age variable to a 1/0 binary variable with the switch at age 12. We then updated our simulations (for a white-male) in the two age groups and the difference in therapy durations reduced to about 33% (recall that the durations were about 50% longer for 9 year olds vs. 15 year olds). Second, in addition to the changes above, we (d) truncated our data at 12 months of follow-up period and, (e) removed the quadratic and cubic terms from our hazard rate specification. The reasons for these two additional changes were that Marcus et al. (2005) data were truncated at 12 months and, because they used a Weibul hazard. A Weibul hazard imposes a monotonic increasing or decreasing hazard (unlike the generalized Weibul, which they did not use, which allows non-monotonic hazard). Getting rid of the quadratic and the cubic term from our specification also imposes monotonicity on our hazard function.

When we updated our simulations (for a white-male) with these two additional changes, the difference in therapy durations reduced to about 23% across the two age groups, which brought it in accordance with the Marcus et al. (2005) estimate of 21%. Thus, we contend that our estimate is much more accurate since it does not impose a monotonic hazard, is based on a data series that is much longer and not truncated at 12 months and, the definition of an event itself is not as restrictive given that some children may not be using medication over weekends and other mini-holidays.

4.5. **Limitations.** Our results are robust to alternative empirical specifications as well as to alternative definitions of discontinuation. However, a number of limitations apply and need to be discussed.

First, we do not actually know the reasons for the discontinuation of drug therapy. For instance, the discontinuation may actually be prescribed, i.e., in the physician and parents view, the symptoms

may have been curbed and the child 'cured', in which case discontinuation is a desirable outcome. Ideally, we would like to conduct separate analyses for these two groups but data limitations prevented us from doing so. Thus, we would like to know how many of the children who stop their drug therapy were doing so under clinical recommendations. While a chart review of some randomly selected cases would be informative, it was not feasible. However, research on ADHD indicates that the majority of patients continue to have the diagnosis into adolescence and would thus be likely to need to continue medication. For instance, Barkley et al. (1990) followed 123 children with ADHD for eight years and found that 80% continued to have signs consistent with the diagnosis. Similarly, Biederman et al. (1996) studied 140 children diagnosed with ADHD ages 6-17 and followed them for 4 years and found that 85% continued to have the disorder. This suggests that the vast majority of children with ADHD have persistence of the syndrome at least for 4-8 years from diagnosis and would be unlikely to discontinue medication because of "growing out" of the disorder.

In our own data set we found that among those who discontinued drug therapy (per the three month 10 days definition) 1,765 children stopped using drugs sometime during 01/01/2000 and 12/31/2001. Of these, 281 (or 15.92%) left the Kaiser health plan at some point prior to 12/31/2005 and had still not restarted the drug use. However, of the remaining 1,484 who were still with Kaiser until 12/31/2005, 1195 (80.5%) restarted the drug therapy and 289 (19.5%) did not. Thus the majority of patients appear to need to be on medication for prolonged periods of time.[14]

Second, copay, age at initiation as well as other variables are predictors of duration and do not necessarily imply causality. The usual concerns regarding endogeneity vis-à-vis selection and omitted variables (our specifications are parsimonious) may both be present. For instance, we do not know if parents of children who anticipate staying on drug therapy for a longer time, are self-selecting into lower pharmacy copay plans. While this can potentially be a serious limitation, we do not think that self-selection is a large issue in this specific study group: Employers certainly have a choice of plans (Kaiser managed care plans as well as non-Kaiser plans), however, once they (i.e. the employers) pick a specific Kaiser managed care product, the employees within that firm typically do not have a choice across different Kaiser plans. Thus, to self-select into a specific Kaiser plan, parents would typically have to switch employers so that the desired Kaiser plan is available to them at the new place of employment. Similarly, other factors that are omitted from our specifications which may be correlated with both, the duration and our covariates include, (a) poor response to medication, (b) side effects of medication that bother the patient or the family or side effects of medical consequence, such as poor weight gain, (c) degree to which patient or family is reluctant to take or continue medication and, (d) severity of symptoms of ADHD.

[14]Further, in the practice of one of the authors who is a clinician at Northern California Kaiser Permanente, only 13 of 243 patients (5%), have come off medication for physician recommended reasons.

Finally, we acknowledge that the underlying problem is one of multiple spells, i.e., a child may start, stop, and restart medication therapy multiple times over the course of their childhood (and even into adulthood). However, our single event model still captures important determinants and risk factors of discontinuation. Future studies should extend this model to multiple spells and to other population groups.

5. Discussion

Compliance with drug therapy is of major concern to clinicians as well as policy makers since uncontrolled symptoms due to noncompliance present health risks for patients and may lead to social costs. This paper demonstrates how to implement a discrete time hazard rate model on pharmacy refills data to estimate the impact of child and family characteristics on the probability of discontinuing ADHD drug therapy. While the hazard rate approach is not a new statistical method, it has not been widely used in the compliance literature on ADHD. For instance Kemner and Lage (2006) use ANACOVA on durations and Lage and Hwang (2004) use multivariate regression analysis. The hazard rate approach makes efficient use of the information provided by censored observations (incomplete therapy spells) and allows us to incorporate time varying covariates and unobserved heterogeneity. The Marcus et al. (2005)) study on ADHD compliance imposes a non-flexible hazard function as well a very strict definition of an event (as discussed earlier in subsection 4.4).

We discuss the results on time varying covariates first, and then the results on age at initiation of therapy followed by those on race and ethnicity.

Copay, Comorbidities, Drug Switches and Seasonality: Compared to children who have a copay in the range of $1-$9.99, those with zero copay are less likely to discontinue drug therapy. However, the result is not statistically significant for all specifications and there is no statistical difference in exit probabilities for those in excess of $10 copay with the $1-$9.99 comparison group. Our result is consistent with Huskamp et al. (2005).[15] Without controlling for other factors, the mean duration time for children with zero comorbidities is 10.66 months while for those with two or more comorbidities is 13.99 months (see Table 1). However, our hazard rate analysis finds no statistical difference in the discontinuation probabilities for children with zero, one or two or more comorbidities (see Table 3). Finally, we find that children who either never switched their drug or switched it frequently (2 or more times) are about 15% more likely to quit drug therapy than those that switched the drug only once. Further, children that never switched their drug are not necessarily those who initiated drug therapy on a short-term trial basis: in our sample,

[15] They do not have a zero copay compared with a positive amount in their study but report that increases in copay for brand name drugs were not associated with a significant change in probability of discontinuation of drug therapy.

2,539 children never switched their drug and among these 336 (13.23%) did not discontinue therapy before the end of the observation period and, the remaining 2,203 children (86.77%) had an average time on therapy of 7.16 months (see Table 1). This suggests that some children are not being switched to find an adequate medication when necessary – perhaps because the poor response to initial drug is not being reported back to the physician – and hence eventually discontinue drug therapy. Additionally, those who switch the drug frequently and discontinue may be struggling to find a drug that suits them. Like some other studies (Hugtenburg et al., 2005, Marcus et al., 2005, Huskamp et al., 2005), we also control for seasonality and the association with summer months and find that children are more likely to discontinue drug therapy during the June-August summer months (34% more likely). This could be indicative of optimal treatment patterns, for instance, for families that are unsure about whether to continue with medication, it would make sense to use summer as the time to try discontinuing. However, if in fact the intent is not to discontinue drug therapy altogether, greater caution should be exercised when prescribing a 'drug-holiday' (whether prescribed by physicians or chosen by parents).

Age at Initiation: There are several studies that define compliance via medication possession ratio and find that younger children are more compliant (Firestone, 1982, Gau et al., 2006, Marcus et al., 2005, Thiruchelvam et al., 2001).[16] Our result, that children initiating therapy at a later age are at higher risk of discontinuing therapy, is consistent with these studies and implies that the exit probability for a child that initiates therapy at age 10 is 26.4% higher than for a child starting therapy at age nine.

It is worth noting that age at initiation itself is not necessarily a causal factor but rather children who start the medications at earlier ages are likely to be different in several unmeasured ways that would predispose them to better adherence - they, their parents, and their teachers may be more likely to have favorable attitudes about medications, and they are also likely to be more severe cases (since more severe cases may be detected earlier).[17] This is consistent with Thiruchelvam et al. (2001) and Faraone et al. (2007) who report low severity to be associated with low adherence and would explain why the coefficient on age is positive, i.e. children initiating therapy at a later age are at a higher risk of discontinuing therapy. More importantly, this would also imply that the correlation with age at initiation is purely spurious and any policy that changes the average age at which children begin treatment would not necessarily have an effect on adherence.

[16] An exception is Perwien et al. (2004) who report that mean length of compliance is higher for adults than for children (49.5 days vs. 34.2 days).

[17] We have adopted our language from the referee report to make this point very explicit and also thank the referee for pointing out that exits during summer months may be consistent with optimal treatment patterns.

However, it is also possible that age is a causal factor in itself – older children are more likely to refuse medication (Sleator et al., 1982, Swanson, 2003). Children who initiate therapy at a younger age may be more compliant even at older ages simply due to habit. In fact, Faraone et al. (2007) who control for severity of ADHD explicitly, report the children initiating therapy at an older age were less likely to adhere to drug therapy. Thus, if age is a causal factor, then policies that change the average age of initiation may also inadvertently change the compliance with drug therapy more generally.

Our finding that therapy initiation at a younger age is associated with greater therapy compliance is particularly interesting in light of developments that may make early detection and diagnosis of ADHD less likely. Increasingly state and federal laws are being enacted that prevent teachers and other school personnel from requiring the use of a psychotropic drug for any student, especially as a precondition for attending classes. These laws are motivated in part by the concern that without such protections children are wrongly diagnosed and stigmatized as mentally disordered. However, some states have tightened such laws even further: Connecticut passed a law in 2001 (AB 5701) prohibiting school personnel from even *recommending* the use of psychotropic drugs to parents for any child, which was followed by similar laws in Illinois and Virginia in 2002 (SB 1719 and HB 90 respectively). At the federal level, the pendulum appears to be swinging in the other direction as well: under a policy change to Individuals with Disabilities Education Act (IDEA), the Department of Education issued a policy clarification memorandum in 1991 stating that schools not only had to provide special services and accommodations for children with sufficiently severe ADHD, they also had to evaluate all children suspected by their parents and local education agencies of having the disorder.[18] However, a current proposed bill (HR 2387, introduced 5/17/2007) states that no federal funds may be used to establish or implement any universal or mandatory mental health, psychiatric, or socioeconomic screening program. Since ADHD symptoms are often detected in the school settings, our result suggests that these efforts may be detrimental to the wellbeing of the child and could lead to greater social costs as early detection and diagnosis of ADHD may be less likely in this legislative environment.[19]

Race: It is well-documented that minorities face many barriers to health care, including less access to health service providers, less insurance coverage, and less ability to pay for treatment. Consistent with this explanation, several studies have reported lower rates of ADHD diagnosis among African-American and Hispanic children as well as lower use of medication therapy for treatment (Schneider

[18] See memorandum from U.S. Department of Education, Sep 21, 1991 "Clarification of Policy to Address the Needs of Children with Attention Deficit Disorders within General and/or Special Education". A copy is posted on http://www.reedmartin.com/1991memo.htm

[19] In a survey conducted in Washington D.C. area, Sax and Kautz (2003) found that in 52.4% of cases, ADHD diagnosis was first suggested by a child's teacher or other school personnel.

and Eisenberg, 2006, Cox et al., 2003, Stevens et al., 2005, Bokhari et al., 2005). However, even after controlling for differences in income and copay – which may be correlated with access to health care (e.g., ability to pay), we find that minority children are more likely to discontinue drug therapy compared to white children. For instance, African-American children, per specification (8) are about 42.2% more likely to discontinue drug therapy, or equivalently have about 32% shorter durations (18.05 months for white males vs. 12.19 months for African-American males per Table 4 for $\theta_i = 1$). Once again, our estimates by race and ethnicity are larger in magnitude than those reported by Marcus et al. (2005) but the reasons are the same as those discussed earlier in the context of age at initiation.

Race differentials in continuation of treatment have been noted in other areas as well. For instance, our findings that African-American children have a higher probability of discontinuation than white children are consistent with studies showing that adherence to diabetes and asthma medications are lower among African-Americans compared to white Americans or drug treatment for congestive heart failure (Williams et al., 2007a,b, Bagchi et al., 2007, Schectman et al., 2002). The greater discontinuation risk in our adjusted models may be the result of, among others, any of the following factors: (a) poor proxies for access to care, (b) selection by other unobserved factors, and (c) differential response to drug therapy.

Levels of insurance, copay and incomes are some of the usual proxies of access to health care and may hence also affect continuation of care. However, since the population under consideration is insured, then either copay and income are poor controls of access to and continuation of medical care, or there are other dimensions of access not captured by these measures. For instance, income per number of household members may be a more relevant measure rather than just income given that minority households tend to be larger (U.S. Census Bureau, 2006). Other dimensions include household and workplace locations relative to Kaiser facilities, which impact travel and time costs and may differ across racial and ethnic lines, as well as cultural differences between physicians and patients (e.g., language and cultural background).

Alternatively, minority children who receive ADHD medications may be a select group. For example, we may speculate that minority children who start treatment have, on average, more severe symptoms of ADHD. However, if the degree of severity differs for minorities in our sample, we would expect them to have longer therapy spells since severity of ADHD is documented to be positively correlated with adherence (see Thiruchelvam et al. (2001) and Faraone et al. (2007)). Given that we observe minority children to discontinue ADHD therapy earlier, selection by severity may either not be present in our samples or our other covariates (e.g., age at initiation and comorbidities) are capturing unobserved factors other than severity.

Lastly, differences in discontinuation rates by race and ethnicity may be due to differential response to medication in home and school environments. While the literature on efficacy by race and ethnicity is relatively sparse, dosReis et al. (2003) surveyed about 250 parents with children being treated with ADHD medications and found that parents of non-white children were less satisfied with medication therapy overall as well as less satisfied with the improvement in school grades and school behavior. More research is needed to understand what other unobserved factors are associated with race that make minorities more likely to have lower compliance with drug therapy.

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