Changing Patterns of Alpha Agonist Medication Use in Children 2009-2011

Running Head: Alpha Agonist Use in Children

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Abstract

Objectives: To describe patterns of long- and short-acting alpha agonist use in a primary care population following Food and Drug Administration (FDA) approval of the long-acting alpha agonists guanfacine and clonidine.

Methods: Using a retrospective cohort design, children aged 4-18 years who received an alpha agonist prescription between 2009-2011 were identified from a national sample of 45 primary care practices in two electronic health record-based research networks. To focus on the treatment of behavior problems, children with hypertension were excluded. Alpha agonist receipt was identified using National Drug Codes (NDCs) and medication names. The proportion of children receiving long- and short-acting prescriptions in each year was calculated and examined with respect to reported mental health diagnoses and whether indications for use were on-label, had evidence from clinical trials, or no trial evidence.

Results: In a cohort of 282,875 children, 4,227 children (1.5%) received at least one prescription for an alpha agonist during the study period. Rates of long-acting alpha agonist use increased over 20-fold from 0.2% to 4% ($P<0.001$), while rates of short-acting alpha agonist receipt among children receiving psychotropic medication grew slightly between 2009 and 2011 from 10.6% to 11.3%. Only 20% of alpha agonist use was on-label (use of long-acting formulations for ADHD). Most children (68%) received alpha agonists for indications with evidence of efficacy from clinical trials but no FDA approval, primarily use of short-acting formulations for ADHD and autism; 12% received alpha agonists for diagnoses lacking randomized clinical trial evidence in children, including sleep disorders and anxiety, or for which there was no documented mental health diagnosis.

Conclusion: Long-acting alpha agonist use increased dramatically from 2009-2011, while short-acting use remained relatively stable. The safety and efficacy of off-label use warrant further investigation.

Key Words: Alpha Agonist, Primary Care, Electronic Health Record

Introduction

In September 2009 and October 2010, the United States Food and Drug Administration (FDA) approved long-acting forms of the alpha-2 adrenergic agonists, guanfacine and clonidine, respectively, as treatment for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents (hereafter "children") (Intuniv 2011, Kapvay 2010). Prior to these approvals, no form of alpha agonist had been approved for use in neurodevelopmental disorders among children. However, short-acting alpha agonists have been used off-label for many years as a treatment for ADHD (Hirota, et al. 2014). In addition, alpha agonists have been widely used off-label as a first-line pharmacological treatment for moderate or severe tics (Weisman, et al. 2013), and have been frequently prescribed for insomnia symptoms in children with ADHD, anxiety, and mood disorders (Owens, et al. 2010).

Although there is evidence that alpha agonist use has increased over time (Fontanella, et al. 2013, Rubin, et al. 2012), changes in prescribing patterns of alpha agonists after FDA approval, both on- and off-label, have not been studied in primary care settings. Even though primary care practitioners are often less comfortable than subspecialists in prescribing psychotropic medications (Fremont, et al. 2008), a majority of psychotropic medications are prescribed in primary care (Goodwin, et al. 2001). In this study, we used electronic health record (EHR) data from a national sample of primary care pediatric practices to describe prescription patterns of alpha-agonists from 2009-2011. These data include all children seen in a primary care setting, regardless of contact with behavioral health specialists.

Methods

Setting: This study was conducted within two EHR-based pediatric practice-based research

networks: The Pediatric Research Consortium (PeRC) of The Children's Hospital of Philadelphia, a two-state (Pennsylvania and New Jersey), hospital-owned, primary care network including 26 practices and >200,000 children (Fiks, et al. 2012), and the national Electronic Pediatric Research in Office Settings (ePROS) network, a sub-network of the American Academy of Pediatrics (AAP) Pediatric Research in Office Settings (PROS) consisting, at the time of this study, of 19 practices using seven different EHR vendors and serving approximately 90,000 children in 15 states.

Design and Sample Selection: We conducted a retrospective review of EHRs from these practices to identify a cohort of children aged 4-18 years old seen in-office between January 1, 2009 and December 31, 2011. To focus on the use of alpha agonists for behavioral complaints, children with an EHR diagnosis of hypertension were excluded.

Outcome: The primary outcome measure was receipt of an alpha agonist prescription at any time during the study period. Alpha agonist use was identified from the 11-digit national drug code (NDC) specific to each drug, as well as by examining medication names. The medications included long-acting and short-acting forms of clonidine hydrochloride and guanfacine hydrochloride. We included any form of alpha agonist that appeared in the EHR, either because it was prescribed by the practice or abstracted into the EHR as part of medication reconciliation. We did not capture data on prescriptions from outside of primary care that were never entered into a child's primary care medical record.

Independent variables included patient sex, age in months, and mental health diagnoses. Mental health diagnoses identified from encounters with codes from the International Classification of Diseases, Ninth Revision (ICD-9) classification (see footnote of Table 1).

Level of Evidence for Alpha Agonist Indication: We classified the diagnoses of children who

received alpha agonists into three categories based on a review of clinical trial evidence in the literature. First, "on-label" use was classified as use of a long-acting alpha agonist for ADHD, alone or with a stimulant medication, as this is the only FDA-approved indication in children (Intuniv 2011, Kapvay 2010) and is recommended by the AAP (Wolraich, et al. 2011). Second, we defined a category of "off-label with evidence from clinical trials" for indications for which alpha agonists are not FDA-approved but have shown efficacy at reducing symptoms in clinical trials. This category included use of a short-acting alpha agonist for ADHD (with or without comorbid tics or aggression) (Chappell, et al. 1995, Hazell, Stuart 2003, Palumbo, et al. 2008, Tourette's Syndrome Study Group, 2002), tic disorders (Cummings, et al. 2002, Du, et al. 2008), autism (Fankhauser, et al. 1992, Handen, et al. 2008), or aggression (defined as Conduct Disorder or oppositional defiant disorder (ODD))(Kemph, et al. 1993). All other uses of alpha agonists (e.g., sleep) were categorized as "off-label with no randomized clinical trial evidence in children," based on our review of Cochrane Database of Systematic Reviews (Cochrane Database, 2014), the Agency for Healthcare Research and Quality (AHRQ) evidence-based reports (AHRQ, 2014), available pediatric psychotropic medication practice parameters (AACAP, 2014) and pediatric sleep disorder guidelines parameters (Morgenthaler, et al. 2006).

Statistical Analysis: Analyses were descriptive. First, we tabulated the number of children in the cohort receiving any psychotropic medication prescription and the proportion receiving at least one alpha agonist prescriptions during the study period, stratified by short- and long-acting alpha agonists. We then calculated the proportion of children in the cohort receiving a psychotropic medication who received at least one long-acting or short-acting alpha agonist prescription in each year of the study (2009-2011), and the proportion of children receiving alpha agonists prescriptions who had a record in the EHR of any of the mental health diagnoses specified in

Table 1, also stratified by long- and short-acting forms. We compared patterns of use among children with each of the three levels of evidence for alpha agonist use (on-label, off-label with evidence from clinical trials, off-label with no randomized clinical trial evidence). We then calculated the proportion of children receiving an alpha agonist each year who were classified at each evidence level to determine whether on-label use increased as a proportion of all alpha agonist use.

All analyses were conducted in SAS software version 9.3 (SAS Institute Inc., Cary, NC) and Stata version 13.0 (StataCorp, College Station, TX). The Institutional Review Board (IRB) at the AAP approved this study and the IRB at CHOP determined this study to be IRB exempt.

Results

Study Population: The study cohort included 282,875 children (51% male, 44% ≥12 years of age). 9.8% (27,671 children) received at least one prescription for a psychotropic medication during the study, and 1.5% (4,227) received at least one prescription for an alpha agonist during the study period. Of those children prescribed an alpha agonist, 725 (17.2%) received a long-acting alpha agonist only, 3,162 (74.8%) received a short-acting alpha agonist only, and 340 (8.0%) received at least one prescription for both a long and short-acting alpha agonist. Compared to the overall cohort, children receiving alpha agonists were more likely to be male (74.6%) and ≥12 years of age (59.4%).

Overall Trends in Alpha Agonist Use: Among children receiving any psychotropic medication, overall rates of alpha agonist use increased from 10.7% in 2009 to 14.4% in 2011, largely driven by increases in long-acting alpha agonists, which increased over 20-fold from 0.2% to 4% (Figure 1A). The proportion of children receiving short-acting alpha agonists grew only slightly, from 10.6% to 11.3%.

Diagnoses of Children on Alpha Agonists by Level of Evidence: Of the 1,065 children who received a long-acting alpha agonist, 863 (81%) had an ADHD diagnosis (Table 1). Of those children, 98% were between the ages of 6 and 17, the FDA-approved age range for alpha agonists among children. Very few children received long-acting alpha agonists for other indications. Of the 3,502 children who received short-acting alpha agonists, over two-thirds had an ADHD diagnosis. The next largest categories were autism (8%) and tic disorders (5%), indications for which clinical trials have provided evidence but for which FDA approval has not been obtained. Three hundred thirty-two children (7.9%) received an alpha agonist without a mental health diagnosis documented in the EHR.

Of all 4,227 children receiving alpha agonists at any time during the study period, 863 (20%) received prescriptions that were on-label (long-acting for ADHD only), 2,877 (68%) for indications that were off-label with evidence from clinical trials, and 487 (12%) for indications that were off-label with no randomized clinical trial evidence in children. Following the FDA approval of long-acting alpha agonists in 2009, the proportion of alpha agonist use that was on-label increased over time, from 1% in 2009 to 22% in 2011 (Figure 1B). No clear trend was observed for use without clinical trial evidence.

Discussion

In this study of children in primary care settings, we found substantial growth in prescribing of long-acting forms of alpha agonists following FDA approval of the drugs clonidine and guanfacine. Although rates of short-acting alpha agonist use grew only slightly, there was a more than 20-fold increase in use of long-acting alpha agonists among children receiving any psychotropic medication, largely driven by prescribing for ADHD. However, despite this increase in prescribing of long-acting alpha agonists, the majority of alpha agonist

prescriptions received in this study were for short-acting forms. A majority of children (68%) received alpha agonists for indications for which there was some clinical trial evidence but no FDA approval, and 12% of children received alpha agonists for indications such as anxiety and sleep disorders for which there was no evidence from randomized clinical trials in children.

The increase in long-acting alpha agonist use in a broad sample of primary care practices after licensure is consistent with the growing use of long-acting medications in ADHD treatment, a change associated with better adherence for ADHD medications in general and especially stimulants (Adler, Nierenberg 2010, Spencer, et al. 2011). Further growth in long acting alpha-agonist prescribing is likely as clinicians look for medications to use either concurrently with or instead of stimulants and as long-acting alpha agonists appear on an increasing number of insurance company formularies. In the context of these trends, comparative effectiveness research will be warranted to better understand the response to and side effects from these treatments in actual practice settings. In addition, in those disorders where there is some evidence for use of a short-acting alpha agonist (e.g., autism), it is anticipated that further studies of the use of long-acting formulations will follow. The sustained predominance of short-acting forms over the course of the study period is consistent with prior research that found slow and inconsistent adoption of new psychotropic medications (Huskamp, et al. 2013), and could also indicate a preference for focusing on symptoms confined to particular times of day (e.g., before bedtime).

The AAP recently released a policy statement that "off-label" use does not indicate improper or contraindicated use, and that the purpose of off-label medication use is to benefit individual patients based on the judgment of their clinician (Frattarelli, et al. 2014). Much remains, however, to be learned about medication use in conditions with little or no published

clinical trial evidence. We found approximately 12% of alpha agonist prescriptions were received by children with indications with no trial evidence, primarily sleep disorders and anxiety. Though there are some older, open trials examining the use of alpha agonists in children with post-traumatic stress disorder (Perry 1994), results from this study support increased research to document the benefits and risks of alpha agonist use in these disorders. Interestingly, close to 8% received an alpha agonist without a documented mental health diagnosis, raising additional concerns about documentation. This finding may reflect a lack of clinician documentation of an existing diagnosis, a lack of awareness by the primary pediatrician regarding a diagnosis made through the mental health system, or a child treated without receiving a specific diagnosis.

This study used EHR data from a national sample of primary care practices. Given the substantial increase in EHR use over the past decade (Hsiao, Hing 2014), these databases have become an increasingly important resource to study the usage patterns of psychotropic medications among children. In addition, the presence of blood pressure, growth, and laboratory and diagnostic test results in EHRs, outside the scope of the present study, further supports the use of the EHR to detect effectiveness, safety, and side effects of psychopharmacology. These data will be used in future studies that build upon the results presented.

This study had several limitations. First, EHRs commonly lack medication end dates; as a result, we conservatively credited children for receiving alpha agonists only for new entries in the EHR. This method might understate the duration of use. Second, although medication reconciliation is a regular part of pediatric practice, medications prescribed by mental health professionals may have been missed if those children failed to attend recommended health maintenance visits and/or physicians failed to document use of psychopharmacology prescribed

by outside clinicians. Third, certain diagnoses treated with alpha agonists, such as sleep problems, may be inconsistently documented in EHR data. As a result, the actual use of alpha agonists for sleep problems may be greater than that observed. Fourth, given the national sample of practices included in this study, we lack data on formulary restrictions at different sites that may have shaped prescribing for newly licensed alpha agonists. Use is likely to grow as these medications are increasingly covered by insurance. Finally, this study focused on three years of data around the licensing of the long-acting alpha agonists. As such, we lack data on longitudinal trends in alpha agonist use among individual children followed from the first use of psychotropic medications.

Conclusion

In this large national cohort of children receiving primary care, long-acting alpha agonist use increased from 2009-2011, driven largely by prescribing for ADHD, which was approved for use by the FDA in 2009, while use of short-acting alpha agonists remained relatively stable. A majority of alpha agonist use was off-label, although the proportion of on-label use increased over time. The safety and efficacy of off-label use, especially in the context of sleep and anxiety, warrant further investigation.

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Clinical Significance

In this large national sample, long-acting alpha agonist use increased over time, and many children received alpha agonists for indications with little clinical trial evidence, such as anxiety, sleep disorders, or no documented mental health problem. Additional study is needed to document effectiveness and safety in these conditions.

References:

1. Intuniv. [package insert]. Wayne, Pa, Shire Pharmaceuticals, Inc; 2011.
2. Kapvay. [package insert]. Atlanta, GA, Shionogi Pharma, Inc.; 2010.
3. Hirota T, Schwartz S and Correll CU. Alpha-2 agonists for attention-deficit/hyperactivity disorder in youth: a systematic review and meta-analysis of monotherapy and add-on trials to stimulant therapy. Journal of the American Academy of Child and Adolescent Psychiatry. 53:153-173, 2014.
4. Weisman H, Qureshi IA, Leckman JF, Scahill L and Bloch MH. Systematic review: pharmacological treatment of tic disorders--efficacy of antipsychotic and alpha-2 adrenergic agonist agents. Neurosci Biobehav Rev. 37:1162-1171, 2013.
5. Owens JA, Rosen CL, Mindell JA and Kirchner HL. Use of pharmacotherapy for insomnia in child psychiatry practice: A national survey. Sleep Med. 11:692-700, 2010.
6. Fontanella CA, Hiance DL, Phillips GS, Bridge JA and Campo JV. Trends in Psychotropic Medication Use for Medicaid-Enrolled Preschool Children. Journal of Child and Family Studies.1-15, 2013.
7. Rubin D, Matone M, Huang YS, dosReis S, Feudtner C and Localio R. Interstate variation in trends of psychotropic medication use among Medicaid-enrolled children in foster care. Children and Youth Services Review. 34:1492-1499, 2012.
8. Goodwin R, Gould MS, Blanco C and Olfson M. Prescription of psychotropic medications to youths in office-based practice. Psychiatr Serv. 52:1081-1087, 2001.
9. Fremont WP, Nastasi R, Newman N and Roizen NJ. Comfort level of pediatricians and family medicine physicians diagnosing and treating child and adolescent psychiatric disorders. International journal of psychiatry in medicine. 38:153-168, 2008.
10. Fiks AG, Grundmeier RW, Margolis B, Bell LM, Steffes J, Massey J and Wasserman RC. Comparative effectiveness research using the electronic medical record: an emerging area of investigation in pediatric primary care. J Pediatr. 160:719-724, 2012.
11. Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT and Visser S. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 128:1007-1022, 2011.
12. Chappell PB, Riddle MA, Scahill L, Lynch KA, Schultz R, Arnsten A, Leckman JF and Cohen DJ. Guanfacine treatment of comorbid attention-deficit hyperactivity disorder and Tourette's syndrome: preliminary clinical experience. J Am Acad Child Adolesc Psychiatry. 34:1140-1146, 1995.
13. Hazell PL and Stuart JE. A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. Journal of the American Academy of Child and Adolescent Psychiatry. 42:886-894, 2003.
14. Palumbo DR, Sallee FR, Pelham WE, Jr., Bukstein OG, Daviss WB and McDermott MP. Clonidine for attention-deficit/hyperactivity disorder: I. Efficacy and tolerability outcomes. Journal of the American Academy of Child and Adolescent Psychiatry. 47:180-188, 2008.
15. Tourette's Syndrome Study Group. Treatment of ADHD in children with tics: a randomized controlled trial. Neurology. 58:527-536, 2002.

16. Cummings DD, Singer HS, Krieger M, Miller TL and Mahone EM. Neuropsychiatric effects of guanfacine in children with mild tourette syndrome: a pilot study. Clin Neuropharmacol. 25:325-332, 2002.
17. Du YS, Li HF, Vance A, Zhong YQ, Jiao FY, Wang HM, Wang MJ, Su LY, Yu DL, Ma SW and Wu JB. Randomized double-blind multicentre placebo-controlled clinical trial of the clonidine adhesive patch for the treatment of tic disorders. The Australian and New Zealand journal of psychiatry. 42:807-813, 2008.
18. Fankhauser MP, Karumanchi VC, German ML, Yates A and Karumanchi SD. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. J Clin Psychiatry. 53:77-82, 1992.
19. Handen BL, Sahl R and Hardan AY. Guanfacine in children with autism and/or intellectual disabilities. J Dev Behav Pediatr. 29:303-308, 2008.
20. Kemph JP, DeVane CL, Levin GM, Jarecke R and Miller RL. Treatment of aggressive children with clonidine: results of an open pilot study. Journal of the American Academy of Child and Adolescent Psychiatry. 32:577-581, 1993.
21. The Cochrane Database of Systematic Reviews. Chichester, Wiley; 2014. Available at http://www.thecochranelibrary.com/view/0/index.html#http://www.thecochranelibrary.com/view/0/browse.html. Accessed on September 17, 2014.
22. Pediatric Conditions: Evidence-Based Reports. Rockville, M.D., Agency for Healthcare Research and Quality; 2014. Available at http://www.ahrq.gov/research/findings/evidence-based-reports/clinical/pediatric/index.html Accessed on September 17, 2014.
23. Practice Parameters. Washington, D.C., American Academy of Child & Adolescent Psychiatry; 2014. Available at http://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Home.aspx?hkey=fdafcb6b-8f72-42c2-8ea4-29ce3679bec1. Accessed on September 17, 2014.
24. Morgenthaler TI, Owens J, Alessi C, Boehlecke B, Brown TM, Coleman J, Jr., Friedman L, Kapur VK, Lee-Chiong T, Pancer J, Swick TJ and American Academy of Sleep M. Practice parameters for behavioral treatment of bedtime problems and night wakings in infants and young children. Sleep. 29:1277-1281, 2006.
25. Adler LD and Nierenberg AA. Review of medication adherence in children and adults with ADHD. Postgraduate medicine. 122:184-191, 2010.
26. Spencer TJ, Mick E, Surman CB, Hammerness P, Doyle R, Aleardi M, Kotarski M, Williams CG and Biederman J. A randomized, single-blind, substitution study of OROS methylphenidate (Concerta) in ADHD adults receiving immediate release methylphenidate. Journal of attention disorders. 15:286-294, 2011.
27. Huskamp HA, O'Malley AJ, Horvitz-Lennon M, Taub AL, Berndt ER and Donohue JM. How quickly do physicians adopt new drugs? The case of second-generation antipsychotics. Psychiatr Serv. 64:324-330, 2013.
28. Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM and Van Den Anker JN. Off-label use of drugs in children. Pediatrics. 133:563-567, 2014.
29. Perry BD. Neurological sequelae of childhood trauma: PTSD in children. In: Catecholamine Function in Posttraumatic Stress Disorder: Emerging Concepts. Edited by Murburg MM. Washington, D.C., American Psychiatric Press; 1994, pp. 223-255.

30. Hsiao CJ and Hing E. Use and characteristics of electronic health record systems among office-based physician practices: United States, 2001-2013. NCHS data brief.1-8, 2014.

Figure Legends

Figure 1A. Proportion of Children Receiving Psychotropic Medication that Received Alpha Agonists in Each Study Year (2009-2011). Note- the proportion of the entire cohort that received any psychotropic medication increased from 7.7% in 2009 to 8.4% in 2011. PM=Psychotropic Medication. AA=Alpha Agonist.

Figure 1B. Change in the Proportion of Alpha Agonist Use at Each Level of Evidence Over Time (2009-2011). AA=Alpha Agonist.

Table 1. Common Diagnoses[1] among Children Receiving Long- or Short-Acting Alpha Agonists

	Long-Acting Alpha Agonist Level of Evidence[2] (n=1,065)		Short-Acting Alpha Agonist Level of Evidence[2] (n=3,502)	
Diagnosis	On-Label	Off-Label No Randomized Clinical Trial Evidence in Pediatrics	Off-Label Evidence from Clinical Trials	Off-Label No Randomized Clinical Trial Evidence in Pediatrics
Attention-Deficit/Hyperactivity Disorder (ADHD)	863 (81.0%)[5]	N/A	2,392 (68.3%)	N/A
Tic Disorder[3]	N/A	26 (2.0%)	161 (4.6%)	N/A
Conduct Disorder[4]	N/A	0 (0.0%)	6 (0.2%)	N/A
Oppositional Defiant Disorder[4]	N/A	4 (0.4%)	27 (0.8%)	N/A
Autism[4]	N/A	48 (4.5%)	291 (8.3%)	N/A
Sleep Disorder[4]	N/A	10 (0.9%)	N/A	127 (3.6%)
Anxiety[4]	N/A	9 (0.8%)	N/A	65 (1.9%)
Other Diagnosis	N/A	25 (2.3%)	N/A	168 (4.8%)
No Diagnosis	N/A	80 (7.5%)	N/A	265 (7.6%)

[1] The following diagnostic categories were included: any mental health diagnosis (ICD-9 codes 290-319.99), ADHD (314-314.99), autism (299-299.99), schizophrenia (295-295.99), bipolar (296.00-296.10, 296.36-296.89), anxiety (300.00-300.29, 301.4), obsessive-compulsive disorder (300.3), conduct disorder (312.00, 312.89), depression (311, 296.20-296.35), oppositional defiant disorder (ODD) (313.81), sleep disorder (780.50-780.59, 327.0-327.8, 307.4, V69.4, V69.5), tic disorder (307.2-307.29, 333.3) and seizure disorder (345.00-345.99).

[2] On Label indicates FDA approval, which has only been obtained for long-acting alpha agonists for ADHD among children aged 6-17 years. Off-Label with Evidence from Clinical Trials indicates that review of the literature identified trials describing efficacy of alpha agonists for these indications, but FDA approval has not been obtained. Off-Label with No Trial Evidence indicates that there were not published trials for these indications.

[3] Children with comorbid ADHD and tics were counted in the ADHD group; these children did not have a diagnosis of ADHD

[4] These children did not have a diagnosis of ADHD or Tic Disorder

[5] Of these children, 848 (98%) were between the ages of 6-17, the age group for whom FDA approval was obtained.

*340 Children who received both long and short-acting alpha agonists are counted in both columns

Figure 1A.

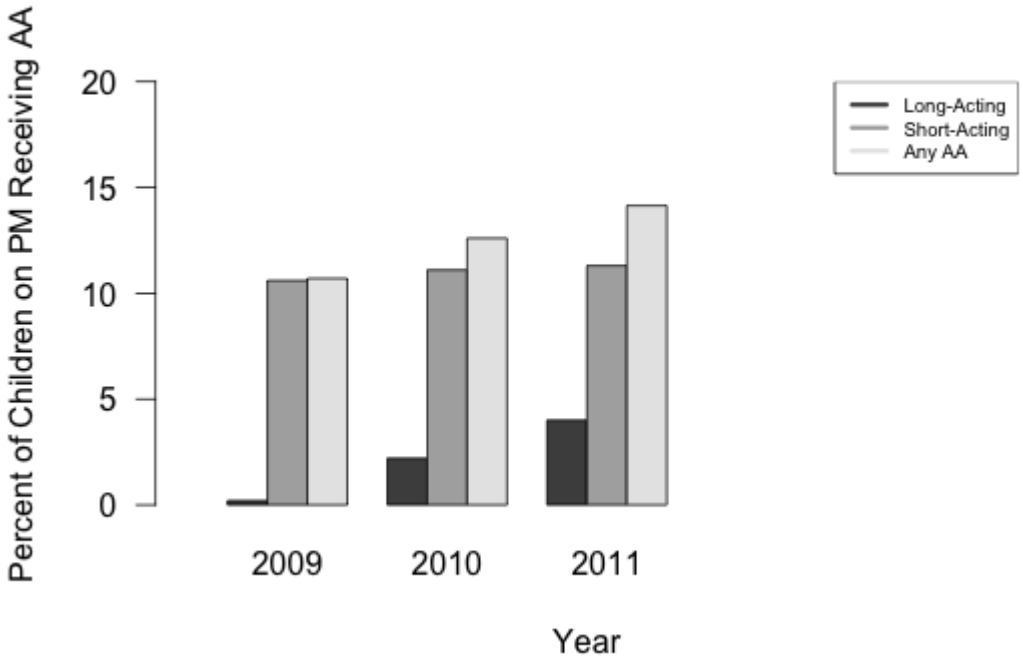
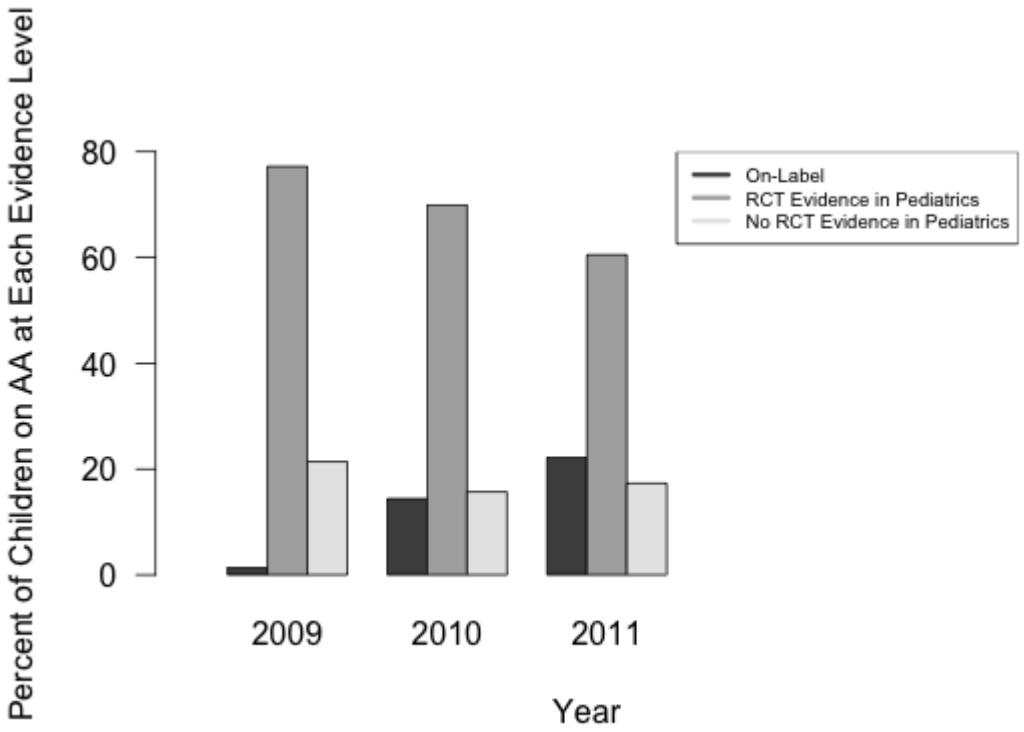

Percent of Children on PM Receiving AA
20
15
10
5
0
2009
2010
2011
Year
Long-Acting
Short-Acting
Any AA

Figure 1B.


Percent of Children on AA at Each Evidence Level
80
60
40
20
0
2009
2010
2011
Year
On-Label
RCT Evidence in Pediatrics
No RCT Evidence in Pediatrics