USE OF ATTENTION DEFICIT/HYPERACTIVITY DISORDER PHARMACOLOGICAL TREATMENT FOLLOWING THE PUBLIC DISCUSSION ON CARDIOVASCULAR SAFETY AND THE INTRODUCTION OF MEDICATION GUIDES FOR CENTRAL NERVOUS SYSTEM STIMULANTS AND ATOMOXETINE

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2010
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To my parents
ACKNOWLEDGMENTS

I want to thank my advisor, Almut Winterstein, for her continuous support and guidance. I especially appreciate that she held a high standard and never stopped challenging me. I would also like to thank my supervisory committee members Regina Bussing, Abraham Hartzema, Richard Segal, and Jon Shuster for their expertise, advice and encouragement. I extend my appreciation to all faculty members and staff in the department of Pharmaceutical Outcomes and Policy for their support and for everything they taught me during my study at the University of Florida.

I express gratitude to Florida’s Agency for Health Care Administration (AHCA) for the provision of Medicaid data. I appreciate Paul Duncan and Heather Steingraber from University of Florida-Florida Center for Medicaid & the Uninsured, and, Chris Mallison from Florida AHCA for their help on facilitating data access.

I want to thank my family—grandparents, parents, aunties, uncles, brother and cousins—for their infinite support throughout my life. I am grateful to Szu-Ping Lee for his company and emotional support throughout my graduate study. Finally, I thank my fellow graduate students and my friends for their friendship.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>4</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>8</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>10</td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>1 INTRODUCTION</td>
<td>15</td>
</tr>
<tr>
<td>Background</td>
<td>15</td>
</tr>
<tr>
<td>Need for Study</td>
<td>16</td>
</tr>
<tr>
<td>Purpose of Study</td>
<td>16</td>
</tr>
<tr>
<td>Study Significance</td>
<td>17</td>
</tr>
<tr>
<td>Research Questions and Hypotheses</td>
<td>17</td>
</tr>
<tr>
<td>Part I: Testing of the Change(s) in Stimulant Utilization</td>
<td>18</td>
</tr>
<tr>
<td>Part II: Comparability Test among Subgroups</td>
<td>19</td>
</tr>
<tr>
<td>2 LITERATURE REVIEW</td>
<td>29</td>
</tr>
<tr>
<td>Part I</td>
<td>29</td>
</tr>
<tr>
<td>The Role of Stimulants in ADHD Treatment</td>
<td>29</td>
</tr>
<tr>
<td>Stimulant Utilization among ADHD Patients</td>
<td>30</td>
</tr>
<tr>
<td>Factors associated with stimulant utilization</td>
<td>30</td>
</tr>
<tr>
<td>Factors associated with stimulant persistence</td>
<td>31</td>
</tr>
<tr>
<td>Stimulants and Cardiovascular Risk</td>
<td>32</td>
</tr>
<tr>
<td>Part II</td>
<td>33</td>
</tr>
<tr>
<td>New Drug Safety Information and Patients' or Health Care Providers'</td>
<td></td>
</tr>
<tr>
<td>Behavior</td>
<td>33</td>
</tr>
<tr>
<td>Dear healthcare professional letters</td>
<td>33</td>
</tr>
<tr>
<td>Public regulatory warnings and/or media reports of new safety</td>
<td>34</td>
</tr>
<tr>
<td>information</td>
<td></td>
</tr>
<tr>
<td>Factors mediate the impact of new drug safety information on drug</td>
<td>35</td>
</tr>
<tr>
<td>utilization</td>
<td></td>
</tr>
<tr>
<td>3 METHODOLOGY</td>
<td>42</td>
</tr>
<tr>
<td>Study Design</td>
<td>42</td>
</tr>
<tr>
<td>Data Source</td>
<td>42</td>
</tr>
<tr>
<td>Study Population</td>
<td>43</td>
</tr>
<tr>
<td>Cohort of New Episode ADHD Patients</td>
<td>43</td>
</tr>
<tr>
<td>Cohort of New Stimulant Users</td>
<td>44</td>
</tr>
<tr>
<td>Study Measures</td>
<td>44</td>
</tr>
<tr>
<td>Stimulant Initiation</td>
<td>44</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>Regulatory actions/discussions on stimulant cardiovascular safety</td>
<td>27</td>
</tr>
<tr>
<td>1-2</td>
<td>Evidence regarding safety concerns in recent drug utilization studies</td>
<td>28</td>
</tr>
<tr>
<td>2-1</td>
<td>Lists of stimulants approved for ADHD</td>
<td>39</td>
</tr>
<tr>
<td>2-2</td>
<td>Summary of FDA communication methods of drug safety information</td>
<td>40</td>
</tr>
<tr>
<td>2-3</td>
<td>Major factors affecting health services utilization</td>
<td>41</td>
</tr>
<tr>
<td>3-1</td>
<td>Stimulant refill patterns</td>
<td>54</td>
</tr>
<tr>
<td>3-2</td>
<td>Second-line ADHD treatment refill patterns</td>
<td>54</td>
</tr>
<tr>
<td>4-1</td>
<td>Summary of analysis time frame, eligible population, and event count</td>
<td>66</td>
</tr>
<tr>
<td>4-2</td>
<td>Patient and provider characteristics in stimulant initiation trend analysis</td>
<td>67</td>
</tr>
<tr>
<td>4-3</td>
<td>Testing results for stimulant initiation trend</td>
<td>69</td>
</tr>
<tr>
<td>4-4</td>
<td>Specification for stimulant initiation trend</td>
<td>69</td>
</tr>
<tr>
<td>4-5</td>
<td>Testing results for oral stimulant+ initiation trend</td>
<td>69</td>
</tr>
<tr>
<td>4-6</td>
<td>Specification for oral stimulant+ initiation trend</td>
<td>69</td>
</tr>
<tr>
<td>4-7</td>
<td>Comparability test results for stratified stimulant initiation trend</td>
<td>70</td>
</tr>
<tr>
<td>4-8</td>
<td>Patient and provider characteristics in stimulant discontinuation trend analysis</td>
<td>71</td>
</tr>
<tr>
<td>4-9</td>
<td>Testing results for stimulant discontinuation trend</td>
<td>73</td>
</tr>
<tr>
<td>4-10</td>
<td>Specification for stimulant discontinuation trend</td>
<td>73</td>
</tr>
<tr>
<td>4-11</td>
<td>Comparability test results for stratified stimulant discontinuation trend</td>
<td>74</td>
</tr>
<tr>
<td>4-12</td>
<td>Patient and provider characteristics in stimulant initial daily dose trend analysis</td>
<td>75</td>
</tr>
<tr>
<td>4-13</td>
<td>Testing results for stimulant initial daily dose trend</td>
<td>77</td>
</tr>
<tr>
<td>4-14</td>
<td>Specification for stimulant initial daily dose trend</td>
<td>77</td>
</tr>
<tr>
<td>4-15</td>
<td>Comparability test results for stratified stimulant initial daily dose trend</td>
<td>78</td>
</tr>
</tbody>
</table>
4-16  Patient and provider characteristics in stimulant maintenance daily dose 
trend analysis ................................................................. 79
4-17  Testing results for stimulant maintenance daily dose trend ...................... 81
4-18  Specification for stimulant maintenance daily dose trend .......................... 81
4-19  Comparability test results for stratified stimulant maintenance daily dose 
trend .................................................................................. 82
4-20  Patient and provider characteristics in pre-treatment electrocardiograph 
(ECG) use trend analysis ....................................................... 83
4-21  Testing results for pre-treatment electrocardiograph use trend .................... 85
4-22  Specification for pre-treatment electrocardiograph use trend ..................... 85
4-23  Comparability test results for stratified pre-treatment electrocardiograph use 
trend .................................................................................. 86
5-1   Age distribution of Florida Medicaid fee-for service population during 2001-
2008. ..................................................................................... 132
5-2   Age distribution of newly-diagnosed ADHD patient in Florida Medicaid fee-
for service population during 2001-2008. ............................................. 133
LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-1</td>
<td>Original and deseasonalized trends. A) stimulant initiation. B) stimulant discontinuation</td>
<td>55</td>
</tr>
<tr>
<td>4-1</td>
<td>Stimulant initiation trend</td>
<td>87</td>
</tr>
<tr>
<td>4-2</td>
<td>Stimulant initiation trend (oral products only)</td>
<td>89</td>
</tr>
<tr>
<td>4-3</td>
<td>Stimulant and atomoxetine initiation trend</td>
<td>88</td>
</tr>
<tr>
<td>4-4</td>
<td>Stimulant initiation trend by age (&lt; 5 years versus 5-13 years)</td>
<td>90</td>
</tr>
<tr>
<td>4-5</td>
<td>Stimulant initiation trend by age (14-20 years old versus 5-13 years old)</td>
<td>90</td>
</tr>
<tr>
<td>4-6</td>
<td>Stimulant initiation trend by gender</td>
<td>91</td>
</tr>
<tr>
<td>4-7</td>
<td>Stimulant initiation trend by race (Blacks versus Whites)</td>
<td>92</td>
</tr>
<tr>
<td>4-8</td>
<td>Stimulant initiation trend by race (Hispanics versus Whites)</td>
<td>92</td>
</tr>
<tr>
<td>4-9</td>
<td>Stimulant initiation trend by eligibility (Supplemental security income [SSI] versus Temporary assistance for needy family [TANF])</td>
<td>93</td>
</tr>
<tr>
<td>4-10</td>
<td>Stimulant initiation trend by eligibility (Foster care vs Temporary assistance for needy family [TANF])</td>
<td>93</td>
</tr>
<tr>
<td>4-11</td>
<td>Stimulant initiation trend by comorbidity status</td>
<td>94</td>
</tr>
<tr>
<td>4-12</td>
<td>Stimulant initiation trend by provider type</td>
<td>95</td>
</tr>
<tr>
<td>4-13</td>
<td>Stimulant discontinuation trend</td>
<td>96</td>
</tr>
<tr>
<td>4-14</td>
<td>Stimulant discontinuation trend by age group (&lt; 5 years versus 5-13 years)</td>
<td>97</td>
</tr>
<tr>
<td>4-15</td>
<td>Stimulant discontinuation trend by age group (5-13 years versus 14-20 years)</td>
<td>97</td>
</tr>
<tr>
<td>4-16</td>
<td>Stimulant discontinuation trend by gender</td>
<td>98</td>
</tr>
<tr>
<td>4-17</td>
<td>Stimulant discontinuation trend by race (Blacks versus Whites)</td>
<td>99</td>
</tr>
<tr>
<td>4-18</td>
<td>Stimulant discontinuation trend by race (Hispanics versus Whites)</td>
<td>99</td>
</tr>
<tr>
<td>4-19</td>
<td>Stimulant discontinuation trend by eligibility status (Supplemental security income [SSI] versus Temporary assistance for needy family [TANF])</td>
<td>100</td>
</tr>
<tr>
<td>Section</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>4-20</td>
<td>Stimulant discontinuation trend by eligibility status (Foster care versus Temporary assistance for needy family [TANF])</td>
<td>100</td>
</tr>
<tr>
<td>4-21</td>
<td>Stimulant discontinuation trend by comorbidity status</td>
<td>101</td>
</tr>
<tr>
<td>4-22</td>
<td>Stimulant initial daily dose trend</td>
<td>102</td>
</tr>
<tr>
<td>4-23</td>
<td>Stimulant initial daily dose trend by age group (&lt; 5 years versus 5-13 years)</td>
<td>103</td>
</tr>
<tr>
<td>4-24</td>
<td>Stimulant initial daily dose trend by age group (14-20 years versus 5-13 years)</td>
<td>103</td>
</tr>
<tr>
<td>4-25</td>
<td>Stimulant initial daily dose trend by gender</td>
<td>104</td>
</tr>
<tr>
<td>4-26</td>
<td>Stimulant initial daily dose trend by race (Blacks versus Whites)</td>
<td>105</td>
</tr>
<tr>
<td>4-27</td>
<td>Stimulant initial daily dose trend by race (Hispanics versus Whites)</td>
<td>105</td>
</tr>
<tr>
<td>4-28</td>
<td>Stimulant initial daily dose trend by eligibility status (Supplemental security income [SSI] versus Temporary assistance for needy family [TANF])</td>
<td>106</td>
</tr>
<tr>
<td>4-29</td>
<td>Stimulant initial daily dose trend by eligibility status (Foster care versus Temporary assistance for needy family [TANF])</td>
<td>106</td>
</tr>
<tr>
<td>4-30</td>
<td>Stimulant initial daily dose trend by comorbidity status</td>
<td>107</td>
</tr>
<tr>
<td>4-31</td>
<td>Stimulant initial daily dose trend by provider type</td>
<td>108</td>
</tr>
<tr>
<td>4-32</td>
<td>Stimulant maintenance daily dose trend</td>
<td>109</td>
</tr>
<tr>
<td>4-33</td>
<td>Stimulant maintenance daily dose trend by age group (&lt; 5 years versus 5-13 years)</td>
<td>110</td>
</tr>
<tr>
<td>4-34</td>
<td>Stimulant maintenance daily dose trend by age group (14-20 years versus 5-13 years)</td>
<td>110</td>
</tr>
<tr>
<td>4-35</td>
<td>Stimulant maintenance daily dose trend by gender</td>
<td>111</td>
</tr>
<tr>
<td>4-36</td>
<td>Stimulant maintenance daily dose trend by race (Blacks versus Whites)</td>
<td>112</td>
</tr>
<tr>
<td>4-37</td>
<td>Stimulant maintenance daily dose trend by race (Hispanics versus Whites)</td>
<td>112</td>
</tr>
<tr>
<td>4-38</td>
<td>Stimulant maintenance daily dose trend by eligibility status (Supplemental security income [SSI] versus Temporary assistance for needy family [TANF])</td>
<td>113</td>
</tr>
<tr>
<td>4-39</td>
<td>Stimulant maintenance daily dose trend by eligibility status (Foster care versus Temporary assistance for needy family [TANF])</td>
<td>113</td>
</tr>
<tr>
<td>4-40</td>
<td>Stimulant maintenance daily dose trend by comorbidity status</td>
<td>114</td>
</tr>
<tr>
<td>Section</td>
<td>Title</td>
<td>Page</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>4-41</td>
<td>Pre-treatment ECG use trend</td>
<td>115</td>
</tr>
<tr>
<td>4-42</td>
<td>Pre-treatment electrocardiography use trend by age group (&lt; 5 years versus 5-13 years)</td>
<td>116</td>
</tr>
<tr>
<td>4-43</td>
<td>Pre-treatment electrocardiography use trend by gender</td>
<td>117</td>
</tr>
<tr>
<td>4-44</td>
<td>Pre-treatment electrocardiography use trend by race (Black versus Whites)</td>
<td>118</td>
</tr>
<tr>
<td>4-45</td>
<td>Pre-treatment electrocardiography use trend by race (Hispanics versus Whites)</td>
<td>118</td>
</tr>
<tr>
<td>4-46</td>
<td>Pre-treatment electrocardiography use trend by eligibility status (Supplemental security income [SSI] versus Temporary assistance for needy family [TANF])</td>
<td>119</td>
</tr>
<tr>
<td>4-47</td>
<td>Pre-treatment electrocardiography use trend by eligibility status (Foster care versus Temporary assistance for needy family [TANF])</td>
<td>119</td>
</tr>
<tr>
<td>4-48</td>
<td>Pre-treatment electrocardiography use trend by comorbidity status</td>
<td>120</td>
</tr>
<tr>
<td>4-49</td>
<td>Pre-treatment electrocardiography use trend by provider type</td>
<td>121</td>
</tr>
</tbody>
</table>
Abstract

Intense public discussion and some regulatory action occurred in 2005-2007 following a safety signal regarding the cardiovascular (CV) risk of central nervous system stimulants (stimulant) and atomoxetine. Our objective was to describe changes in stimulant utilization and pre-treatment electrocardiography (ECG) screening after this safety signal.

A time-series design including 96 months (2001-2008) of Florida Medicaid claims data was used to describe changes in trends of stimulant utilization. Joinpoint regression models were used to detect the number of change points, to estimate the magnitude of change in monthly outcome trends, and to test comparability of trend change(s) among patient subgroups.

Both the initial and maintenance daily dose declined by 6 milligram (mg) methylphenidate equivalent dose from a previously steady dose of 26 mg after Canada withdrew one stimulant product (Adderall XR) in 02/05; the trend rebounded to a consistently lower dose (23 mg) after the remarketing of Adderall XR and a debate in
the U.S. over issuing a boxed warning on stimulant CV safety in early 2006. The monthly initiation rate increased by 3.9% (95% CI -1.0, 9.1) after the boxed warning debate, but started to decline by 2.4%(-3.6,-1.2) after patient medication guides (MedGuides) released in 02/07. Monthly ECG screening increased by 3.2% (2.3, 4.2) after Canada withdrew Adderall XR and further increased by 13 % (4.2, 23) after the American Heart Association recommended pre-stimulant-treatment ECG. The decline in treatment initiation differed by patient age, presence of mental comorbidities or disability; the reduction in treatment intensity, however, did not show significant difference among subgroups. A more pronounced increase in ECG use was observed among patients with less complicated mental conditions or patients who were diagnosed by psychiatrists.

Practitioners reacted to stimulant CV safety signal with immediate reduction in dosing and an increase in preventive screening, affecting however only a marginal proportion of patients. Utilization rates started to drop only after release of MedGuides and affected only initiation but not chronic use of stimulants. Change in stimulant use was not significant among vulnerable subgroups, such as young patients, patients with mental comorbidities or disability. Clinical consequences of these changes are uncertain.
CHAPTER 1
INTRODUCTION

Background

Intense public discussion and regulatory action have taken place during 2005 and 2007 regarding the cardiovascular (CV) safety of central nervous system (CNS) stimulants and atomoxetine (Table 1-1). In 2005, Health Canada, the national regulatory agency in Canada suspended the extended-release (ER) form of mixed amphetamine salts (Adderall XR, Shire, Canada) for 6 months (February to August) following 20 reports of cardiac sudden deaths.\(^1\)\(^-\)\(^3\) A review by the US Food and Drug Administration (FDA) revealed reports of sudden death in patients with underlying heart conditions, and reports of stroke and heart attack in adults with cardiac problems while taking stimulants.\(^4\) A heated debate followed in February / March 2006 because two FDA expert advisory panels proposed conflicting actions on this issue.\(^5\), \(^6\) The Drug Safety and Risk Management Advisory Committee voted to add a black-box warning about the CV risk. This recommendation was based on the proven potential for sympathomimetic agents to raise heart rate and blood pressure, serious adverse effects described for other members of this drug class,\(^7\) and the rapid increase in stimulant use.\(^5\) The Pediatric Advisory Committee suggested that a black-box warning may not be warranted, given the strong evidence on treatment effectiveness and the weak evidence on risk.\(^6\) The FDA decided against the boxed warning but required a product labeling change to reflect concerns about adverse CV events. Furthermore, beginning in February 2007, all ADHD (Attention Deficit/hyperactivity Disorder) drugs (including stimulants and atomoxetine) have been required to be dispensed with a medication guide (MedGuide) to notify patients about CV adverse events.\(^8\)
This study aims to evaluate the possible impact of the public discussions of CV safety concerns and the FDA requirement for a MedGuide for stimulants on trends in stimulants utilization, and explore patient and physician characteristics that might mediate such effects.

**Need for Study**

Stimulants and atomoxetine are the only drug treatments approved for ADHD by the FDA. ADHD affects 3-7% of children and 4.4% of adults in the United States. An estimated 2.5 million youths and 1.5 million adults take medication for ADHD. No study has examined whether the discussions on CV safety concerns have resulted in changes in pharmaceutical therapy and what patient groups were more affected by such change.

The uncertainty about the magnitude and generalizability of CV safety concerns further makes this study an intriguing case, since existing drug utilization research has been focused on warnings that were triggered by information indicating a strong association or revealing a causal relationship between the drug(s) and the adverse event(s) (Table 1-2). We will take advantage of the opportunity to understand how people react while there are conflicting opinions in the interpretation of existing evidence.

**Purpose of Study**

The study intends to examine the effect of CV safety warnings on stimulant treatment utilization among beneficiaries of a southern state Medicaid program. We first assess if trends in stimulant utilization and pre-treatment screening for CV risk changed between 2001 to 2008 and inspect the impact of three critical events: (1) Health Canada’s announcement of suspending the approval for Adderall XR in February 2005; (2) the FDA Drug Safety and Risk Management (DSRM) Advisory Committee
recommendation of a black-box warning for stimulants in February 2006; and (3) the FDA mandate for the distribution of MedGuides in February 2007. Specifically, this study evaluates the changes relevant to stimulant CV safety warnings from the following perspectives:

- Whether the proportion of ADHD patients who were exposed to stimulants and the intensity of stimulant treatment (i.e., the prescribed dosage) have changed
- Whether the proportion of ADHD patients who switched to second-line treatment options (i.e., bupropion, tricyclic antidepressant, atypical antipsychotics) changed and what alternative pharmacological treatments were chosen if stimulants were discontinued;
- Whether the proportion of patients who underwent pre-treatment screening for CV risk (i.e., electrocardiogram [ECG]) has changed.

The second part of this study investigates if the change in stimulant use differed by patients’ socio-economic status or clinical characteristics, or by physician specialty.

**Study Significance**

To our knowledge, this is the first study to investigate how ADHD pharmacological treatment utilization changed since the discussion about stimulant safety issues arose. Determining how physicians and patients responded to safety warnings related to stimulants will bring insights in the effectiveness of risk communication in ADHD management.

**Research Questions and Hypotheses**

The research questions in this dissertation are grouped into two sections. Statistical significance is assumed at an α level of 0.05, if not otherwise specified. \( H_0 \) refers to a null hypothesis and \( H_a \) to an alternative hypothesis.
Part I: Testing of the Change(s) in Stimulant Utilization

Research question-1a: What is the trend in stimulant initiation from 2001 to 2008?

General form of hypothesis-1a: \( H_0: \) there are \( k_{\text{min}} \) change point(s) in the trend of stimulant initiation. \( H_a: \) there are \( k_{\text{max}} \) change point(s) in the trend of stimulant initiation.

Research question-1b: What is the trend in stimulant discontinuation from 2001 to 2008?

General form of hypothesis-1b: \( H_0: \) there are \( k_{\text{min}} \) change point(s) in the trend of stimulant discontinuation. \( H_a: \) there are \( k_{\text{max}} \) change point(s) in the trend of stimulant discontinuation.

Research question-1c: What is the trend in stimulant initial daily dose from 2001 to 2008?

General Form of Hypothesis-1c: \( H_0: \) there are \( k_{\text{min}} \) change point(s) in the trend of stimulant initial daily dose. \( H_a: \) there are \( k_{\text{max}} \) change point(s) in the trend of stimulant initial daily dose.

Research question-1d: What is the trend in stimulant maintenance daily dose from 2001 to 2008?

General form of hypothesis-1d

\( H_0: \) there are \( k_{\text{min}} \) change point(s) in the trend of stimulant maintenance daily dose. \( H_a: \) there are \( k_{\text{max}} \) change point(s) in the trend of stimulant maintenance daily dose.

Research question-1e: What is the trend in treatment switching to 2nd line ADHD drug from 2001 to 2008?
**General form of hypothesis-1e:** $H_0$: there are $k_{\text{min}}$ change point(s) in the trend of treatment switching to 2\textsuperscript{nd} line ADHD drug. $H_a$: there are $k_{\text{max}}$ change point(s) in the trend of treatment switching to 2\textsuperscript{nd} line ADHD drug.

**Research question-1f:** What is the trend in pre-treatment ECG use from 2001 to 2008?

**General form of hypothesis-1f:** $H_0$: there are $k_{\text{min}}$ change point(s) in the trend of pre-treatment ECG use. $H_a$: there are $k_{\text{max}}$ change point(s) in the trend of pre-treatment ECG use.

The sequential testing started from $k_{\text{min}} = 0$ and $k_{\text{max}} = 3$. If $H_0$ was rejected, the testing moved on to $k_{\text{min}} = 1$ and $k_{\text{max}} = 3$; if $H_a$ was rejected the testing moved on to $k_{\text{min}} = 0$ and $k_{\text{max}} = 2$; testing continued until the model with the lowest number of change point was determined. If $k_{\text{max}}$ joinpoint model was selected, testing proceeded to $k_{\text{max}}$ vs $k_{\text{max}} + 1$.

**Part II: Comparability Test among Subgroups**

**Research question-2a-1:** Was the trend in stimulant initiation comparable between young children and older children from 2001 to 2008?

**Research question-2a-2:** Was the trend in stimulant initiation comparable between older children and adolescents from 2001 to 2008?

**Research question-2a-3:** Was the trend in stimulant initiation comparable between female and male patients from 2001 to 2008?

**Research question-2a-4:** Was the trend in stimulant initiation comparable between Blacks and Whites from 2001 to 2008?

**Research question-2a-5:** Was the trend in stimulant initiation comparable between Hispanics and Whites from 2001 to 2008?
**Research question-2a-6:** Was the trend in stimulant initiation comparable between children eligible due to SSI status and children eligible under other plans from 2001 to 2008?

**Research question-2a-7:** Was the trend in stimulant initiation comparable between foster care children and children eligible under other plans from 2001 to 2008?

**Research question-2a-8:** Was the trend in stimulant initiation comparable between patients with mental comorbidity and patients without mental comorbidity from 2001 to 2008?

**Research question-2a-9:** Was the trend in stimulant initiation comparable between patients diagnosed by primary care physicians and patients diagnosed by psychiatrists from 2001 to 2008?

**General form of hypotheses 2a-1a to 2a-9a (for testing parallelism):**

- $H_0$: The stimulant initiation trends are parallel between the two groups (i.e., share the same change point[s] and the same slope[s] in each segment).
- $H_a$: The stimulant initiation trends are not parallel between the two groups.

**General form of hypotheses 2a-1b to 2a-9b (for testing coincidence):**

- $H_0$: The stimulant initiation trends are identical between the two groups (i.e., share the same change point[s] and the same slope and interception in each segment).
- $H_a$: The stimulant initiation trends are not identical between the two groups.

**Research question-2b-1:** Was the trend in stimulant discontinuation comparable between young children and older children from 2001 to 2008?

**Research question-2b-2:** Was the trend in stimulant discontinuation comparable between older children and adolescents from 2001 to 2008?
**Research question-2b-3:** Was the trend in stimulant discontinuation comparable between female and male patients from 2001 to 2008?

**Research question-2b-4:** Was the trend in stimulant discontinuation comparable between Blacks and Whites from 2001 to 2008?

**Research question-2b-5:** Was the trend in stimulant discontinuation comparable between Hispanics and Whites from 2001 to 2008?

**Research question-2b-6:** Was the trend in stimulant discontinuation comparable between children eligible due to SSI status and children eligible under other plans from 2001 to 2008?

**Research question-2b-7:** Was the trend in stimulant discontinuation comparable between foster care children and children eligible under other plans from 2001 to 2008?

**Research question-2b-8:** Was the trend in stimulant discontinuation comparable between patients with mental comorbidity and patients without mental comorbidity from 2001 to 2008?

**General form of hypotheses 2b-1a to 2b-8a (for testing parallelism):**

$H_0$: The stimulant discontinuation trends are parallel between the two groups (i.e., share the same change point[s] and the same slope[s] in each segment). $H_a$: The stimulant discontinuation trends are not parallel between the two groups

**General form of hypotheses 2b-1b to 2b-8b (for testing coincidence):**

$H_0$: The stimulant discontinuation trends are identical between the two groups (i.e., share the same change point[s] and the same slope and interception in each segment). $H_a$: The stimulant discontinuation trends are not identical between the two groups
**Research question-2c-1:** Was the trend in stimulant initial daily dose comparable between young children and older children from 2001 to 2008?

**Research question-2c-2:** Was the trend in stimulant initial daily dose comparable between older children and adolescents from 2001 to 2008?

**Research question-2c-3:** Was the trend in stimulant initial daily dose comparable between female and male from 2001 to 2008?

**Research question-2c-4:** Was the trend in stimulant initial daily dose comparable between Blacks and Whites from 2001 to 2008?

**Research question-2c-5:** Was the trend in stimulant initial daily dose comparable between Hispanics and Whites from 2001 to 2008?

**Research question-2c-6:** Was the trend in stimulant initial daily dose comparable between children eligible due to SSI status and children eligible under other plans from 2001 to 2008?

**Research question-2c-7:** Was the trend in stimulant initial daily dose comparable between foster care children and children eligible under other plans from 2001 to 2008?

**Research question-2c-8:** Was the trend in stimulant initial daily dose comparable between patients with mental comorbidity and patients without mental comorbidity from 2001 to 2008?

**Research question-2c-9:** Was the trend in stimulant initial daily dose comparable between patients diagnosed by primary care physicians and patients diagnosed by psychiatrists from 2001 to 2008?

**General form of hypotheses 2c-1a to 2c-9a (for testing parallelism):** $H_0$: The stimulant initial daily dose trends are parallel between the two groups (i.e., share the
same change point[s] and the same slope[s] in each segment). \( H_0 \): The stimulant initial daily dose trends are not parallel between the two groups.

**General form of hypotheses 2c-1b to 2c-9b (for testing coincidence):** \( H_0 \): The stimulant initial daily dose trends are identical between the two groups (i.e., share the same change point[s] and the same slope and interception in each segment). \( H_a \): The stimulant initial daily dose trends are not identical between the two groups.

**Research question-2d-1:** Was the trend in stimulant maintenance daily dose comparable between young children and older children from 2001 to 2008?

**Research question-2d-2:** Was the trend in stimulant maintenance daily dose comparable between older children and adolescents from 2001 to 2008?

**Research question-2d-3:** Was the trend in stimulant maintenance daily dose comparable between female and male from 2001 to 2008?

**Research question-2d-4:** Was the trend in stimulant maintenance daily dose comparable between Blacks and Whites from 2001 to 2008?

**Research question-2d-5:** Was the trend in stimulant maintenance daily dose comparable between Hispanics and Whites from 2001 to 2008?

**Research question-2d-6:** Was the trend in stimulant maintenance daily dose comparable between children eligible due to SSI status and children eligible under other plans from 2001 to 2008?

**Research question-2d-7:** Was the trend in stimulant maintenance daily dose comparable between foster care children and children eligible under other plans from 2001 to 2008?
Research question-2d-8: Was the trend in stimulant maintenance daily dose comparable between patients with mental comorbidity and patients without mental comorbidity from 2001 to 2008?

General form of hypotheses 2d-1a to 2d-8a (for testing parallelism): $H_0$: The stimulant maintenance daily dose trends are parallel between the two groups (i.e., share the same change point[s] and the same slope[s] in each segment). $H_a$: The stimulant maintenance daily dose trends are not parallel between the two groups.

General form of hypotheses 2d-1b to 2d-8b (for testing coincidence): $H_0$: The stimulant maintenance daily dose trends are identical between the two groups (i.e., share the same change point[s] and the same slope and interception in each segment). $H_a$: The stimulant maintenance daily dose trends are not identical between the two groups.

Research question-2e-1: Was the trend in stimulant treatment switching comparable between young children and older children from 2001 to 2008?

Research question-2e-2: Was the trend in stimulant treatment switching comparable between older children and adolescents from 2001 to 2008?

Research question-2e-3: Was the trend in stimulant treatment switching comparable between female and male from 2001 to 2008?

Research question-2e-4: Was the trend in stimulant treatment switching comparable between Blacks and Whites from 2001 to 2008?

Research question-2e-5: Was the trend in stimulant treatment switching comparable between Hispanics and Whites from 2001 to 2008?
**Research question-2e-6:** Was the trend in stimulant treatment switching comparable between children eligible due to SSI status and children eligible under other plans from 2001 to 2008?

**Research question-2e-7:** Was the trend in stimulant treatment switching comparable between foster care children and children eligible under other plans from 2001 to 2008?

**Research question-2e-8:** Was the trend in stimulant treatment switching comparable between patients with mental comorbidity and patients without mental comorbidity from 2001 to 2008?

**General form of hypotheses 2e-1a to 2e-8a (for testing parallelism):**

\[ H_0: \text{The stimulant treatment switching trends are parallel between the two groups (i.e., share the same change point[s] and the same slope[s] in each segment).} \]

\[ H_a: \text{The stimulant treatment switching trends are not parallel between the two groups} \]

**General form of hypotheses 2e-1b to 2e-8b (for testing coincidence):**

\[ H_0: \text{The stimulant treatment switching trends are identical between the two groups (i.e., share the same change point[s] and the same slope and interception in each segment).} \]

\[ H_a: \text{The stimulant treatment switching trends are not identical between the two groups.} \]

**Research question-2f-1:** Was the trend in pre-treatment ECG use comparable between young children and older children from 2001 to 2008?

**Research question-2f-2:** Was the trend in pre-treatment ECG use comparable between older children and adolescents from 2001 to 2008?

**Research question-2f-3:** Was the trend in pre-treatment ECG use comparable between female and male from 2001 to 2008?
**Research question-2f-4:** Was the trend in pre-treatment ECG use comparable between Blacks and Whites from 2001 to 2008?

**Research question-2f-5:** Was the trend in pre-treatment ECG use comparable between Hispanics and Whites from 2001 to 2008?

**Research question-2f-6:** Was the trend in pre-treatment ECG use comparable between children eligible due to SSI status and children eligible under other plans from 2001 to 2008?

**Research question-2f-7:** Was the trend in pre-treatment ECG use comparable between foster care children and children eligible under other plans from 2001 to 2008?

**Research question-2f-8:** Was the trend in pre-treatment ECG use comparable between patients with mental comorbidity and patients without mental comorbidity from 2001 to 2008?

**Research question-2f-9:** Was the trend in pre-treatment ECG use comparable between patients diagnosed by primary care physicians and patients diagnosed by psychiatrists from 2001 to 2008?

**General form of hypotheses 2f-1a to 2f-9a (for testing parallelism):**

- $H_0$: The pre-treatment ECG use trends are parallel between the two groups (i.e., share the same change point[s] and the same slope[s] in each segment).
- $H_a$: The pre-treatment ECG use trends are not parallel between the two groups.

**General form of hypotheses 2f-1b to 2f-9b (for testing coincidence):**

- $H_0$: The pre-treatment ECG use trends are identical between the two groups (i.e., share the same change point[s] and the same slope and interception in each segment).
- $H_a$: The pre-treatment ECG use trends are not identical between the two groups.
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<tr>
<td>2005</td>
<td>February</td>
<td>Health Canada suspends Adderall XR sale</td>
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<tr>
<td></td>
<td>August</td>
<td>Adderall XR re-enters Canadian market</td>
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<td>2006</td>
<td>February</td>
<td>FDA Drug Safety &amp; Risk Management Advisory Board proposes boxed warning</td>
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<td></td>
<td>March</td>
<td>FDA Pediatric Advisory Board votes against proposal for boxed warning</td>
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<tr>
<td></td>
<td>May</td>
<td>FDA advises labeling change for all stimulants</td>
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<tr>
<td>2007</td>
<td>February</td>
<td>FDA requires stimulant medication guide (MedGuide)</td>
</tr>
<tr>
<td>Drug/drug class</td>
<td>Adverse event</td>
<td>Source of evidence</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Cisapride (Propulsid)</td>
<td>Serious drug-drug interactions (i.e., cardiac arrhythmias and death) with macrolide antibiotics or imidazole antifungals</td>
<td>341 case reports, including 80 deaths.</td>
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<tr>
<td>Estrogen+progesteron (Hormone replacement therapy)</td>
<td>Breast cancer and CV event (i.e., heart attacks, strokes, venous thromboembolism)</td>
<td>Randomized control trial</td>
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<tr>
<td>SSRI antidepressants</td>
<td>Suicidality and suicidal death</td>
<td>Meta-analysis of randomized control trial</td>
</tr>
<tr>
<td>Rosiglitazone (Avendia)</td>
<td>Myocardial ischemic event (i.e., angina, myocardial infarction)</td>
<td>Meta-analysis of randomized control trial</td>
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CHAPTER 2
LITERATURE REVIEW

This chapter is divided into two parts, first, an overview of the role of stimulants in ADHD treatment, determinants of stimulant utilization, and stimulant cardiovascular risk; second, A review of existing research on the influences of new drug safety information on drug utilization pattern.

Part I
The Role of Stimulants in ADHD Treatment

ADHD is a common child psychiatric disorder characterized by a persistent pattern of impulsiveness and inattention, with or without hyperactivity.\(^{16}\) It is a chronic disorder with 30 to 50% of individuals diagnosed in childhood continuing to have symptoms into early adulthood.\(^{17}\) ADHD is associated with social, educational, occupational, and interpersonal difficulties as well as a higher risk for accidents,\(^{18}\) and psychiatric comorbidities. Pharmacotherapy, specifically with central nervous system stimulants or atomoxetine, and/or behavioral interventions are the most recommended treatment options for ADHD.\(^{19}\) The efficacy of stimulants in treating ADHD has been documented in randomized controlled trials. A meta-analysis found that the use of stimulants improved teachers’ and parents’ ratings of disruptive behavior; however it did not improve academic achievement.\(^{20}\) Stimulants neither increased nor decreased rates of delinquency or substance abuse at 3 years of treatment.\(^{20}\) No significant differences between the various drugs in terms of efficacy or side effects have been found.\(^{21, 22}\) Stimulants have been found to be safe in clinical trials,\(^{23}\) though, no study has assessed the adverse effect of treatment beyond two years and assessments have usually occurred in small samples.\(^{20}\)
Stimulant Utilization among ADHD Patients

Amphetamines and amphetamine-like stimulants were introduced in the 1940s (Table 2-1). Stimulants are now used chronically in more than five percent of American children and in a rapidly growing number of adults. Longitudinal comparisons suggest that both the diagnosis and treatment of childhood ADHD have continued to increase over the last decade.  

Factors associated with stimulant utilization

According to the latest CDC (center of disease control) survey, only 56% of ADHD patients were reported to be taking medication for this disorder. Initial decision regarding utilization of stimulant treatment has been found to be based on patients’ clinical conditions, and also be influenced by patients’ socio-demographic characteristics and provider characteristics.  

- Patient characteristics

The probability of stimulant initiation was found to decrease if the patient has a comorbid mental condition. Importantly, the presence of a more complex mental health diagnosis, such as bipolar disorders, schizophrenia, or autism, showed a more significant impact on the likelihood for stimulant use. In contract, the presence of hyperactivity increased the probability of stimulant initiation.

Stimulant initiation is higher among male, white, and school-age children. The disparities by race/ethnicity may relate to differences in cultural constructs regarding deviant behavior, help-seeking, and appropriate treatments. Stimulant use prevalence for youths is lowest in the western US and highest in the South. Patients living in rural areas were found to be more likely to start stimulant treatment than those who lived in urban areas.
Children without insurance show lower levels of stimulants use relative to children with insurance. Some studies have reported that stimulant use is higher among Medicaid than among privately insured youths, while another study found that stimulant use is more likely among privately insured children than their publicly insured counterparts, once an ADHD diagnosis has been established. These studies did not adjust for patients' demographic or clinical characteristics, as well as, administrative differences in the insurance plan (i.e. the proportion of patients under capitated or fee-for-service arrangements). How insurance type predicts stimulant initiation is still controversial. Among Medicaid beneficiaries, those who were eligible due to foster care had the highest propensity to initiate stimulants, compared to those in TANF or SCHIP programs.

• Provider characteristics

Youths who were diagnosed by psychiatrists were less likely to receive ADHD drugs than those diagnosed by primary care physicians.

Factors associated with stimulant persistence

Early stimulant discontinuation is common in the community care of ADHD. One study revealed that 54% of children who were prescribed stimulants received only 1 prescription, 19% received 2 prescriptions, 16% received 3 or 4 prescriptions, and only 11% of the children received 5 or more prescriptions during a 1-year period. The persistence of stimulant treatment varies greatly among ADHD youths with only half of new users receiving stimulant after the first year of treatment, yet, another 17% continuing for 5 years or more.

Decision on stimulant continuation has been associated mostly with patients' socio-demographic or clinical characteristics or their drug regimens. Younger age,
Whites, foster care status or receiving Medicaid due to disabilities predicts greater treatment persistence. The racial/ethnic difference is believed to reflect cultural variation in parental acceptability regarding stimulant treatment. Fewer ADHD symptoms, absence of hyperactivity, as well as, presence of ADHD family history or certain mental comorbidities (i.e., bipolar disorder, tic disorder, oppositional defiant disorder) determine lower treatment persistence. High starting dose, use of extended-release formulations or other psychotropic co-medications increases stimulant persistence.

Stimulants and Cardiovascular Risk

Stimulants are closely related to sympathomimetic biological amines (i.e., epinephrine, norepinephrine). The cardiovascular effects (i.e., increase heart rate and stroke volume, constrict arterioles) of sympathomimetic amines have been thoroughly described in the medical literature. As for manifestation of CV disease, case reports of sudden death, stroke, myocardial infarction and cardiomyopathy has been associated with stimulant use. Stimulants demonstrate increases in blood pressure and heart rates in clinical trials, but are typically described as mild, of short duration, and responsive to dosing or timing adjustments. A large scale observational study, consisting of ~55,000 youths (~125,000 person-year observation) among 3 to 20 years olds who were newly diagnosed with ADHD, reported that stimulant use was associated with an increase in emergency department and physician office visits for cardiac symptoms, such as syncope, tachycardia, or palpitations. This study also found the incidence rates of cardiac events requiring hospitalization (i.e., myocardial infarction, hypertensive disease, angina, aortic or thoracic aneurysm and arrhythmia) to be small and similar to national background rates, suggesting that a manifestation of severe
heart disease secondary to cardiac symptoms is likely rare within the age group and follow-up time period studied. Nevertheless, it is still not clear whether stimulants can cause manifestation of severe heart disease in adult populations or chronic drug users.

**Part II**

**New Drug Safety Information and Patients’ or Health Care Providers’ Behavior**

Product label changes and “Dear healthcare professional” letters to disseminate information regarding drug labeling changes have long been the most common way for the FDA (Table 2-2) to communicate new drug safety issues to healthcare providers in the U.S. In recent years, new information on drug safety has spread through methods that are more approachable to the general public, such as regulatory public health advisories or media (refers to principle means of communicating to the general public, such as newspapers, radio, television, magazines, journals, the internet, etc.)

Presently, only a handful of studies in the literature inform on the impact of communicating new drug safety information on drug-taking or prescribing behavior. Some case studies have evaluated the effectiveness of “Dear healthcare professional” letters on drug utilization patterns; the others have examined changes in drug utilization pattern after widely-circulated safety warnings.

**Dear healthcare professional letters**

The literature generally favors the conclusion that “Dear healthcare professional” letters are not particularly effective in changing prescribing behavior among physicians. Two U.S. studies quantified the impact of cisapride (Propulsid, Ortho McNeil Janssen) on prescribing pattern following labeling changes and “Dear healthcare professional” letters indicating serious drug-drug interactions with macrolide antibiotics or imidazole antifungals. The background contraindicated use rate was found to be 4-5% in
prevalent cisapride users or 26-60% in new users, depending on selection of study populations and definition of contraindicated use. The warnings only demonstrated a 1-2% crude reduction, or 3-25% relative reduction, annually in the rate of this potentially fatal drug use. Another study examined the impact of four “Dear healthcare professional” letters to provide information about troglitazone (Rezulin, Pfizer) label changes regarding the recommendation for periodic liver enzyme monitoring during the course of treatment. This study found that the baseline testing (i.e., the testing before drug initiation) among troglitazone users increased from 15% before FDA monitoring recommendations to 44.6% following the four letters, though, less than 5% of users received the adequate follow-up liver enzyme tests by the third month of continuous use.

Public regulatory warnings and/or media reports of new safety information

Case studies on widespread new drug safety alerts reveal that physicians and patients often respond quickly to the publicity of new safety information. The Women's Health Initiative (WHI) Estrogen Plus Progestin Trial demonstrated that standard-dose conjugated estrogens/medroxyprogesterone acetate (Prempro, Wyeth Pharmaceuticals Inc) resulted in a slightly increased risk of cardiac adverse events. Following the publication of WHI trial results in July 2002, hormone therapy prescriptions declined in successive months: relative to January-June 2002, prescriptions from January-June 2003 declined by 66% for the conjugated estrogens/medroxyprogesterone acetate. In 2003, after the FDA issued a public health advisory about selective serotonin reuptake inhibitors (SSRIs) related suicidal risk in the pediatric population, utilization of SSRIs among depressed patients (both pediatric and adult cases) was reduced by 58% in the following 24 months. Likewise, a meta-analysis reported increased cardiovascular
risk associated with rosiglitazone in May, 2007 and resulted in a black-box warning for heart failure. The average number of claims (per day per million people) for rosiglitazone began to decrease immediately, falling to 41.0 in December 2007, for a total decrease of 58.6% from the February 2007 peak (99.1).61

Factors Mediate the Impact of New Drug Safety Information on Drug Utilization

Factors found to be associated with health services utilization can be categorized as individual, institutional and environmental factors (Table 2-3).62, 63 Over the past 30 years, there has been considerable interest in integrating those factors into conceptual models to guide the conduct of research for understanding who uses health care services and who does not and why.64 According to Williams and Torrens,64 those models can be broadly divided into two categories: system and patient decision-making models. The system framework represents a macro perspective and usually tries to address whether services are fairly or equitably distributed or how a change in the environment (e.g., regulatory change) impacts the delivery of health care; the patient decision-oriented frameworks represents a micro perspective and focus on illustrating the psychosocial dynamics underlying decisions to seek medical care.

The systems approach is represented to a considerable extent by the Behavioral Model of Health Services Utilization introduced by Ronald Andersen in 1968.65, 66 It focuses on predisposing (i.e., demographic, social structure and health beliefs), enabling (i.e., personal/family, community, insurance coverage), and need (i.e., perceived, evaluated) factors as variables explaining the use of health services.65 It views utilization as conditioned on individuals’ beliefs about medical care, and their need for help, their access to economic and geographic resources and their subjective evaluation of the potential outcomes of their health care use.67 Anderson’s model
integrated a range of institutional and individual factors to explain decisions to seek care. It has been criticized, however, for not recognizing the importance of social and cultural practices and attitudes in health service utilization. More recently, researchers have begun to develop models to incorporate environmental or, sociocultural, influences on health service use. The Network-Episode Model (NEM), proposed by Bernice Pescosolido in early 1990s, proposes social networks, within the community (the social support system) or within the health care system (the treatment system), as the mechanism through which individuals recognize and evaluate health problems, determine when and where to seek professional medical help, and decide whether or not to comply with medical advice; the “structure” of networks (defined as characteristics that describe the form of the network or the geometry of ties, such as size, frequency of contact, multiplicity, density, strength of tie and scope/range) calibrates the amount of social influence and the “context” of networks (defined as the characteristics that describe the substance of the network, the things that flow across the ties. Examples of this concept include positive or negative valence, attitudes and beliefs held and cultural meanings) determined the direction of the force, i.e., either toward or away from the formal medical system.

The Health Belief Model (HBM) is one of the patient-decision making models that have been subject to considerable empirical testing. In the HBM, a variety of diverse demographic, sociopsychological, and structural factors may influence behavior. They are, however, believed to work through their effects on the individual’s subjective perceptions and motivations (beliefs), rather than functioning as direct causes of the behavior themselves. This model proposes that individuals’ general and specific
health beliefs (e.g. willingness to seek and accept medical direction, beliefs about the severity of symptoms), preferences (e.g. perceived benefits of treatment), experiences (e.g. with problems and providers), and knowledge about the health problem in question and types of treatment affect their decision to seek care and their health behavior.\textsuperscript{72}

Both system and patient decision models provide complementary views on factors that influence utilization behavior,\textsuperscript{64} nevertheless, empirical support on using either types of model to identify factors underlying the impact of new drug safety information on drug utilization is scarce.

From the macro perspective, Guay et.al.\textsuperscript{73} identified effect modification of the influence of WHI publications on hormone replaced therapy (HRT) persistence from patients’ socio-economic status and drug regimen. Women who were on social assistance after the release of WHI publication were less likely to stop HRT than those in the pre-WHI publication period; instead, women who used high dose HRT in the post-WHI publication period were more likely to cease HRT than those in the pre-WHI publication period. Several studies implied effect modification from the specialty of health care provider. After the warning on SSRI related suicidal risk, the drug utilization rate among depressed youths who were seen by “generalists” (i.e. pediatricians and primary care physicians) decreased more pronouncedly than those who were seen by psychiatrists.\textsuperscript{59, 60}

Gerend et.al.\textsuperscript{74} conducted the only study that applied the patient-decision making model (the HBM framework) to explore factors associated with HRT use before and after the WHI study. The proposed model demonstrated adequate fit to data. The study supported that, after the release of WHI findings, the relative role of cognitive factors—
perceived benefits versus perceived barriers—in HRT use decision-making was changed; whereas perceived benefits was the stronger predictor of intentions in pre-WHI periods, benefits dropped away as a predictor of post-WHI HRT use and barriers moved to the forefront. Women who were older or who expressed higher perceived barriers to HRT use were more likely to be motivated by the announcement of WHI findings to stop HRT use.

In summary, previous research has provided evidence on the influence of some patients’ socio-demographic characteristics, psychological factors and drug regimen on the effect of new drug safety information on drug utilization. This proposed study will further examine how other factors, particularly patients’ clinical characteristics (i.e. comorbidities and co-medications) and physician specialty, mediate such change.

Medication Guides

Of particular interest in the study at hand is the fact that the increased risk is supported by weaker evidence than any of the previous therapeutic eras that were examined in the above mentioned studies. How decisions are made and to what extent utilization changes when evidence is heavily debated has not been investigated.
<table>
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<tr>
<th>Brand name</th>
<th>Generic name</th>
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<th>Approved year</th>
<th>Manufacturer</th>
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<td>Amphetamines</td>
<td>≥ 3 year-old</td>
<td>1960</td>
<td>Duramed Research Inc</td>
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<td>Amphetamines (extended release)</td>
<td>≥ 6 year-old</td>
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<td>Concerta</td>
<td>Methylphenidate (long acting)</td>
<td>≥ 6 year-old</td>
<td>2000</td>
<td>Ortho McNeil Janssen</td>
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<td>Daytrana</td>
<td>Methylphenidate patch</td>
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<td>Methamphetamine hydrochloride</td>
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<td>Ritalin</td>
<td>Methylphenidate</td>
<td>≥ 6 year-old</td>
<td>1955</td>
<td>Novartis</td>
</tr>
<tr>
<td>Ritalin SR</td>
<td>Methylphenidate (extended release)</td>
<td>≥ 6 year-old</td>
<td>1982</td>
<td>Novartis</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>Methylphenidate (long acting)</td>
<td>≥ 6 year-old</td>
<td>2002</td>
<td>Novartis</td>
</tr>
<tr>
<td>Strattera</td>
<td>Atomoxetine</td>
<td>≥ 6 year-old</td>
<td>2002</td>
<td>Lilly</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>Lisdexamfetamine dimesylate</td>
<td>≥ 6 year-old</td>
<td>2007</td>
<td>New River Pharms</td>
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</table>

<table>
<thead>
<tr>
<th>Type of communication</th>
<th>Content</th>
<th>Target audience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labeling</td>
<td>Summary of essential information needed for safe and effective use of the drug.</td>
<td>Healthcare providers</td>
</tr>
<tr>
<td>“Dear healthcare professional” letter</td>
<td>Information regarding a significant hazard to health, an important change in product labeling, or a correction to drug advertising or labeling.</td>
<td>Healthcare providers</td>
</tr>
<tr>
<td>Patient-directed labeling (i.e., patient package insert or Medication Guides)</td>
<td>Summary of essential information needed for safe and effective use of the drug. (in nontechnical language)</td>
<td>Patients</td>
</tr>
<tr>
<td>Public health advisory</td>
<td>Information and advice regarding an emerging drug safety issue or other important public health information</td>
<td>General Public</td>
</tr>
<tr>
<td>Patient information sheets</td>
<td>Concise summary in plain language of the most important information about a drug that is a new molecular entity or a marketed drug with new safety information.</td>
<td>Patients and/or lay caregivers, and interested members of the general public</td>
</tr>
<tr>
<td>Healthcare professional sheets</td>
<td>Concise summary of an important, and often emerging, drug safety issues, including background information about the detection of the issue and points to consider for clinical decision-making</td>
<td>Healthcare professionals</td>
</tr>
<tr>
<td>Alerts on patient information and healthcare professional sheets</td>
<td>Summary of an important, and often emerging, drug safety issue, including a statement that reflects the stage of the analysis with respect to regulatory decision making or other potential limitations on the interpretation of the safety information.</td>
<td>Healthcare professionals, patients and/or lay caregivers, and interested members of the general public</td>
</tr>
</tbody>
</table>

Table 2-3. Major factors affecting health services utilization

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual factor</td>
<td>Patient characteristics</td>
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</tr>
<tr>
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<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Provider characteristics</td>
<td>Age/recency of professional training, gender, specialty</td>
</tr>
<tr>
<td>Institutional factor</td>
<td>Treatment system characteristics</td>
</tr>
<tr>
<td>Environment factor</td>
<td>Treatment network structure</td>
</tr>
<tr>
<td></td>
<td>Treatment context</td>
</tr>
<tr>
<td></td>
<td>Social support system structure</td>
</tr>
<tr>
<td></td>
<td>Social support system context</td>
</tr>
</tbody>
</table>

CHAPTER 3
METHODOLOGY

Study Design

A time-series design was used to describe changes in trends of several measures of stimulant utilization between 2001 and 2008. The study included 8 years of claims data for Florida Medicaid beneficiaries, segmented into 96 months. Joinpoint regression models were used to detect the number of change points, to estimate the magnitude of change in monthly outcome trends, and to test comparability of trend change(s) among subgroups, defined by several patient and provider characteristics.

Data Source

The dataset was assembled from the Florida Medicaid fee-for-service program and included monthly subject-specific information on eligibility and demographic information, as well as all healthcare claims submitted for reimbursement. The dataset covered the years 2001-2008, thus including a roughly equal time frame (4 years) before and after the first publicized concern related to stimulant CV safety (i.e. Canada’s withdrawal of Adderall XR in February, 2005).

The validity of Medicaid claims data with regard to measuring the incidence of ADHD diagnosis or stimulant use has not been investigated. However, it has been recognized that the validity of Medicaid pharmacy claims data in capturing psychotropic exposure is good, with reported percent agreement, positive predictive value and negative predictive value over 85%. According to this study the validity in capturing dosage for psychotropics was also high, with $\kappa$ ranges from 0.52-0.81. ADHD is diagnosed predominantly among children and adolescents. The pediatric population is often under-represented in national surveys that allow investigating...
medication utilization (e.g., the National Ambulatory Medical Care Survey [NAMCS], or the Medical Expenditure Panel Survey [MEPS]). As Florida Medicaid Fee for service recipients represent 18% of the youth under 18 years residing in the state, the size of the represented population is the greatest strength of our dataset.

Study Population

Two cohorts were extracted from the dataset. A cohort of patients with a new ADHD episode was used to assess trend in stimulants initiation; the second cohort of new stimulant treatment episode was used to investigate stimulant discontinuation, treatment switching, and treatment intensity (i.e., initial dose, average daily dose) and pre-treatment screening for cardiac risk (i.e., electrocardiogram [ECG]). Assembly of these cohorts is described below.

Cohort of New Episode ADHD Patients

All beneficiaries aged 0-64 years with new ADHD diagnosis between 01/2001 and 12/2008 were included. Diagnosis of ADHD was determined based on the presence of at least two inpatient or outpatient claims with International Classification of Disease Clinical Modification Version 9 (ICD9-CM) code 314.xx (hyperkinetic syndrome of childhood) during the study period. Their first-listed ADHD diagnosis date was identified as the index date. A minimum of six months continuous Medicaid eligibility before the index date was required to allow identification of a new ADHD episode. These six months could not include ADHD diagnosis or any stimulant claims. Patients were also required to have more than 30 days continuous insurance coverage after the index date to provide sufficient follow-up time to determine stimulant initiation.
The requirement of “having at least two in- or out-patient services with ADHD diagnosis” in order to be categorized as ADHD cases attempted to reduce misclassification in the cohort.

**Cohort of New Stimulant Users**

ADHD patients who received stimulant treatment between 01/2001 and 12/2008 were identified from the datasets. New episode users are those who had a stimulant prescription (defined based on National Drug Code [NDC], see Appendix A) preceded by at least six months “stimulant-free period”. Patients contributed only the earliest episode to the analysis. The first-listed prescription filling date was identified as the index date. A minimum of six months continuous insurance eligibility before the index date was required to allow identification of prior drug exposure.

The analyses excluded patients who received atomoxetine (N=2,020), since atomoxetine had a separate warning on suicidal risk in 2005 and is commonly classified as non-stimulant. Thus, utilization patterns were expected to be different from the rest of ADHD drugs. However, atomoxetine utilization was plotted separately to explore whether changes in utilization might have affect stimulant use. Patients who had missing or zero value in the “days-supply” field (N=1,572) were also excluded since it prohibited the calculation of several study measures.

**Study Measures**

**Stimulant Initiation**

Stimulant initiation was defined as having at least one pharmacy claim for central nervous stimulants (i.e. excluding atomoxetine) within 30 days of the first-listed ADHD diagnosis date.
Stimulant Discontinuation

Treatment discontinuation occurred if a patient’s proportion of days covered (PDC)\(^2\) for stimulants was lower than 40\%\(^3\). PDC is calculated by dividing the number of days of medication supplied (numerator) by the number of days (denominator) in a given time interval. For this study, the numerator was the sum of days of medication supplied on each prescription identified from drug initiation through six months after the first prescription date. The denominator was 180. For prescriptions written near the end of the observation window that had more days supply than were left in the observation window, the days supplied were counted as only the number of days between that prescription date and the end of the observation window.

For the analysis of treatment discontinuation, stimulant users were required to have at least six months continuous insurance coverage after treatment initiation for calculating the metric. Patients only contributed the first treatment episode in the analysis as the probability of discontinuation differs among treatment episodes.

ADHD Treatment Switching

Treatment switching was defined as a drug claim that was followed by a 45-day interval without a refill or a claim for a new stimulant, but a new claim for a second-line ADHD treatment (i.e., bupropion, desipramine, imipramine or nortriptyline, see Appendix B and C). The length of the observation window was selected empirically by the distribution of the difference between refill interval (i.e. days between two consecutive stimulant claims for the same patient) minus the days of medication supplied on the earlier stimulant claim (Table 3-1); if stimulant treatment was continued, it was refilled within 45 days after the end of medication supply, 90\% of the time. To be sure that the initiation of a second-line drug was truly treatment switching, the claim was further
required to be followed by another second-line medication claim within 60 days of the end of medication supply. The 60 days interval was chosen using the same logic as above (Table 3-2).

For the analysis of treatment switching, stimulant users were required to have at least four months continuous insurance coverage after treatment initiation for identifying switching events. Patients only contributed the first treatment episode in the analysis as the probability of switching differs among treatment episodes.

**Stimulant Initial Daily Dose**

The initial dose was identified from a patient’s first stimulant claim. The total quantity supplied was converted to methylphenidate (MPH)-equivalents based on the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) index (see Appendix D), and then divided by the “days of supply” listed on that claim.

Patients who received an abnormal dose (i.e. higher than the largest recommended daily dose) were excluded from the analysis. The analysis also only included users who initiated stimulants within 30 days of diagnosis since the prescription filling date would be close to the time of physician’s decision-making.

**Stimulant Maintenance Daily Dose**

The total stimulant dose prescribed to a patient within 6 months of treatment initiation was also converted to MPH-equivalents dose, and then divided by 180 to derive the average daily dose.

Patients who received an abnormal dose (i.e. higher than the largest recommended daily dose) were excluded from the analysis. Users were required to have at least six months consecutive eligibility and continue stimulant treatment (with
PDC greater than 40%) for at least 6 months after drug initiation to calculate maintenance dose.

**Pre-treatment Screening (for Cardiac Risk)**

Receiving pre-treatment screening for cardiac risk refers to having an electrocardiogram (ECG) (identified based on Current Procedural Terminology [CPT] codes, see Appendix E) within 30 days before initiating stimulants.

Patients who got their first ADHD diagnosis from a hospital, or those who were hospitalized for any causes within one month prior to first diagnosis during the same period were excluded from the analysis of pre-treatment screening, since their ECG charges might be aggregated into hospitalization charges and would therefore not be detectable from our data.

**Data Analysis**

**Part I: Joinpoint Analysis**

Joinpoint (JP) analysis was used to detect change(s) in outcome trends. The JP model characterizes trend data by a number of continuous linear segments and change points (i.e., points at which trends change):

\[ Y = E[Y|X] = \beta_0 + \beta_0 X + \delta_1(X - \tau_1)^+ + \ldots + \delta_k(X - \tau_k)^+ \]

Where

- \( Y = \) monthly stimulant outcome rate
- \( X = \) study month (e.g., 01/2001= 1, 02/2004=2, ..., 12/2008= 96)
- \( \tau_k \)'s= the unknown change points
- \( a^+ = a \) for \( a > 0 \), \( a^+ =0 \) for \( a \leq 0 \)

JP analysis can identify a simplest (i.e. least change point) best-fitting combination of line segments and join points through a sequential hypothesis testing and a series of permutation tests, as well as, characterize the trend (i.e. locate the change points and estimate the trend change in each segment). This test algorithm has been applied to
investigate changes in cancer incidence\textsuperscript{78} and mortality trends and antidepressants utilization rate after safety warnings on drug-related suicidal risk.\textsuperscript{79, 80}

**Model-fitting specification**

The dependent variables of the analyses on stimulant initiation, stimulant discontinuation, treatment switching and ECG use are the natural logarithms of monthly outcome rates (i.e. outcome event count per 1,000 patient-days for initiation or discontinuation; outcome event count per 100,000 patient-days for ECG use). Data were fitted to an independent errors join point model (i.e. no correlation between successive error in the model) assuming the outcome rates follow a Poisson-like distribution, where the variance is proportional to the mean. The dependent variables for the analyses on initial or maintenance daily dose are the natural logarithms of monthly means of prescribed MPH-equivalent daily dose (per patient). Data were fit to a heteroscedastic model with inputted standard error (SE), derived by dividing the standard deviation of monthly mean dose by the square root of the monthly patient count.

**Hypothesis testing**

Due to computation efficiency considerations, the test started from setting the possible number of change points at a maximum of 3. It began from testing: $H_0: k_0=0$ (no joinpoint) vs. $H_a: k_a= 3$ (three joinpoints) and proceeded sequentially, increasing the number of joinpoints under $H_0$ by 1 if the null hypothesis was rejected and decreasing the number of joinpoints under the alternative hypothesis if $H_0$ was accepted. A Bonferroni correction was applied to ensure the probability of a type I error was less than 0.05. If the three joinpoint model were selected, a second sequential testing would be performed with the maximum change points set at 4.
Joinpoint Software, version 3 (National Cancer Institute, Bethesda, MD) was used for data analysis. The number/location of the probable change point(s) and the monthly percent change (MPC, calculated from the estimated slope in each segment) in trends were reported. The impact of CV safety concerns on stimulant utilization was assessed by the temporal relationship between the change point(s) and the following three events: 1) Health Canada withdrew Adderall XR in 02/2005; 2) FDA DSRM Advisory Board proposed boxed-warning in 02/2006; 3) FDA required a medication guide (MedGuide) in 02/2007.

**Adjustment for seasonality**

An initial inspection confirmed seasonality in stimulant initiation and discontinuation trends. As suggested in the literature patients are likely to stop taking stimulants during summer breaks, which violated the assumption of heteroscedastic data. Therefore, the trends were deseasonalized by the following steps before fitting the model:

**Step 1:** Let $Y$ be the mean of the observed values (of the outcome) per calendar month during the study period.

**Step 2:** Rank the study months and let $X$ equal to the average rank per calendar month. For example, if January ranks are 1,13,25,37,49,61,73, and 85, then $X_{Jan} = 43$.

**Step 3:** Fit $Y = \beta_0 + \beta_1 X + \epsilon$ by an ordinary least squares model using the 12 $(Y, X)$ pairs. The slope ($\beta_1$) depicts a trend due to observed time.

**Step 4:** Let the calendar month with the lowest $Y$ be the reference month. Let $Y'_{Jan}$, $Y'_{Feb}$, ..., $Y'_{Dec}$ equal to $(Y_{Jan} - Y_{ref})$, $(Y_{Feb} - Y_{ref})$, ..., $(Y_{Dec} - Y_{ref})$ and $X'_{Jan}$, $X'_{Feb}$, ..., $X'_{Dec}$ equal to $(X_{Jan} - X_{ref})$, $(X_{Feb} - X_{ref})$, ..., $(X_{Dec} - X_{ref})$.

**Step 5:** Calculate the deseasonalized value for each study month.

Deseasonalized value of month $i = \text{Observed value of month } i - Y'$ calendar time of $i$ (1) - $\beta_1 * X'$ calendar time of $i$ (2)
The first step reduces the seasonal fluctuation (i.e. impact of calendar time) on the observed value. The second step adjusts for errors due to the observed time. For example, if there were an increasing trend over the study period (i.e., $\beta_1 > 0$), $Y'$ would be larger than it would have been for the months with more observed time than the reference month, and, it would be smaller for the months with less observed time than the reference month (the situation would be reverse if the trend were decreasing [i.e. $\beta_1 < 0$]).

Figure 3-1 illustrates the original and deseasonalized initiation and discontinuation trends.

**Part II Sub-group Analysis**

Stratified analyses were performed based on 7 patient or provider characteristics that are associated with stimulant utilization. The selection of subgroups was based on a literature review and their availability in the datasets. Since age is a significant factor for drug use and the adult population was small, people over 21 years of age were excluded in these analyses.

Subgroups were obtained based on patient and provider characteristics as described below:

**Patient demographic characteristic**

- Age
- Gender
- Race
- Medicaid eligibility type

Information on demographic characteristics was extracted from the insurance enrollment files for the index date (i.e., the first ADHD diagnosis for model 1 and 2 or the first stimulant claim for model 3-6). Four age groups were defined for the study.
population, less than 5 years of age, 5 to 9 years of age, 10 to 14 years of age, and 15 to 20 years of age. Beneficiaries were classified as Caucasian (non-Hispanic), Black (non-Hispanic), Hispanic, or other race (American Indian, Asian, and others) according to Medicaid categories. Medicaid eligibility status was classified as Temporary assistance for Needy Family (TANF), foster care, Supplemental Security Income (SSI, those who met federal qualifications for assistance through disability) or other (other programs within Medicaid).

**Patient clinical characteristics**

- Presence of mental comorbidity
- Presence of pre-existing heart conditions

Patients with mental disorders other than ADHD were identified by the presence of an inpatient or outpatient claim at any time in the study period with any of the following diagnoses: adjustment disorder (identified by ICD-9 CM code 309–309.80, 309.82–309.99, and 313.89), anxiety (300–300.09, 300.2–300.29, 300.3, 309.81, and 308.xx), autism (299.0x), bipolar disorder (296–296.19, 296.4–296.99, and 301.13), conduct disorder (312–313.88 and 313.9x), depression (296.2–296.39, 300.4, and 311.xx), learning disorders (315.xx, 307.0, and 307.9), schizophrenia (295.0x–295.9x), and tic disorders (307.2x and 307.3x). To assure that the identified conditions presented concurrently with the diagnosis of ADHD or stimulant initiation, at least one inpatient or outpatient claim had to be present in the 180 day period before the index date and another claim for the same condition observed in the 180 day period after the index date.

Preexisting heart disease was defined as the presence of any inpatient or outpatient claim within 6 months before the index date with any of the following codes:
diseases of the circulatory system (390.xx to 459.xx), syncope (780.2x), tachycardia or palpitation (785.0x, 785.1x), chest pain (786.50), congenital anomalies of the heart and other hereditary diseases that affecting the circulatory system (hereditary hemolytic anemia [282.xx], hemophilia [286.0x to 286.4x], anomalies of bulbus cordis and cardiac septal closure [745.xx], other congenital anomalies of heart [746.xx]), congenital anomalies of circulatory system [747.0–747.4xx], Down syndrome [758.0x], gonadal dysgenesis [758.6x], and Fragile X syndrome [759.83]).

Provider characteristics

- Specialty of physician who diagnosed ADHD or prescribed stimulant

Provider specialty was identified from the medical encounter claim that was closest to (but not exceeding) the index date and was categorized into one of the following: psychiatry; primary care, including family practice, general practice, and pediatrics; or other (including unspecified). Treatment discontinuation and average daily dose were not stratified by this variable since attribution to one provider might be invalid.

Model-fitting Specification

Similar to the main analyses, the dependent variables were the natural logarithms of the monthly outcome rates for stimulants initiation, discontinuation and ECG use. Data were fit to a heteroscedastic (i.e. uncorrelated) model assuming the outcome rates follow a Poisson distribution. The dependent variables for the analyses on initial or maintenance daily dose were the natural logarithms of monthly means of prescribed MPH-equivalent daily dose (per patient). Data were fit to a heteroscedastic model with standard error (SE), derived by dividing the standard deviation of monthly mean dose by the square root of the monthly patient count.
Hypothesis Testing

The study population was paired as the following for testing comparability of the outcome trends:

- Male versus Female
- Whites versus Blacks
- Whites versus Hispanics
- Age < 5 years old versus 5-13 years of age
- 5-13 years of age versus age 14-20 years of age
- TANF beneficiaries versus beneficiaries with SSI status
- TANF beneficiaries versus beneficiaries receiving foster care
- Patients with mental comorbidities versus those without (pure ADHD patients)
- Patients with pre-existing heart disease versus those without
- Patient diagnosis by primary care physician versus patient diagnosis by psychiatrist

A ‘parallel test’ was performed for each pair:

\[ H_0 \] The outcome trends are parallel between the two groups
\[ (i.e., \text{share the same change point[s] and the same slope[s] in each segment}) \]
\[ H_a \] The outcome trends are not parallel between the two groups

If the test failed to reject parallelism, a ‘coincidence test’ was performed

\[ H_0 \] The outcome trends are identical between the two groups
\[ (i.e., \text{share the same change point[s] and the same slope and interception in each segment}) \]
\[ H_a \] The outcome trends are not identical between the two groups

Joinpoint Software, version 3 (National Cancer Institute, Bethesda, MD) was used for data analysis. A maximum number of change point \( \kappa_{max} \) was assigned in each test based on the main analyses. The null hypothesis was rejected if the p-value was lower than 0.05. The p-value for the comparability tests was reported. The specification of the outcome trends (i.e., number/location of the change point(s) and MPC) were reported for the pairs with significant difference.
**Table 3-1. Stimulant refill patterns**

<table>
<thead>
<tr>
<th>Refill interval - drug supply (day)</th>
<th>Cumulative percentage</th>
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<td>0-7</td>
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<td>30-45</td>
<td>89</td>
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<tr>
<td>45-60</td>
<td>91</td>
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<tr>
<td>&gt;60</td>
<td>100</td>
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</tbody>
</table>

**Table 3-2. Second-line ADHD treatment refill patterns**

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<th>Refill interval - drug supply (day)</th>
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<td>0-7</td>
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<tr>
<td>45-60</td>
<td>90</td>
</tr>
<tr>
<td>&gt;60</td>
<td>100</td>
</tr>
</tbody>
</table>
Figure 3-1. Original and deseasonalized trends. A) stimulant initiation. B) stimulant discontinuation.
CHAPTER 4
RESULTS

Table 4-1 summarizes the size of the selected cohorts and the duration of the study period available for the analyses. The duration varied due to different requirements for post index date continuous eligibility and the availability of specific information needed for calculating outcome measures (i.e. data prior to year 2002 were excluded from the analysis of discontinuation, switching, initial dose and maintenance dose trends because the “days-supply” field in the pharmacy claim had a significant proportion of missing values). For analysis of medication switching JP model fitting was infeasible due to the rare occurrence of switching events, and this measure was dropped from the analyses; similarly, stratified analyses on pre-existing heart condition were dropped due to the low prevalence (3-4%) of cardiovascular disease in the study cohorts (Table 4-2, 4-8, 4-12, 4-16).

Stimulant Initiation Trend

Table 4-2 summarizes the patient and provider characteristics of the cohort for stimulant initiation trend analysis (N=44,571). There was a decrease in the eligible population during the period after stimulant CV safety warnings (570 per month in 2005, and 298 per month in 2008, Table 4-2). Patient demographic characteristics were similar to what had been previously reported with larger representation of males, school-aged children, and Whites. However, average age was higher at the end of study period, which was attributable to the increased proportion of adult patients. There was a drop in the proportion of patients who were diagnosed by psychiatrists over the study period, suggesting a shift of provider type in ADHD care (Table 4-2).
Thirty-seven percent of newly diagnosed ADHD patients (N=16,327) initiated stimulant treatment within the first month of diagnosis (Table 4-2). The initiation rate ranged between 240 to 540 per 1,000 patient-months (Figure 4-1). Four joinpoints were found in the initiation trend (Table 4-3). Two points were located during the pre-warning periods (prior to February 2005) (Figure 4-1). This fluctuation was likely due to the market redistribution. We fitted the initiation trend of atomoxetine and plotted the trend against that of stimulants (Figure 4-2). It appears that the stimulant initiation rate was decreasing since the time (07/2002, 95% confidence interval [CI]: 03/2001-02/2003) when atomoxetine entered the market (September 2002). Because of the concern on atomoxetine-related suicidal risk, which later led to the issued of a boxed warning (09/2005), atomoxetine initiation decreased during mid 2005 to early 2006, while the stimulant initiation rate rebounded gradually.

During the post-warning period (after February 2005), stimulant initiation rate went up from 370 per 1,000 patient-months to 540 per 1,000 patient-months (3.9% per month, -1.0, 9.1); it then dropped from 540 per 1,000 patient-months to 354 per 1,000 patient-months (2.4% per month, -3.6, -1.2) in 03/2007 (08/2006-04/2008), closely after the introduction of a required MedGuide (Figure 4-1; Table 4-4).

Since the rise in stimulant initiation was close to the time a new stimulant product, Daytrana™ patch, entered the market (April 2006), we further examined the initiation of only oral stimulant products (Figure 4-3). The joinpoint model failed to find a significant increase in initiation in 07/2006 (Figure 4-3, Table 4-5, 4-6), though, the raw data trends are almost identical (Figure 4-1; Figure 4-3), suggesting issues with statistical power.
Thus, the marketing of Daytrana™ was not likely the only cause of the elevation in stimulant initiation in mid 2006.

Subgroup analyses of the initiation trend excluded periods before 2004 to reduce the impact from change points that were not relevant to stimulant CV concerns. Table 4-7 shows the results of comparability tests for the stratified trends. Stimulant initiation rate was the highest among 5- to 13-year-old children, and lowest among adolescents (14- to 20-year-old). Prior to Canada’s withdrawal of Adderall, the difference of initiation rates between 5-13 years and < 5 years ranged 20-50 per 1,000 patient-months; it ranged 20-170 per 1,000 patient-months thereafter (Figure 4-4). In contrast, the gap between 5-13 years and adolescents ranged consistently 170-270 per 1,000 patient-months from 2004-2008 (Figure 4-5). The initiation rate did not change after CV warnings in younger children (< 5 years), but the change was significant and comparable between older children (5-13 years) and adolescents (Figure 4-4, 4-5).

There was likely an interaction between age and gender regarding treatment initiation; the trends were identical among male and female only after excluding the younger children (Figure 4-6). The JP model has limited capability to handle interactions, thus, the stratified analyses of other subgroups were restricted to patients who were 5 to 20 years of age.

Foster care children had the lowest stimulant initiation rate, followed by SSI children and the normal Medicaid population (TANF). Difference in treatment initiation rate between SSI children and TANF children ranged from 10-80 per 1,000 patient-months prior to CV warnings and 30-310 per 1,000 patient-months after the warnings (Figure 4-4). The gap between foster care children and TANF children ranged 160-290.
Changes in treatment initiation were not comparable across patients’ eligibility status; safety warnings did not have an impact on initiation trend among SSI children (Figure 4-9, 4-10).

Initiation rate was greater (160-190 per 1,000 patient-months before the warnings, 20-190 per 1,000 patient-months after the warnings) among patients with mental comorbidities compared to those without other psychiatric conditions, and the trend did not change among more complicated patients after the warnings (Figure 4-11). Stimulants were initiated the most among whites and the least among Hispanics (difference in treatment initiation rates between Whites and Hispanics was 75-540 per 1,000 patient-months, Figure 4-8; between Whites and Blacks 150-210 per 1,000 patient-months, Figure 4-7), and more often among those who were diagnosed by primary care physicians (difference in treatment initiation rate ranged 400-700 per 1,000 patient-months, Figure 4-12). No significant difference by patients’ race or provider type was found in terms of the change in treatment initiation after the warnings (Figure 4-7, 4-8, 4-12).

**Stimulant Discontinuation Trend**

Table 4-8 summarizes the patient and provider characteristics in the stimulant discontinuation trend analysis (N=16,372). Similar to the new episode patient cohort, there was a decrease in the eligible population during the period after stimulant CV safety warnings (250 per month in 2005, and 142 per month in 2008, Table 4-8). Demographic characteristics were similar to those for stimulant initiation, except for age. Different from the initiation sample, which includes all patients with new ADHD episodes and which shows an increasing age over the study period, the discontinuation cohort includes all patients with newly initiated treatment and with continuous Medicaid
coverage for more than 180 days post-stimulant initiation. In this sample, younger age groups were increasingly represented in late study years.

Thirty percent of new stimulant users (N=4,947) had a PDC lower than 40% within 180 days of treatment initiation (Table 4-8). Stimulant discontinuation rate ranged between 30 and 45 per 1,000 patient-months and did not change after safety warnings on CV risk (Figure 4-13, Table 4-9, 4-10).

The discontinuation rate was the lowest among 5- to 13-year-old children and was similar among those younger than 5 years or adolescents (Figure 4-14, 4-15). The difference in discontinuation rate was 15 per 1,000 patient-months between children 5-13 years and the younger age group, and was 20 per 1,000 patient-months between children 5-13 years and adolescents. The rate was highest among Hispanics, and lowest among Whites (Figure 4-17, 4-18), highest among children with SSI status and lowest among those in foster care (Figure 4-19, 4-20). Compared to Whites, the discontinuation rate was higher by 90 per 1,000 patient-months for Hispanics and by 50 per 1,000 patient-months for Blacks; Compared to TANF groups, the discontinuation rate was higher by 40 per 1,000 patient-months for SSI youths and lower by 50 per 1,000 patient-months for foster care children. Treatment discontinuation rate also was greater in males (by 5 per 1,000 patient-months, Figure 4-16) and in patients with other mental comorbidity (by 4 per 1,000 patient-months, Figure 4-21), however, there were less Whites and more Hispanics in male patients and more younger children and adolescents in those with other mental disorders. No significant difference among subgroups was found in terms of the change in treatment discontinuation after the warnings (Table 4-11).
Stimulant Initial Daily Dose Trend

A total of 13,058 new episode stimulant users who initiated treatment within 30 days of diagnosis were eligible for the analysis of initial dose trend (Table 4-12). Patient characteristics were similar to the discontinuation cohort (Table 4-8), except for race and mental comorbidity status. Unlike the discontinuation cohort, which includes all new stimulant users with at least 6 months continuous eligibility, this cohort includes only users who initiated treatment within first month of diagnosis, and included a higher proportion of Whites, as well as patients with no mental comorbidities. The initial dose sample also had a higher proportion of patients who were diagnosed by primary care physicians, as compared to the new episode ADHD patients (Table 4-2). The sample size decreased during the period after CV safety warnings (186 per month in 2005, and 97 per month in 2008, Table 4-12). Patient characteristics were similar across study periods, but fewer patients received stimulant treatment from a psychiatrist, which is consistent to the shift of care found in the new ADHD patient cohort.

The two-joinpoint model was the final selected model (Table 4-13). Stimulant initial daily dose declined sharply (-6% per month, -14; -1.9) from a steady 26mg MPH-equivalents since 05/2005 (03/2005-07/2007), closely after Canada withdrew Adderall XR. The trend rebounded to a consistently lower dose (~23 milligram [mg]) since 09/2005 (07/2005-12/2005); close to the time when Adderall XR was reintroduced on the market (Figure 4-22, Table 4-14).

The initial treatment intensity did not differ by patient gender (Figure 4-25), race (Figure 4-26, 4-27), or mental comorbidity status (Figure 4-30), but increased with patients’ age. It was 9-11 mg/day higher among 5-13 years children than younger age groups before CV concerns were voiced, and 4-9 mg/day greater thereafter (Figure 4-
it was 12-15 mg/day higher among adolescents than 5-13 years-old children prior to any CV warnings, and 12-18 mg/day larger subsequently. Daily initial treatment strength among youths diagnosed by psychiatrists was slightly larger (~1-2 mg) than that among those diagnosed by primary care physicians (Figure 4-31). Treatment intensity among SSI children was also a higher (~2 mg) (Figure 4-28, 4-29), however, SSI children had the greatest proportion of adolescents. Change in initial dose trend after warnings was not significantly different among most groups, except that treatment intensity for younger children (age less than 5 years) or adolescents (age greater than 14 years) did not drop due to concerns on stimulant CV risk (Table 4-15).

**Stimulant Maintenance Daily Dose Trend**

A total of 5,222 new episode stimulant users who continued treatment for at least 6 months were eligible for the analysis of maintenance dose trend (Table 4-16). This cohort had similar inclusion criteria as the discontinuation cohort (Table 4-8), but differed from the latter in requiring more than 6-month chronic stimulant use. Patient characteristics in the two samples were similar, but chronic stimulant users were slightly younger, had a higher proportion of Whites and patients with no comorbidities than the discontinuation sample. There was a decrease in the eligible population during the post-CV warning period (163 per month in 2005, and 90 per month in 2008, Table 4-16). Chronic stimulant users’ demographics and clinical characteristics were also similar across study periods.

The three-joinpoint model was the final selected model. Stimulant maintenance daily dose declined (-2.1% per month, -2.6; -1.5) from a steady 26mg MPH-equivalents since 12/2004 (07/2004-06/2005), around the time when Canada withdrew Adderall XR. The point estimated of the change point was earlier then the first CV safety warning with
confidence interval that crossed the pre- and post-warning periods. The trend rebounded to a consistently lower dose (~22-23 mg) in early 2006 (09/2005-06/2006). The point estimate of this change point (04/2006) was close to the FDA’s Advisory Boards debate about the proposal of a boxed warning, but the lower bound of the confidence interval (09/2005) was close to remarketing of Adderall XR (Figure 4-32, Table 4-17, 4-18).

Maintenance treatment intensity did not differ by gender or patients’ mental comorbidity status (Figure 4-35, 4-40), but increased with age (Figure 4-33, 4-34). The maintenance daily dose in 5- to 13 year-old children was higher (~6 mg) than among younger children and was lower (8-10 mg) than in adolescents (Figure 4-33, 4-34). The intensity among Whites was lesser (~4mg/day) than in Hispanics and in Blacks (~2mg/day) (Figure 4-36, 4-37). The dose strength among foster care children was larger (~2 mg/day) than in children covered by other insurance types (Figure 4-38, 4-39). Change in stimulant maintenance dose was not significant different among subgroups (Table 4-19, Figure 4-33-4-40).

Pre-treatment ECG Use Trend

A total of 30,139 new stimulant users were eligible for the analysis of pre-treatment ECG trends (Table 4-20). This cohort had similar, but more generous inclusion criteria as the initial dose cohort (Table 4-12). Different from the initial dose sample, which restricted to new episode ADHD patients who initiated treatment within the first months of diagnosis, the ECG use cohort includes all new episode ADHD patients who initiated stimulant treatment anytime after diagnosis and were covered by Medicaid a month before treatment initiation. Patient characteristics in the two cohorts were comparable, except that ECG use cohort had a slightly larger representation of
Whites. There was a decrease in the eligible population during the period after stimulant CV safety warnings (342 per month in 2005, and 151 per month in 2008, Table 4-20). Patient characteristics were similar across study periods, but fewer patients received stimulant treatment from a psychiatrist, which is consistent to the shift of care found in the new ADHD patient cohort and the initial dose cohort (Table 4-2, 4-12).

On average three percent of new stimulant users had an ECG test (N=852) before treatment initiation (Table 4-20). Two change points were detected in the trend (Table 4-21). The pre-treatment ECG use rate was steady around 34 per 1,000 patient-months, (range: 16-58 per 1,000 patient-months) from 2000 to mid 2004; it increased by 3.2% (2.3, 4.2) per month since 06/2004 (07/2003-06/2005) and further increased by 13 % (4.2-23) per month after 02/2008 (07/2007-11/2008). The point estimate of the first change point was earlier than Canada’s action (062/2005) with a confidence interval (07/2003-06/2005) that crosses the pre- and post-CV warning periods (Figure 4-41, Table 4-22). The second change point was close to the release of an American Heart Association report (05/2008), which recommended all ADHD children have an ECG screening prior to starting stimulants.82, 83

Pre-treatment ECG use was rare (30 events during the study period) among adolescents, and this age group was excluded from the stratified analysis. The pre-treatment ECG use rate was similar across age groups and gender (Figure 4-42, 4-43). It was higher among Hispanics (Figure 4-44, 4-45), foster care children (Figure 4-46, 4-47), and patients with other mental disorders (Figure 4-48). The difference in pre-treatment ECG use rate between Hispanics and Whites was 12 per 1,000 patient-months during the pre-CV warning period and was 15-75 per 1,000 patient-months
thereafter (Figure 4-45). Prior to Canada’s withdrawal of Adderall, foster care children had a steady 9 per 1,000 patient-months higher screening rate than others. The difference ranged from 10-50 per 1,000 patient-months subsequently (Figure 4-47). The difference in ECG screening rates between patients with and without mental comorbidity was 24-30 per 1,000 patient-months before the warnings and 1-24 per 1,000 patient-months after the warnings (figure4-48). In most subgroups, the changes in trends after warnings were equivalent (Table 4-27, 4-28), however, change in the trend was sharper among patients without mental comorbidity (4.9, 3.7-6.0) than patients with more complicated mental status (3.3, 1.8-4.8) and among patients diagnosed by psychiatrists (5.9, 4.5-7.4) than those diagnosed by primary care physicians (4.1, 2.5-5.7) (Table 4-23, Figure 4-48, 4-49).
<table>
<thead>
<tr>
<th>Study measures</th>
<th>Time frame for analysis (duration, months)</th>
<th>Eligible patients (average patients per month)</th>
<th>Event counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulant initiation</td>
<td>01/2001-11/2008 (95)</td>
<td>44,571 (469)</td>
<td>16,327</td>
</tr>
<tr>
<td>Stimulant discontinuation</td>
<td>01/2002-06/2008 (78)</td>
<td>16,327 (209)</td>
<td>4,947</td>
</tr>
<tr>
<td>Switching to second-line treatment</td>
<td>01/2002-08/2008 (80)</td>
<td>19,244 (240)</td>
<td>135</td>
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<tr>
<td>Initial daily dose</td>
<td>01/2002-11/2008 (83)</td>
<td>13,058 (157)</td>
<td>-</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>01/2002-06/2008 (78)</td>
<td>10,635 (136)</td>
<td>-</td>
</tr>
<tr>
<td>Pre-treatment electrocardiography use</td>
<td>01/2001-11/2008 (95)</td>
<td>30,139 (317)</td>
<td>852</td>
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Table 4-2. Patient and provider characteristics in stimulant initiation trend analysis

<table>
<thead>
<tr>
<th></th>
<th>Pre-warning</th>
<th>Post-warning</th>
<th>Post-warning</th>
<th>Post-warning</th>
<th>Post-warning</th>
<th>Post-warning</th>
<th>Total</th>
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</thead>
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<tr>
<td></td>
<td>01/2001-</td>
<td>02/2005-</td>
<td>01/2006-</td>
<td>01/2007-</td>
<td>01/2008-</td>
<td>01/2001-</td>
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<tr>
<td>ADHD patients (n)</td>
<td>26,769</td>
<td>6,268</td>
<td>5,182</td>
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<td>3,282</td>
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<td>Follow-up time (pt-mo)</td>
<td>19,227</td>
<td>4,464</td>
<td>3,729</td>
<td>2,528</td>
<td>2,375</td>
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<td>Avg. patient per month</td>
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<td>570</td>
<td>432</td>
<td>305</td>
<td>298</td>
<td>469</td>
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<tr>
<td>Stimulant use (n)</td>
<td>9,671</td>
<td>2,305</td>
<td>1,892</td>
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<td>1,196</td>
<td>16,327</td>
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<td>Initiation rate*(1000 pt-rr)</td>
<td>356</td>
<td>373</td>
<td>362</td>
<td>441</td>
<td>357</td>
<td>366</td>
<td></td>
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<td>Demographics</td>
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<tr>
<td>Mean age (years)</td>
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<td>8.5</td>
<td>8.4</td>
<td>8.6</td>
<td>9.5</td>
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<tr>
<td>(95% CI)</td>
<td>(8.4-8.5)</td>
<td>(8.3-8.6)</td>
<td>(8.2-8.6)</td>
<td>(8.4-8.8)</td>
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<td>&lt; 5 years (%)</td>
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<td>16</td>
<td>14</td>
<td>15</td>
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<tr>
<td>5-9 years (%)</td>
<td>54</td>
<td>56</td>
<td>57</td>
<td>58</td>
<td>58</td>
<td>55</td>
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<tr>
<td>10-14 years (%)</td>
<td>24</td>
<td>19</td>
<td>17</td>
<td>15</td>
<td>16</td>
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<tr>
<td>15-20 years (%)</td>
<td>6</td>
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<td>6</td>
<td>6</td>
<td>5</td>
<td>6</td>
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<td>&gt;20 years (%)</td>
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<td>3</td>
<td>4</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Male (%)</td>
<td>70</td>
<td>68</td>
<td>68</td>
<td>66</td>
<td>67</td>
<td>69</td>
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<td>White (%)</td>
<td>43</td>
<td>41</td>
<td>43</td>
<td>41</td>
<td>42</td>
<td>42</td>
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<tr>
<td>Black (%)</td>
<td>23</td>
<td>24</td>
<td>23</td>
<td>22</td>
<td>21</td>
<td>23</td>
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<td>Hispanic (%)</td>
<td>18</td>
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<td>20</td>
<td>19</td>
<td>19</td>
<td>19</td>
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<tr>
<td>Other race (%)</td>
<td>16</td>
<td>15</td>
<td>14</td>
<td>17</td>
<td>18</td>
<td>16</td>
<td></td>
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<tr>
<td>Medicaid eligibility status</td>
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<tr>
<td>Temporary assistance for needy family (%)</td>
<td>39</td>
<td>41</td>
<td>38</td>
<td>37</td>
<td>36</td>
<td>39</td>
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<tr>
<td>Supplemental security income (%)</td>
<td>20</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>19</td>
<td></td>
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<tr>
<td>Foster care (%)</td>
<td>11</td>
<td>10</td>
<td>13</td>
<td>13</td>
<td>11</td>
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<tr>
<td>Other category (%)</td>
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<td>32</td>
<td>32</td>
<td>32</td>
<td>34</td>
<td>31</td>
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<tr>
<td>Provider specialty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Primary care physicians (%)</td>
<td>40</td>
<td>42</td>
<td>43</td>
<td>56</td>
<td>46</td>
<td>42</td>
<td></td>
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<tr>
<td>Psychiatrists (%)</td>
<td>31</td>
<td>21</td>
<td>17</td>
<td>11</td>
<td>9</td>
<td>25</td>
<td></td>
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<tr>
<td>Other physicians (%)</td>
<td>8</td>
<td>12</td>
<td>13</td>
<td>15</td>
<td>26</td>
<td>11</td>
<td></td>
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<tr>
<td>Missing (%)</td>
<td>21</td>
<td>25</td>
<td>27</td>
<td>18</td>
<td>19</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

*The rates presented were adjusted for seasonality. Abbreviations: pt-mo, patient-months, Avg.: average, CI: confidence interval, CV: cardiovascular.
### Table 4-3. Testing results for stimulant initiation trend

<table>
<thead>
<tr>
<th>Hypothesis testing</th>
<th>P-value</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>((H_0)=0) joinpoint versus ((H_a)=4) joinpoints*</td>
<td>0.0002</td>
<td>0.0125</td>
</tr>
<tr>
<td>((H_0)=1) joinpoint versus ((H_a)=4) joinpoints*</td>
<td>0.0002</td>
<td>0.0167</td>
</tr>
<tr>
<td>((H_0)=2) joinpoint versus ((H_a)=4) joinpoints*</td>
<td>0.0002</td>
<td>0.025</td>
</tr>
<tr>
<td>((H_0)=3) joinpoint versus ((H_a)=4) joinpoints*</td>
<td>0.022</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Selected model; **tests were performed with the Bonferroni correction at an overall significance level of 0.05.

### Table 4-4. Specification for stimulant initiation trend

<table>
<thead>
<tr>
<th>Segment</th>
<th>MPC (95% CI)</th>
<th>Joinpoint (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (01/2001-07/2002)</td>
<td>1.9 (0.7, 3.0)</td>
<td>07/2002 (03/2001, 02/2003)</td>
</tr>
<tr>
<td>III (07/2003-07/2006)</td>
<td>0.4 (-0.0, 0.8)</td>
<td>07/2006 (07/2003, 07/2007)</td>
</tr>
<tr>
<td>V (03/2007-11/2008)</td>
<td>-2.4 (-3.6, -1.2)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MPC: monthly percent change, CI: confidence interval.

### Table 4-5. Testing results for oral stimulant\* initiation trend

<table>
<thead>
<tr>
<th>Hypothesis testing</th>
<th>P-value</th>
<th>Significance level**</th>
</tr>
</thead>
<tbody>
<tr>
<td>((H_0)=0) joinpoint versus ((H_a)=4) joinpoints*</td>
<td>0.0002</td>
<td>0.0125</td>
</tr>
<tr>
<td>((H_0)=1) joinpoint versus ((H_a)=4) joinpoints*</td>
<td>0.0002</td>
<td>0.0167</td>
</tr>
<tr>
<td>((H_0)=2) joinpoint versus ((H_a)=4) joinpoints*</td>
<td>0.0009</td>
<td>0.025</td>
</tr>
<tr>
<td>((H_0)=3) joinpoint* versus ((H_a)=4) joinpoints</td>
<td>0.168</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Excludes Daytrana patch; **selected model; **tests were performed with the Bonferroni correction at an overall significance level of 0.05.

### Table 4-6. Specification for oral stimulant\* initiation trend

<table>
<thead>
<tr>
<th>Segment</th>
<th>MPC (95% CI)</th>
<th>Joinpoint (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (01/2001-07/2002)</td>
<td>1.8 (0.7, 2.9)</td>
<td>07/2002 (09/2001, 02/2003)</td>
</tr>
<tr>
<td>III (09/2003-07/2007)</td>
<td>0.7 (0.3, 1.0)</td>
<td>05/2007 (02/2004, 07/2008)</td>
</tr>
<tr>
<td>IV (07/2007-11/2008)</td>
<td>-1.7 (-3.2, -0.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Excludes Daytrana patch. Abbreviations: MPC: monthly percent change, CI: confidence interval.
Table 4-7. Comparability test results for stratified stimulant initiation trend (01/2004-11/2008, 59 months)

<table>
<thead>
<tr>
<th>Test pairs</th>
<th>Monthly sample size (range)</th>
<th>P-values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years vs 5-13 years</td>
<td>69 (20-118) vs 313 (177-597)</td>
<td>(0.002, -)</td>
</tr>
<tr>
<td>14-20 years vs 5-13 years</td>
<td>37 (14-62) vs 313 (177-597)</td>
<td>(0.27, 0.0002)</td>
</tr>
<tr>
<td>Female vs male</td>
<td>113 (53-173) vs 250 (138-362)</td>
<td>(0.27, 0.24)</td>
</tr>
<tr>
<td>Blacks vs Whites **</td>
<td>72 (37-108) vs 159 (69-250)</td>
<td>(0.96, 0.0002)</td>
</tr>
<tr>
<td>Hispanics vs Whites **</td>
<td>66 (39-94) vs 159 (69-250)</td>
<td>(0.24, 0.0002)</td>
</tr>
<tr>
<td>Supplemental security income vs Temporary assistance for needy family **</td>
<td>58 (36-80) vs 141 (81-202)</td>
<td>(0.001, -)</td>
</tr>
<tr>
<td>Foster care vs Temporary assistance for needy family **</td>
<td>39 (21-58) vs 141 (81-202)</td>
<td>(0.94, 0.0002)</td>
</tr>
<tr>
<td>Primary care physician vs psychiatrist **</td>
<td>71 (16-126) vs 172 (88-256)</td>
<td>(0.05, 0.0002)</td>
</tr>
<tr>
<td>ADHD+ mental comorbidities vs ADHD only **</td>
<td>108 (46-170) vs 255 (145-365)</td>
<td>(0.03, -)</td>
</tr>
</tbody>
</table>

*Significance level= 0.05; ** excluded patients less than 5 years of age.
### Table 4-8. Patient and provider characteristics in stimulant discontinuation trend analysis

<table>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADHD patients (n)</strong></td>
<td>8,587</td>
<td>2,750</td>
<td>2,379</td>
<td>1,807</td>
<td>849</td>
<td>16,372</td>
</tr>
<tr>
<td><strong>Follow-up time (pt-mo)</strong></td>
<td>51,522</td>
<td>16,500</td>
<td>14,274</td>
<td>10,842</td>
<td>5,094</td>
<td>98,232</td>
</tr>
<tr>
<td><strong>Avg. patient per month (n)</strong></td>
<td>232</td>
<td>250</td>
<td>198</td>
<td>151</td>
<td>142</td>
<td>210</td>
</tr>
<tr>
<td><strong>Stimulant discontinuation (n)</strong></td>
<td>2,549</td>
<td>871</td>
<td>699</td>
<td>538</td>
<td>290</td>
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<tr>
<td><strong>Discontinuation rate</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>(1000 pt-mo)</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Mean age (years-old)</strong></td>
<td>8.2</td>
<td>8.2</td>
<td>7.9</td>
<td>7.9</td>
<td>7.7</td>
<td>8.1</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(8.1-8.3)</td>
<td>(8.0-8.4)</td>
<td>(7.7-8.1)</td>
<td>(7.7-8.1)</td>
<td>(7.4-8.0)</td>
<td>(8.0-8.2)</td>
</tr>
<tr>
<td><strong>&lt; 5 years (%)</strong></td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td><strong>5-9 years (%)</strong></td>
<td>61</td>
<td>62</td>
<td>66</td>
<td>67</td>
<td>71</td>
<td>63</td>
</tr>
<tr>
<td><strong>10-14 years (%)</strong></td>
<td>23</td>
<td>20</td>
<td>18</td>
<td>16</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td><strong>15-20 years (%)</strong></td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<td>4</td>
</tr>
<tr>
<td><strong>&gt;20 years (%)</strong></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>71</td>
<td>69</td>
<td>70</td>
<td>68</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td><strong>White (%)</strong></td>
<td>42</td>
<td>41</td>
<td>41</td>
<td>42</td>
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<td>42</td>
</tr>
<tr>
<td><strong>Black (%)</strong></td>
<td>25</td>
<td>26</td>
<td>25</td>
<td>25</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td><strong>Hispanic (%)</strong></td>
<td>17</td>
<td>18</td>
<td>21</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td><strong>Other race (%)</strong></td>
<td>16</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>15</td>
<td>15</td>
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<td>Medicaid eligibility status</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Temporary assistance for needy family (%)</td>
<td>43</td>
<td>45</td>
<td>43</td>
<td>43</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>Supplemental security income (%)</td>
<td>18</td>
<td>15</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Foster care (%)</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>13</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Other category (%)</td>
<td>30</td>
<td>29</td>
<td>30</td>
<td>28</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Clinical condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing CV condition (%)</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mental comorbidity (%)</td>
<td>41</td>
<td>47</td>
<td>44</td>
<td>43</td>
<td>42</td>
<td>42</td>
</tr>
</tbody>
</table>

*The rates presented were adjusted for seasonality. Abbreviations: pt-mo, patient-months, Avg.: average, CI: confidence interval, CV: cardiovascular*
Table 4-9. Testing results for stimulant discontinuation trend

<table>
<thead>
<tr>
<th>Hypothesis testing</th>
<th>P-value</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>((H_0)=0) joinpoint versus ((H_a)=3) joinpoints</td>
<td>0.21</td>
<td>0.0167</td>
</tr>
<tr>
<td>((H_0)=0) joinpoint' versus ((H_a)=2) joinpoints</td>
<td>0.08</td>
<td>0.0167</td>
</tr>
<tr>
<td>((H_0)=0) joinpoint'' versus ((H_a)=1) joinpoints</td>
<td>0.05</td>
<td>0.0167</td>
</tr>
</tbody>
</table>

*Selected model,* **tests were performed with the Bonferroni correction at an overall significance level of 0.05

Table 4-10. Specification for stimulant discontinuation trend

<table>
<thead>
<tr>
<th>Segment</th>
<th>MPC (95% CI)</th>
<th>Joinpoint (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (01/2002-06/2008)</td>
<td>0.0 (-0.1,0.1)</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: MPC: monthly percent change, CI: confidence interval.
Table 4-11. Comparability test results for stratified stimulant discontinuation trend

<table>
<thead>
<tr>
<th>Test pairs</th>
<th>Monthly sample size (range)</th>
<th>P-values (Parallel test, coincident test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years vs 5-13 years</td>
<td>22 (21-24) vs 109 (43-176)</td>
<td>(0.14, 0.0002)</td>
</tr>
<tr>
<td>14-20 years vs 5-13 years</td>
<td>15 (7-23) vs 109 (43-176)</td>
<td>(0.43, 0.0002)</td>
</tr>
<tr>
<td>Female vs male</td>
<td>37 (24-51) vs 104 (44-164)</td>
<td>(0.22, 0.003)</td>
</tr>
<tr>
<td>Blacks vs Whites</td>
<td>36 (19-53) vs 58 (29-88)</td>
<td>(0.65, 0.0002)</td>
</tr>
<tr>
<td>Hispanics vs Whites</td>
<td>25 (12-38) vs 58 (29-88)</td>
<td>(0.64, 0.0002)</td>
</tr>
<tr>
<td>Supplemental security income vs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporary assistance for needy family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foster care vs Temporary assistance for</td>
<td>15 (7-23) vs 63 (30-97)</td>
<td>(0.31, 0.0002)</td>
</tr>
<tr>
<td>needy family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD+ mental comorbidities vs ADHD only</td>
<td>56 (33-80) vs 85 (35-135)</td>
<td>(0.13, 0.001)</td>
</tr>
</tbody>
</table>

*Significance level= 0.05
## Table 4-12. Patient and provider characteristics in stimulant initial daily dose trend analysis

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD patients (n)</td>
<td>6866</td>
<td>1968</td>
<td>1787</td>
<td>1368</td>
<td>1069</td>
</tr>
<tr>
<td>Avg. patient per month (n)</td>
<td>186</td>
<td>179</td>
<td>149</td>
<td>114</td>
<td>97</td>
</tr>
<tr>
<td>Mean dose (mg/day) (95% CI)</td>
<td>26.9</td>
<td>23.8</td>
<td>21.1</td>
<td>22.6</td>
<td>22.2</td>
</tr>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years-old) (95% CI)</td>
<td>7.8</td>
<td>7.9</td>
<td>7.7</td>
<td>7.7</td>
<td>7.5</td>
</tr>
<tr>
<td>&lt; 5 years (%)</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>5-9 years (%)</td>
<td>62</td>
<td>65</td>
<td>67</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>10-14 years (%)</td>
<td>20</td>
<td>17</td>
<td>16</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>15-20 years (%)</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>&gt;20 years (%)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Male (%)</td>
<td>70</td>
<td>67</td>
<td>70</td>
<td>65</td>
<td>70</td>
</tr>
<tr>
<td>White (%)</td>
<td>52</td>
<td>52</td>
<td>51</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>Black (%)</td>
<td>21</td>
<td>23</td>
<td>22</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>12</td>
<td>12</td>
<td>14</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Other race (%)</td>
<td>15</td>
<td>14</td>
<td>13</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------</td>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>----------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Temporary assistance for needy family (%)</td>
<td>43</td>
<td>44</td>
<td>43</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>Supplemental security income (%)</td>
<td>16</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Foster care (%)</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>11</td>
<td>9</td>
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<tr>
<td>Other category (%)</td>
<td>33</td>
<td>34</td>
<td>34</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>Clinical condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing CV condition (%)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mental comorbidity (%)</td>
<td>29</td>
<td>29</td>
<td>30</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Provider specialty</td>
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<td></td>
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<td></td>
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<tr>
<td>Primary care physicians (%)</td>
<td>61</td>
<td>64</td>
<td>65</td>
<td>74</td>
<td>63</td>
</tr>
<tr>
<td>Psychiatrists (%)</td>
<td>19</td>
<td>14</td>
<td>11</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Other physicians (%)</td>
<td>8</td>
<td>11</td>
<td>13</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Missing (%)</td>
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<td>11</td>
<td>8</td>
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</table>

Abbreviations: Avg.: average, CI: confidence interval, CV: cardiovascular
Table 4-13. Testing results for stimulant initial daily dose trend

<table>
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<tr>
<th>Hypothesis testing</th>
<th>P-value</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H₀)=0 joinpoint versus (Hₐ)=3 joinpoints</td>
<td>0.0002</td>
<td>0.0167</td>
</tr>
<tr>
<td>(H₀)=1 joinpoint versus (Hₐ)=3 joinpoints*</td>
<td>0.0002</td>
<td>0.025</td>
</tr>
<tr>
<td>(H₀)=2 joinpoint* versus (Hₐ)=3 joinpoints</td>
<td>0.21</td>
<td>0.05</td>
</tr>
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</table>

*Selected model; **tests were performed with the Bonferroni correction at an overall significance level of 0.05

Table 4-14. Specification for stimulant initial daily dose trend

<table>
<thead>
<tr>
<th>Segment</th>
<th>MPC (95% CI)</th>
<th>Joinpoint (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (01/2002-05/2002)</td>
<td>0.0 (-0.1,0.1)</td>
<td>05/2005 (03/2005, 07/2005)</td>
</tr>
<tr>
<td>III (09/2005-11/2007)</td>
<td>0.3 (0.1, 0.4)</td>
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</tr>
</tbody>
</table>

Abbreviations: MPC: monthly percent change, CI: confidence interval.
Table 4-15. Comparability test results for stratified stimulant initial daily dose trend

<table>
<thead>
<tr>
<th>Test pairs</th>
<th>Monthly sample size (range)</th>
<th>P-values (Parallel test, Coincident test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years vs 5-13 years</td>
<td>19 (7-31) vs 127 (73-181)</td>
<td>(0.002, -)</td>
</tr>
<tr>
<td>14-20 years vs 5-13 years</td>
<td>9 (7-12) vs 115 (49-181)</td>
<td>(0.03, -)</td>
</tr>
<tr>
<td>Female vs male</td>
<td>71 (50-92) vs 105 (65-146)</td>
<td>(0.14, 0.20)</td>
</tr>
<tr>
<td>Blacks vs Whites</td>
<td>37 (15-59) vs 73 (44-102)</td>
<td>(0.34, 0.40)</td>
</tr>
<tr>
<td>Hispanics vs Whites</td>
<td>17 (5-30) vs 73 (44-102)</td>
<td>(0.83, 0.84)</td>
</tr>
<tr>
<td>Supplemental security income vs Temporary assistance for needy family</td>
<td>32 (19-46) vs 72 (46-99)</td>
<td>(0.79, 0.03)</td>
</tr>
<tr>
<td>Foster care vs Temporary assistance for needy family</td>
<td>31 (16-46) vs 72 (46-99)</td>
<td>(0.45, 0.49)</td>
</tr>
<tr>
<td>Primary care physician vs psychiatrist</td>
<td>88 (49-127) vs 28 (2-54)</td>
<td>(0.11, 0.01)</td>
</tr>
<tr>
<td>ADHD+ mental comorbidities vs ADHD only</td>
<td>42 (24-61) vs 111 (59-163)</td>
<td>(0.14, 0.05)</td>
</tr>
</tbody>
</table>

Significance level= 0.05
Table 4-16. Patient and provider characteristics in stimulant maintenance daily dose trend analysis

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<th>Post-warning</th>
<th>Post-warning</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD patients (n)</td>
<td>5522</td>
<td>1789</td>
<td>1602</td>
<td>1183</td>
<td>539</td>
<td>10635</td>
</tr>
<tr>
<td>Avg. patient per month (n)</td>
<td>149</td>
<td>163</td>
<td>134</td>
<td>99</td>
<td>90</td>
<td>138</td>
</tr>
<tr>
<td>Mean dose (n)</td>
<td>26.0</td>
<td>22.8</td>
<td>21.4</td>
<td>22.6</td>
<td>21.4</td>
<td>24.1</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(25.6-26.3)</td>
<td>(22.2-23.4)</td>
<td>(20.8-22.0)</td>
<td>(21.9-23.4)</td>
<td>(20.2-22.5)</td>
<td>(23.9-24.4)</td>
</tr>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Mean age (years-old)</td>
<td>7.9</td>
<td>7.9</td>
<td>7.6</td>
<td>7.8</td>
<td>7.3</td>
<td>7.8</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(7.8-8.0)</td>
<td>(7.7-8.1)</td>
<td>(7.4-7.8)</td>
<td>(7.5-8.1)</td>
<td>(7.0-7.7)</td>
<td>(7.7-7.9)</td>
</tr>
<tr>
<td>&lt; 5 years (%)</td>
<td>10</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
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<tr>
<td>5-9 years (%)</td>
<td>65</td>
<td>65</td>
<td>69</td>
<td>68</td>
<td>74</td>
<td>67</td>
</tr>
<tr>
<td>10-14 years (%)</td>
<td>21</td>
<td>19</td>
<td>16</td>
<td>16</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td>15-20 years (%)</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt;20 years (%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Male (%)</td>
<td>71</td>
<td>69</td>
<td>70</td>
<td>67</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>White (%)</td>
<td>45</td>
<td>46</td>
<td>44</td>
<td>47</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>Black (%)</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>24</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>16</td>
<td>16</td>
<td>18</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Other race (%)</td>
<td>15</td>
<td>13</td>
<td>13</td>
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<td>14</td>
<td>14</td>
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</tbody>
</table>
Table 4-16. Continued

<table>
<thead>
<tr>
<th>Medicaid eligibility status</th>
<th>Pre-warning</th>
<th>Post-warning</th>
<th>Post-warning</th>
<th>Post-warning</th>
<th>Post-warning</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary assistance for needy family (%)</td>
<td>43</td>
<td>46</td>
<td>43</td>
<td>43</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>Supplemental security income (%)</td>
<td>16</td>
<td>14</td>
<td>13</td>
<td>15</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Foster care (%)</td>
<td>10</td>
<td>12</td>
<td>13</td>
<td>15</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Other category (%)</td>
<td>30</td>
<td>29</td>
<td>30</td>
<td>28</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Clinical conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing CV condition (%)</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mental comorbidity (%)</td>
<td>34</td>
<td>40</td>
<td>38</td>
<td>37</td>
<td>37</td>
<td>36</td>
</tr>
</tbody>
</table>

Abbreviations: Avg.: average, CI: confidence interval, CV: cardiovascular.
Table 4-17. Testing results for stimulant maintenance daily dose trend

<table>
<thead>
<tr>
<th>Hypothesis testing</th>
<th>P-value</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>((H_0)=0) joinpoint versus ((H_a)=3) points</td>
<td>0.0002</td>
<td>0.0167</td>
</tr>
<tr>
<td>((H_0)=1) joinpoint versus ((H_a)=3) points</td>
<td>0.0002</td>
<td>0.025</td>
</tr>
<tr>
<td>((H_0)=2) joinpoint versus ((H_a)=3) points</td>
<td>0.0068</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Selected model; **tests were performed with the Bonferroni correction at an overall significance level of 0.05

Table 4-18. Specification for stimulant maintenance daily dose trend

<table>
<thead>
<tr>
<th>Segment</th>
<th>MPC (95% CI)</th>
<th>Joinpoint (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (01/2002-12/2004)</td>
<td>0.1 (-0.1, 0.2)</td>
<td>12/2004 (07/2004, 06/2005)</td>
</tr>
<tr>
<td>IV (07/2006-06/2008)</td>
<td>-0.1 (-0.5, 0.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MPC: monthly percent change, CI: confidence interval.
### Table 4-19. Comparability test results for stratified stimulant maintenance daily dose trend

<table>
<thead>
<tr>
<th>Test pairs</th>
<th>Monthly sample size (range)</th>
<th>P-values (Parallel test, coincident test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years vs 5-13 years</td>
<td>14 (13-15) vs 73 (32-115)</td>
<td>(0.13, 0.0002)</td>
</tr>
<tr>
<td>14-20 years vs 5-13 years</td>
<td>3 (2-4) vs 73 (32-115)</td>
<td>(0.75, 0.0002)</td>
</tr>
<tr>
<td>Female vs male</td>
<td>24 (19-30) vs 67 (32-102)</td>
<td>(0.13, 0.14)</td>
</tr>
<tr>
<td>Blacks vs Whites</td>
<td>24 (13-36) vs 40 (24-57)</td>
<td>(0.22, 0.0002)</td>
</tr>
<tr>
<td>Hispanics vs Whites</td>
<td>14 (8-21) vs 40 (24-57)</td>
<td>(0.20, 0.0002)</td>
</tr>
<tr>
<td>Supplemental security income vs Temporary assistance for needy family</td>
<td>14 (6-23) vs 42 (24-61)</td>
<td>(0.4, 0.31)</td>
</tr>
<tr>
<td>Foster care vs Temporary assistance for needy family</td>
<td>9 (5-14) vs 42 (24-61)</td>
<td>(0.46, 0.0002)</td>
</tr>
<tr>
<td>Presence of mental comorbidities vs ADHD only</td>
<td>29 (24-35) vs 62 (27-97)</td>
<td>(0.68, 0.86)</td>
</tr>
</tbody>
</table>

*Significance level= 0.05*
Table 4-20. Patient and provider characteristics in pre-treatment electrocardiograph (ECG) use trend analysis

<table>
<thead>
<tr>
<th></th>
<th>Pre-warning</th>
<th>Post-warning</th>
<th>Post-warning</th>
<th>Post-warning</th>
<th>Post-warning</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD patients (n)</td>
<td>18964</td>
<td>3760</td>
<td>3374</td>
<td>2377</td>
<td>1664</td>
<td>30139</td>
</tr>
<tr>
<td>Follow-up time (pt-mo)</td>
<td>11159</td>
<td>2099</td>
<td>1819</td>
<td>1107</td>
<td>658</td>
<td>16842</td>
</tr>
<tr>
<td>Avg. patient per month (n)</td>
<td>387</td>
<td>342</td>
<td>281</td>
<td>198</td>
<td>151</td>
<td>317</td>
</tr>
<tr>
<td>ECG use (n)</td>
<td>382</td>
<td>94</td>
<td>137</td>
<td>109</td>
<td>130</td>
<td>852</td>
</tr>
<tr>
<td>ECG use rate (1000 pt-mo)</td>
<td>34</td>
<td>45</td>
<td>75</td>
<td>98</td>
<td>197</td>
<td>51</td>
</tr>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years-old)</td>
<td>7.8</td>
<td>7.7</td>
<td>7.5</td>
<td>7.5</td>
<td>7.6</td>
<td>7.7</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(7.7-7.8)</td>
<td>(7.5-7.8)</td>
<td>(7.4-7.7)</td>
<td>(7.4-7.7)</td>
<td>(7.4-7.8)</td>
<td>(7.7-7.8)</td>
</tr>
<tr>
<td>&lt; 5 yrs (%)</td>
<td>16</td>
<td>16</td>
<td>17</td>
<td>15</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>5-9 yrs (%)</td>
<td>59</td>
<td>62</td>
<td>63</td>
<td>67</td>
<td>67</td>
<td>61</td>
</tr>
<tr>
<td>10-14 yrs (%)</td>
<td>21</td>
<td>16</td>
<td>15</td>
<td>13</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>15-20 yrs (%)</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>&gt;20 yrs (%)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Male (%)</td>
<td>71</td>
<td>70</td>
<td>70</td>
<td>67</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>White (%)</td>
<td>46</td>
<td>45</td>
<td>46</td>
<td>46</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>Black (%)</td>
<td>22</td>
<td>24</td>
<td>23</td>
<td>22</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>16</td>
<td>16</td>
<td>17</td>
<td>16</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Other race (%)</td>
<td>16</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>17</td>
<td>16</td>
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Table 4-20. Continued

<table>
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<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary assistance for needy family (%)</td>
<td>41</td>
<td>43</td>
<td>41</td>
<td>41</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Supplemental security income (%)</td>
<td>18</td>
<td>15</td>
<td>15</td>
<td>14</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Foster care (%)</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>13</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Other category (%)</td>
<td>31</td>
<td>32</td>
<td>33</td>
<td>31</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Clinical conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental comorbidity (%)</td>
<td>29</td>
<td>29</td>
<td>31</td>
<td>25</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Provider specialty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care physicians (%)</td>
<td>48</td>
<td>52</td>
<td>54</td>
<td>66</td>
<td>59</td>
<td>51</td>
</tr>
<tr>
<td>Psychiatrists (%)</td>
<td>27</td>
<td>17</td>
<td>14</td>
<td>8</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Other physicians (%)</td>
<td>9</td>
<td>13</td>
<td>14</td>
<td>14</td>
<td>26</td>
<td>11</td>
</tr>
<tr>
<td>Missing (%)</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>12</td>
<td>10</td>
<td>16</td>
</tr>
</tbody>
</table>

Abbreviations: pt-mo, patient-months, Avg.: average, CI: confidence interval.
### Table 4-21. Testing results for pre-treatment electrocardiograph use trend

<table>
<thead>
<tr>
<th>Hypothesis testing</th>
<th>P-value</th>
<th>Significance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>((H_0)=0) joinpoint versus ((H_a)=3) joinpoints</td>
<td>0.0002</td>
<td>0.0167</td>
</tr>
<tr>
<td>((H_0)=1) joinpoint versus ((H_a)=3) joinpoints</td>
<td>0.003</td>
<td>0.025</td>
</tr>
<tr>
<td>((H_0)=2) joinpoint versus ((H_a)=3) joinpoints</td>
<td>0.051</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Selected model; tests were performed with the Bonferroni correction at an overall significance level of 0.05.

### Table 4-22. Specification for pre-treatment electrocardiograph use trend

<table>
<thead>
<tr>
<th>Segment</th>
<th>MPC (95% CI)</th>
<th>Joinpoint (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (01/2001-06/2004)</td>
<td>-0.6 (-1.5, 0.4)</td>
<td>06/2004 (07/2003, 06/2005)</td>
</tr>
<tr>
<td>III (02/2008-11/2008)</td>
<td>13.2 (4.2-23)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MPC: monthly percent change, CI: confidence interval.
<table>
<thead>
<tr>
<th>Test pairs</th>
<th>Monthly sample size (range)</th>
<th>P-values (parallel test, coincident test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years vs 5-13 years</td>
<td>50 (8-61) vs 246 (83-341)</td>
<td>(0.09, 0.07)</td>
</tr>
<tr>
<td>14-20 years vs 5-13 years</td>
<td>17 (3-26) vs 246 (83-341)</td>
<td>-</td>
</tr>
<tr>
<td>Female vs male</td>
<td>90 (18-99) vs 222 (76-329)</td>
<td>(0.79, 0.83)</td>
</tr>
<tr>
<td>Blacks vs Whites</td>
<td>70 (17-96) vs 142 (47-187)</td>
<td>(0.82, 0.92)</td>
</tr>
<tr>
<td>Hispanics vs Whites</td>
<td>50 (9-57) vs 142 (47-187)</td>
<td>(0.40, 0.006)</td>
</tr>
<tr>
<td>Supplemental security income vs Temporary</td>
<td>52 (12-122) vs 129 (49-144)</td>
<td>(0.30, 0.37)</td>
</tr>
<tr>
<td>assistance for needy family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foster care vs Temporary assistance for needy</td>
<td>33 (8-59) vs 129 (49-144)</td>
<td>(0.26, 0.03)</td>
</tr>
<tr>
<td>family</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care physician vs psychiatrist</td>
<td>160 (51-173) vs 67 (2-163)</td>
<td>(0.01, -)</td>
</tr>
<tr>
<td>ADHD+mental comorbidities vs ADHD only</td>
<td>89 (23-134) vs 224 (71-294)</td>
<td>(0.05, -)</td>
</tr>
</tbody>
</table>

Significance level= 0.05
Figure 4-1. Stimulant initiation trend
Figure 4-2. Stimulant and atomoxetine initiation trend
Figure 4-3. Stimulant initiation trend (oral products only)
Figure 4-4. Stimulant initiation trend by age (< 5 years versus 5-13 years)

Figure 4-5. Stimulant initiation trend by age (14-20 years old versus 5-13 years old)
Figure 4-6. Stimulant initiation trend by gender
Figure 4-7. Stimulant initiation trend by race (Blacks versus Whites)

Figure 4-8. Stimulant initiation trend by race (Hispanics versus Whites)
Figure 4-9. Stimulant initiation trend by eligibility (Supplemental security income [SSI] versus Temporary assistance for needy family [TANF])

Figure 4-10. Stimulant initiation trend by eligibility (Foster care vs Temporary assistance for needy family [TANF])

- TANF
- TANF fitted model
- SSI
- SSI fitted model
- Adderall withdrawal
- Boxed warning debate
- MedGuide distributed
Figure 4-11. Stimulant initiation trend by comorbidity status
Figure 4-12. Stimulant initiation trend by provider type

- **Primary care physicians**
- **Primary care physicians fitted model**
- **Psychiatrists**
- **Psychiatrists fitted model**

Events:
1. Adderall withdrawal
2. Boxed warning debate
3. MedGuide distributed
Figure 4-13. Stimulant discontinuation trend
Figure 4-14. Stimulant discontinuation trend by age group (< 5 years versus 5-13 years)

Figure 4-15. Stimulant discontinuation trend by age group (5-13 years versus 14-20 years)
Figure 4-16. Stimulant discontinuation trend by gender

Per 1,000 patient-months

- Male
- Male fitted model
- Female
- Female fitted model

1. Adderall withdrawal
2. Boxed warning debate
3. MedGuide distributed
Figure 4-17. Stimulant discontinuation trend by race (Blacks versus Whites)

Figure 4-18. Stimulant discontinuation trend by race (Hispanics versus Whites)
Figure 4-19. Stimulant discontinuation trend by eligibility status (Supplemental security income [SSI] versus Temporary assistance for needy family [TANF])

Figure 4-20. Stimulant discontinuation trend by eligibility status (Foster care versus Temporary assistance for needy family [TANF])
Figure 4-21. Stimulant discontinuation trend by comorbidity status

- ADHD only
- ADHD only fitted model
- ADHD+comorbidity
- ADHD+comorbidity fitted model

1. Adderall withdrawal
2. Boxed warning debate
3. MedGuide distributed
Figure 4-22. Stimulant initial daily dose trend
Figure 4-23. Stimulant initial daily dose trend by age group (< 5 years versus 5-13 years)

Figure 4-24. Stimulant initial daily dose trend by age group (14-20 years versus 5-13 years)
Figure 4-25. Stimulant initial daily dose trend by gender

Male
Male fitted model

Female
Female fitted model

1 Adderall withdrawal
2 Boxed warning debate
3 MedGuide distributed
Figure 4-26. Stimulant initial daily dose trend by race (Blacks versus Whites)

Figure 4-27. Stimulant initial daily dose trend by race (Hispanics versus Whites)
Figure 4-28. Stimulant initial daily dose trend by eligibility status (Supplemental security income [SSI] versus Temporary assistance for needy family [TANF])

Figure 4-29. Stimulant initial daily dose trend by eligibility status (Foster care versus Temporary assistance for needy family [TANF])
Figure 4-30. Stimulant initial daily dose trend by comorbidity status
Figure 4-31. Stimulant initial daily dose trend by provider type

- Primary care physicians
- Primary care physicians fitted model
- Psychiatrists
- Psychiatrists fitted model
- 1 Adderall withdrawal
- 2 Boxed warning debate
- 3 MedGuide distributed
Figure 4-32. Stimulant maintenance daily dose trend
Figure 4-33. Stimulant maintenance daily dose trend by age group (< 5 years versus 5-13 years)

Figure 4-34. Stimulant maintenance daily dose trend by age group (14-20 years versus 5-13 years)
Figure 4-35. Stimulant maintenance daily dose trend by gender

- Male
- Male fitted model
- Female
- Female fitted model
- 1. Adderall withdrawal
- 2. Boxed warning debate
Figure 4-36. Stimulant maintenance daily dose trend by race (Blacks versus Whites)

Figure 4-37. Stimulant maintenance daily dose trend by race (Hispanics versus Whites)
Figure 4-38. Stimulant maintenance daily dose trend by eligibility status (Supplemental security income [SSI] versus Temporary assistance for needy family [TANF])

Figure 4-39. Stimulant maintenance daily dose trend by eligibility status (Foster care versus Temporary assistance for needy family [TANF])
Figure 4-40. Stimulant maintenance daily dose trend by comorbidity status
Figure 4-41. Pre-treatment ECG use trend
Figure 4-42. Pre-treatment electrocardiography use trend by age group (< 5 years versus 5-13 years)
Figure 4-43. Pre-treatment electrocardiography use trend by gender
Figure 4-44. Pre-treatment electrocardiography use trend by race (Black versus Whites)

Figure 4-45. Pre-treatment electrocardiography use trend by race (Hispanics versus Whites)
Figure 4-46. Pre-treatment electrocardiography use trend by eligibility status (Supplemental security income [SSI] versus Temporary assistance for needy family [TANF]).

Figure 4-47. Pre-treatment electrocardiography use trend by eligibility status (Foster care versus Temporary assistance for needy family [TANF]).
Figure 4-48. Pre-treatment electrocardiography use trend by comorbidity status
Figure 4-49. Pre-treatment electrocardiography use trend by provider type

- Primary care physicians
- Primary care physicians fitted model
- Psychiatrists
- Psychiatrists fitted model
- Adderall withdrawal
- Boxed warning debate
- MedGuide distributed
Stimulant Utilization after Health Canada’s Withdrawal of Adderall

While prior research on the impact of drug safety warnings found treatment decision-making altered soon after the first signal\(^{58, 61, 84}\), we did not observe an immediate decrease in stimulant initiation or discontinuation after Canada’s action; we, however, found the prescribed dose significantly reduced. The initial daily dose decreased 6% per month from 26 milligram (mg) (MPH-equivalents), and the reduction coincidentally stopped after the time Adderall re-entered the Canadian market at an average of about 20 mg. The maintenance daily dose declined consistently through this time period with a rate of 2% per month from 26 mg per day. The absolute reduction in stimulant treatment intensity was approximately 6 mg, which equates to a 30-60% decrease of the recommended initial dose (5 mg twice daily for immediate-release formulations; 18 mg once daily for extended-release tablets; 20 mg once daily for extended-release capsules) or 20 % of the maintenance dose (30.5 mg) in the landmark ADHD treatment trial, the Multimodal Treatment Study of Children with ADHD (MTA). It raises the question whether treatment effectiveness was compromised in response to Canada’s action, given that the maintenance dose before Canada’s action (≈26mg) was already lower than that in the MTA study (30.5mg). However, it should be noted that the clinical trial population might represent patients with more pronounced symptoms, and that lower doses might suffice for real-world populations of children with mixed symptom severity.
Stimulant Utilization after the Debate on Boxed Warnings

The stimulant CV safety issue was addressed extensively in the U.S. during the debate over the boxed warning proposal. The FDA’s final evaluation of this safety signal was not clear, largely because the available evidence is inconclusive. On one hand, rejection of the boxed warning proposal by the Drug Safety and Risk Management Advisory Board implies the notion that stimulant treatment is generally safe. On the other hand, the requirement of a MedGuide suggests that the safety risk was not was not considered minor, following regulatory guidance that MedGuide are issued for drugs when their side effect possess “serious and significant public health concerns” 85, 86.

The controversial opinions on stimulant CV safety are reflected in the utilization patterns. The observed changes during this period were different from the impact usually attributed to a safety signal. We found stable treatment discontinuation; no further change in initial treatment strength; a 50% (370-540 per 1000 patient-month) increase in stimulant initiation rate, and, a 4mg MPH-equivalents rebound in the maintenance daily dose from the initial decrease after Canada’s action. The increase in treatment initiation and intensity could be attributed to the FDA’s rejection of the boxed warning proposal or the latent impact from the re-marketing of Adderall. Moreover, a new stimulant product (i.e. Daytrana; approval date= 04/2006) was released in this period. The introduction of new products have shown to positively alter overall use and patients’ and providers’ perception about stimulant safety might have been mitigated with new FDA approvals and new marketing efforts.

Stimulant Utilization after the Distribution of MedGuides

The distribution of MedGuides marked a big step in communicating stimulant CV safety concern in a systematic fashion. The MedGuide is a consumer-directed drug
information pamphlet distributed by pharmacies when consumers fill or re-fill a prescription for the target drug. It is supposed to assure that patients receive FDA-approved information regarding risk of severe CV side effects prior to taking stimulants. Nevertheless, the effectiveness of MedGuides as a risk communication tool has been questioned, although it has not been formally assessed. A study that evaluated reading difficulty, content, and format of 40 MedGuides reported the Guides were generally written at a higher reading level than the federal recommendations, including extensive quantities of information (the average length of Medication Guides was 2208 words, or 6–10 pages) and lack of summaries highlighting the most important information for patients. Moreover, interviews of 251 primary care patients at a public hospital clinic suggested that only few (less than a quarter of) patients had looked at MedGuides.

Given concerns about the effectiveness of MedGuides, the decrease in stimulant initiation rate after the release of MedGuides was unexpected. A causal relationship between the release of MedGuides and the reduction in stimulant initiation, however, seems less plausible if we factor in the way the guides were distributed. Currently, MedGuides are delivered at the time of dispensing; they are enclosed with the dispensed medication. It is unlikely that patients are able to make a treatment decision based on the guide for the first prescription since they would not have the chance to read it before they receive the dispensed drug. Only a comparison of prescribing versus dispensing information would be able to discern whether MedGuides influenced prescribers or patients in deciding to initiate therapy.

To provide perspective, we compare our results to those of a study evaluating the impact of regulatory actions related to selective serotonin reuptake inhibitor (SSRI)
antidepressants’ suicidal ideation. The two warnings have similar target populations (children and adolescent with mental disorder) and similar severity of the proposed adverse effect, yet differences in the strength of evidence supporting a causal association. This study, which was also conducted in a Medicaid population, found a decrease in treatment initiation of similar magnitude as the trend in our study (1.6% per month versus 2%). Since the evidence is more concrete, regulatory agencies issued warnings in a stronger tone. For example, the drug regulatory agency in the UK declared the risk-benefits profile of most SSRI antidepressants were unfavorable for the treatment of major depressive disorder in children and adolescents. The US FDA issued a boxed warning. It is therefore surprising that a minor warning might have a comparable effect. However, because evidence on the effectiveness of stimulant treatment is fragmented and because many reports have questioned whether stimulants are over-used, providers and patients might have readjusted their understanding of the risk-benefit profile entirely. Potentially, the observed decrease in stimulant utilization might reflect those patients who received only marginal benefits from treatment. Overall, the reduction in stimulant initiation rate (34%) that could be associated with CV safety warnings was clinically significant.

We found no change in the discontinuation rate after the distribution of MedGuides, similar to what we observed in earlier time periods, which suggests that the primary effect of drug safety warnings occurred at the point of treatment initiation. It also implies that provision of a MedGuide at the time of refilling a prescription might not have a significant impact on treatment decision-making. Thus, emerging safety issues may not be effectively communicated via MedGuides to prevalent drug users. It is also
noteworthy that 30% or one in three stimulant users stopped treatment within 6 months of initiation, throughout the entire study period, raising questions about treatment effectiveness, suboptimal ADHD care or excessive stimulant use.

We found no change in treatment strength after the distribution of MedGuide, which is expected, since dosing decisions are typically made by prescribers, yet the target audiences of the Guide are consumers.

**ECG Utilization after Stimulant CV Safety Warnings**

It is arguable if the first change point observed in the pre-treatment ECG trend is attributable to the CV safety warning since the point estimate is more than half a year earlier than Canada’s action and the confidence interval is wide. In contrast, the increase in the ECG utilization in early 2008 seems more closely tied to the AHA’s recommendation on pre-treatment ECG screening. This finding is encouraging, in particular because prior research has not found that a drug safety warning increases a “preventive action”.\(^{57,88}\) Nevertheless, while ECG utilization significantly rose from 34 per 1,000 patient-months to 400 per 1,000 patient-months, the clinical benefit from such marginal improvement is probably negligible given low ECG test sensitivity.\(^{89-91}\)

**Change in Trends among Subgroups**

Overall, the change in stimulant utilization trends after CV safety warnings was not different among most subgroups. It should be noted that the sample size of the subgroups were small, resulting is limited power to detect differences.

We did not observe a decrease in stimulant initiation trend after safety warnings among younger (< 5 years old) patients, patients with other mental comorbidities, or patients receiving Medicaid benefits due to SSI status (disability). Previous research offers support for an association between age and ADHD severity; patients diagnosed
with ADHD at a younger age were found to have poorer functioning and more aggression than their older counterparts by teacher report and clinician rating.\textsuperscript{92} In addition, an early age-of-onset of ADHD was correlated with a greater rate of parent-reported child externalizing comorbid symptoms\textsuperscript{93}, including several aggressive behaviors. Given the more severe ADHD symptoms, it is likely more difficult to abandon medication treatment among younger patients, and thus, their stimulant initiation rate did not change in comparison to older patients. Likewise, patients with mental comorbidities or disability generally have more complex psychiatric conditions\textsuperscript{39} and control of ADHD symptoms is probably given higher priority than in otherwise healthy patients. Nevertheless, among those patients where ADHD treatment benefit might outweigh risk, stimulants were prescribed at a lower strength after concerns on CV risk were voiced, consistently with their comparison groups.

Change in pre-treatment ECG utilization trend after CV safety warnings differed by patients’ clinical condition and provider type. The higher ECG screening rate prior to warnings among patients with other mental conditions might be due to concerns about their more fragile health status. The increase in ECG use in turn, was sharper among patients with only ADHD. The more pronounced increase in ECG screening among psychiatrists might be due to the fact that specialists adopt new medical information more rapidly than generalists do.\textsuperscript{94-97} Psychiatrists might also feel a greater need for general health assessments since their medical involvement is typically not as holistic as care provided by a primary care provider who might feel in a better position to evaluate presence of cardiac risk factors.
It is noteworthy that stimulant maintenance dose was consistently lower among minorities and higher in foster care children; especially, Hispanic patients received treatment at a 4mg lower strength than Whites. It is not clear if race were a modifier of ADHD severity or stimulant efficacy, however, given that the initial dose is similar across ethnic groups, it is likely that minorities either adjust doses downward or adhere less to a regular dosing schedule. This observation is consistent with different attitudes toward psychotropic use across cultures, and raises the concern that treatment outcomes may be less optimal among minorities. Foster care status has been found previously to be a positive predictor for psychotropic utilization\textsuperscript{27} and similarly, could be a predictor for more aggressive dosing. It is possible that the hurdle of getting foster care children into the health care system and of assuring regular follow-up lead providers to more aggressive treatment regimens to assure positive treatment outcomes.

**Other Important Findings**

We noticed the number of newly diagnosed ADHD patients was shrinking during the post-CV warning period (from 2005 to 2008). Enrollment records from Florida Medicaid showed the cumulative size of fee-for-service beneficiaries per calendar year varied only slightly from 2001 to 2008, as did the age composition of beneficiaries (Table 5-1 and 5-2). Thus, the decrease in the size of new episode patients was probably driven by a reduction of ADHD diagnoses, predominately among the pediatric population (from 0.57% at the end of 2004 to 0.25% at the end of 2008). The association between ADHD diagnosis trend and stimulant CV warnings is not the scope of this study; however, it is possible that drug safety concerns may have affected the disease diagnosis rate as well. The pediatric depression diagnosis rate was lowered significantly after the FDA advisory issued a warning on SSRI suicidality risk\textsuperscript{60}. It is
reasonable to suspect the same applied to ADHD diagnosis pattern and raises questions whether the disorder had been over-diagnosed before or is under-recognized now.

**The Application of Joinpoint Analysis**

Our study is one of few that applied JP analysis to assess the impact of new evidence or regulatory changes on health service utilization. It is unique in that the research questions could not have been answered without JP analysis. Studies using other approaches in quasi-experimental design, including the strongest conventional method—interrupted time-series analysis—require a definite hypothesis on the timing and latency of event(s) that might influence the trend. In our case, the multitude of events and uncertainty of their relative magnitude and latency, as well as the weak evidence and controversial action on stimulant’s CV risk prohibited any explicit a priori hypotheses about change points.

The findings have to be interpreted with caution. The estimation method currently used in the analytical software (i.e. the grid research method) assumes that the joinpoints occur at the observed data points. Therefore, exact timing (i.e. the location) of change in trend can be inaccurate. Also, latent effects are not easily captured by the JP model. As we test for trend change after multiple events, we are not able to attribute a change to a single occasion. However, the immediacy of change and how closer it is related to the event could point to a causal relationship.

**Study Limitations**

In addition to the limitation due to the statistical technique, our study is also restricted by the data source and nature of administrative data. First, this study was based on the Florida Medicaid population, and thus, limited to a single state and biased
towards low-income groups and minorities. The practice of Medicaid providers may not be representative of providers under contract with other types of health insurance programs. Second, claim data reflect only dispensing information and cannot describe the actual medication administration; drug utilization and persistence may be lower than what were found in this study. Nevertheless, the fact that prescriptions were filled suggests some intent to administer medication. Third, patients’ diagnostic information was not confirmed through chart review or other clinical assessments. The requirement of a second diagnostic code increases specificity, but under- or mis-coding of health care encounter information may result in the inclusion of patients who did not have ADHD or in miss-classification of patients’ comorbidity status. Miss-classification decreases our ability to detect a change in utilization pattern; however, it would need to change over time to bias the trend analyses. Forth, we were not able to address disease severity, which is likely to influence treatment decisions. The data source also lacks important contextual factors on patient, family, provider, and treatment systems, which may help to explain socio-cultural contributions to the observed trends. Lastly, some measures were based on small numbers per time unit; this makes the identification of change points arbitrary and highly sensitive to the chosen p-value cut-off, especially in the subgroup analyses. Also, we are not able to run multivariate analysis in JP software, and the ability to stratify analyses was again limited by sample size.

**Summary and Future Research**

Canada’s withdrawal of Adderall had no effect on stimulant initiation but did permanently decrease treatment intensity. Furthermore, a slightly smaller portion of ADHD patients initiated drug treatment in 2008 after release of MedGuides. It is
important to assess how the decrease in stimulant use or intensity translated into clinical outcomes. Sub-populations with unusual trends, such as, young age-of-diagnosis and presence of mental comorbidities or physical illness, should be especially studied.

The findings did not support that the publicity or regulatory actions on stimulant CV safety concerns, including the distribution of MedGuides, altered prevalent drug users’ treatment decisions, as stimulant discontinuation rates remained stable during the study period. The effectiveness of MedGuides as a risk communication tool needs further examination.

Lastly, the declining new ADHD visits and treatment intensity, the differential stimulant maintenance strength among sub-populations and the suboptimal treatment persistence underscore the importance of investigations on the appropriateness of ADHD diagnoses and stimulant treatment.

Conclusions

Practitioners reacted to stimulant CV safety concerns with immediate 6-mg methylphenidate equivalent reduction in dosing and an increase in ECG screening, affecting however only a marginal proportion of patients. While treatment discontinuation remained stable, treatment initiation decreased after the requirement for MedGuides. This decline differed by patient age, presence of mental comorbidities or disability; while the reduction in treatment intensity did not show significant difference by patient or provider characteristics. A more pronounced elevation in ECG use was observed among patients with less complicated mental conditions or patients who were diagnosed by psychiatrists. Clinical consequences of these changes are uncertain.
Table 5-1. Age distribution of Florida Medicaid fee-for service population during 2001-2008.

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* Cumulative count during calendar year; ** proportion of newly diagnosed patients in Florida Medicaid fee for service population.
### APPENDIX A

**NATIONAL DRUG CODE (NDC): STIMULANTS**

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### APPENDIX C

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136
### APPENDIX D

**NATIONAL DRUG CODE: SECOND LINE ADHD TREATMENT (OTHERS)**

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137
APPENDIX D
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LIST OF REFERENCES


76. FDA. Atomoxetine (marketed as Strattera) Information. 2005.


BIOGRAPHICAL SKETCH

Chih-ying Chen was born and raised in Taipei, Taiwan. She received her bachelor’s degree in Pharmacy from National Taiwan University in 2001 and worked at the National Adverse Drug Reaction Reporting Center for one year. In 2004, after she recieved her Master of Health Administration degree from University of Pittsburgh she joined the Department of Pharmaceutical Outcomes & Policy at the University of Florida where she was trained as a pharmacoepidemiologist. Her research interests focus on drug utilization, safety and effectiveness.