ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER IN ADULTS

FINAL PHARMACOECONOMICS REPORT

November 23, 2015

Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the Attention Deficit Hyperactivity Disorder Drug Class Review

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Study Team

Pharmacoeconomics Team: Doug Coyle, Karen Lee, Mirhad Lončar, Kylie Tingley

Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Executive Briefing

- The objective of this study was to review current evidence for the comparative cost-effectiveness of pharmacological treatments for attention deficit hyperactivity disorder (ADHD) and assess the budget impact of alternative policies for reimbursing pharmacotherapies in the treatment of ADHD

- We did not find any published economic evaluations that were eligible for inclusion in our review of the comparative cost-effectiveness of adult ADHD medications; however, we were able to conduct a *post-hoc* literature review to assess the impact of adult ADHD on work performance and criminality

- Findings from this *post-hoc* review were generally supportive of an association between adult ADHD and increased unemployment and poorer work performance and that pharmacological treatment of ADHD symptoms is associated with improved work performance and reduced likelihood of criminal behaviour

- These results have limited applicability in the Canadian context and should be interpreted with caution

- Based on data from OPDP from 2000-2014, spending on adult ADHD medications was $14.6 million in 2014 and is projected to increase to $23.2 million by 2017

- Listing atomoxetine as Limited Use in addition to a general benefit listing for extended release methylphenidate and a limited use listing for brand name only long-acting stimulants with enforced step therapy is expected to result in the greatest reduction (-13%) in overall expenditure for adult ADHD medications by 2017.

List of abbreviations	
ADHD	attention deficit hyperactivity disorder
CEA	cost-effectiveness analysis
CUA	cost-utility analysis
EAP	exceptional access program
EWPS	Endicott Work Productivity Scale
GB	general benefit
LU	limited use
NHS EED	National Health Service Economic Evaluation Database
OPDP	Ontario Public Drug Program

Contents

Executive Summary

Research Questions

RQ1. What is the current evidence for the comparative cost-effectiveness of pharmacological treatments for attention deficit hyperactivity disorder (ADHD)?

RQ2. What is the budget impact of alternative policies for reimbursing pharmacotherapies in the treatment of ADHD?

Systematic Review of Published Economic Evaluations

A total of 93 unique citations relating to the cost-effectiveness of treatments for adults with ADHD were identified from our initial searches and were screened for inclusion in this review. All 93 of the records that were reviewed for inclusion were deemed irrelevant to our research question and were eliminated from our review. Given the lack of evidence regarding the cost-effectiveness of treatments for ADHD among adults, we conducted a *post-hoc* literature review to outline the societal impact of adult ADHD on employment and criminality.

Using a combination of hand-searching and database searching with keywords, we were able to identify some relevant literature regarding the link between adult ADHD and employment/criminality. Findings from these studies were supportive of an association between adult ADHD and increased unemployment and poorer work performance. We also identified a few studies providing evidence that receiving treatment for ADHD helps to improve work performance and reduce criminal behaviour. Again, findings from these studies were generally supportive of the notion that pharmacological treatment of ADHD symptoms is associated with improved work performance and reduced likelihood of criminal behaviour. However, in both instances, the studies we reviewed were generally of poor quality and had several limitations including, small numbers of participants and poor generalizability. There was also little mention of the economic implications of adult ADHD from a broader societal perspective. None of the studies that we reviewed were conducted in the Canadian context, further limiting the applicability of this evidence to our study question.

Based on the findings from both our systematic review and our *post-hoc* literature review, we have determined that little is known about the economic impact of adult ADHD. There is a clear need for more research in this area to address questions of cost-effectiveness and economic burden on the health care system.

For a detailed report of the review of economic literature relative to this drug class, please refer to Appendix A – Systematic Review of Economic Evidence.

Budget Impact Analysis

Among adults (≥18 years) spending on ADHD medications has risen from about $736,000 in 2000 to over $14.5 million in 2014. Similarly, among children expenditure has increased $1.5 million to $10.7 million over the last 15 years. Without changes to current reimbursement for ADHD medications, expenditure is expected to rise to $12.1 million in 2017 for children and $23.2 million for adults.

Listing atomoxetine as limited use in addition to a general benefit listing for extended release methylphenidate and a limited use listing for brand name only long-acting stimulants with enforced step therapy (strategy 3b) would generate the greatest reduction (-13%) in overall expenditure for adult ADHD medications by the end of 2017. Strategy 2b (LU listing for atomoxetine and long-acting stimulants with enforced step therapy) and strategy 3a (GB for extended release methylphenidate and LU listing/step therapy for brand name only long-acting stimulants) would each lead to an 8% decrease in overall adult ADHD medication expenditure. Strategies 1b, 2a and 4 would also result in reductions in overall expenditure for adult ADHD medication from 3-5%.

Appendices

Appendix A – Systematic Review of Economic Evidence

Research Question

What is the current evidence for the comparative cost-effectiveness of pharmacological treatments for attention deficit hyperactivity disorder (ADHD)?

Review of Published Literature

Search Strategy and Search Findings

Search Strategy

A search of the medical literature was conducted in Ovid MEDLINE (indexed, in-process and other non-indexed citations) from 1946 to present (May 01, 2015), as well as EMBASE Classic & EMBASE 1947 to May 01, 2015 in order to capture all literature relevant to our research question. Key words relating to ADHD pharmacotherapies approved for use in Canada (mixed amphetamine salts XR, atomoxetine, bupropion, clonidine, dexmethylphenidate, dextroamphetamine, guanfacine, lisdexamfetamine, methamphetamine, methylphenidate, and modafinil) were coupled with a standardized search strategy for identifying economic analyses adopted by the National Health Service Economic Evaluation Database (NHS EED). The complete search strategy can be found in Appendix A1: Search Strategy.

Additionally, we searched for relevant literature in the Tufts CEA Registry and the NHS EED. Grey literature was identified through the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Care Excellence (NICE) websites. Finally, reference lists of retrieved studies were hand searched for additional relevant literature.

Search Findings

A total of 97 citations relating to the cost-effectiveness of treatments for adults with ADHD were identified from the initial searches, all of which were found through database searching with no additional records identified from grey literature sources. Following the removal of duplicate records, 93 unique citations were retrieved for screening.

One reviewer (KT) reviewed the titles and abstracts of studies identified by the search strategy in order to identify potential articles for critical appraisal, a second reviewer (ML) was available where confirmatory screening was required. We did not identify any articles of potential relevance to our research question from the 93 citations that were screened; therefore, 0 articles were selected for full-text review. Refer to Figure 1 in Appendix A2: Results of Search for more details about the results from our search. A list of excluded studies is included in Appendix A3: List of Excluded Studies.

Given the lack of evidence regarding the cost-effectiveness of treatments for ADHD among

adults, we conducted a *post-hoc* literature review to outline the societal impact of adult ADHD on employment and criminality. To do this, we developed a non-exhaustive search strategy to identify potentially relevant literature regarding the link between ADHD and employment/criminality. We also searched reference lists of relevant articles to identify any additional literature. Findings from this *post-hoc* literature review are reported below.

Findings from post-hoc literature review

Although ADHD is better recognized in childhood, there is increasing evidence that some symptoms remain or present during adulthood and can have an impact on societal factors, such as work performance and retention, and criminality.[1,2] The effectiveness of ADHD treatment on improving societal outcomes is not well understood. The bulk of the studies contributing to the literature base is often methodologically flawed and includes small numbers of adults with ADHD. What follows is a brief review of some of the observational evidence suggesting a link between adult ADHD and employment and criminality. We also review a few studies providing evidence that receiving treatment for ADHD helps to improve work performance and reduce criminal behaviour. By reviewing this evidence, we hope to better understand the potential economic implications of adult ADHD and its treatment from a broader, societal perspective.

There are several studies that have identified an association between adult ADHD and increased unemployment and poorer work performance. A recent study from Germany found that 4.7% (n=78) of 1655 participants met the criteria for adult ADHD based on a self-report screening instrument. Among the 78 participants, authors note a positive and statistically significant association between adult's diagnosed with ADHD and unemployment (odds ratio: 2.1, 95% confidence interval: 1.1-4.0).[3] Similarly, results from the World Health Organization's World Mental Health Survey Initiative found that an average of 3.5% of workers met the DSM-IV criteria for adult ADHD, and that ADHD was significantly associated with 22.1 annual days of lost role performance compared to participants without ADHD.[4] A third survey study conducted in the United States reports an annual rate of 35.0 days lost performance per worker with ADHD.[5] Unlike the previous three studies, Torgersen and colleagues chose a medical chart review in lieu of a survey study design to assess the impairments associated with adult ADHD.[6] Based on the 45 charts of adults diagnosed with ADHD reviewed, only 15.6% (n=7) of participants were employed and 68.8% (n=31) were receiving some social assistance benefit. While these studies do highlight an association between adult ADHD and unemployment and work performance, there are a few limitations of note. First, the use of self-reporting methods for the diagnosis of adult ADHD could lead to an under-estimation of prevalence. Second, the criteria for definitively diagnosing ADHD in adults were developed based on criteria for children and may not be generalizable or less applicable to adults. Finally, at least two of the above mentioned studies make use of multiple imputation methods to estimate ADHD, potentially reducing the precision and generalizability of results. Overall, the evidence linking adult ADHD to increased unemployment and poorer work performance is weak and should be interpreted with caution.

As with unemployment, there have been studies to estimate impact of adult ADHD on criminality. In addition to studying unemployment, Torgersen and colleagues looked at criminality. The authors report that 21 (46.7%) of 45 patients had at least one criminal

sentence, with 11 patients having two or more criminal sentences at the time of assessment.[6] In line with these findings, results from a recent literature review by Küpper and colleagues suggests that adult ADHD can have a negative impact on occupational health.[1]

Impact of treatment on unemployment and criminality

A study from Litchenstein and colleagues used Swedish national registers to identify 26,656 patients born before 1990 (15 years of age and older) with at least one diagnosis of ADHD.[7] In addition to the National Patient register to determine diagnosis, authors used both the Prescribed Drug Register and National Crime Register to examine the association between the use of ADHD medication and criminality. Among men with ADHD (n=16,087), 53.6% had taken an ADHD medication and 36.6% had been convicted of a crime during follow-up. Compared to men, a greater proportion of women with ADHD (n=9569) had taken ADHD medication (62.7%), and fewer had been convicted of a crime (15.4%). For both men and women, results from the analysis suggest that crimes occurred less frequently (32% reduction for men; 41% reduction for women) when patients were receiving medication for their ADHD. Authors also tested for any long-term associations by looking at medication use in 2006 and criminality in 2009, but found no significant associations between receipt of medication and criminality. While the results from this study support the claim that receiving ADHD medication reduces the rate of criminality among adult patients with ADHD, there were some limitations that must be considered. First, there is a risk of bias due to reverse causation (i.e., are patients who are more likely to take treatment, less likely to commit crimes?). Authors attempted to control for this by analyzing data to determine if order of medication status was important and found that the associations remained significant regardless of the order of medication status. The second limitation is the limited follow-up period, which did not allow for extensive analysis of whether associations persist after medication is discontinued. A third limitation is the risk that unmeasured confounders (i.e., confounding by indication) might be influencing the results. Finally, given that this study was conducted using a Swedish population, its applicability to the Canadian context is questionable.

A second Swedish study used an existing cohort of adult males with ADHD undergoing treatment for severe substance abuse disorder to examine the association between receiving ADHD medication and long-term functional outcomes, including employment status.[8] Participants in this study had received compulsory treatment for severe substance abuse between 2004 and 2008 and were followed-up between February 2008 and March 2009 (follow-up ranged from 6 to 45 months). Of the 413 patients that took part in this treatment program, 60 were diagnosed with ADHD according to the DSM-IV-TR and were eligible for this follow-up study. Their ages ranged from 20 to 46 years upon admission to the program. Half of the participants (n=30) were treated with ADHD medication and the other half were not. At the time of follow-up, only 24 patients (15 in the treated group and 9 in the untreated group) were considered for employment status, as the remaining participants were either institutionalized or on sick-leave. Among those considered in the treated group 6/15 were employed, while 4/9 were employed in the untreated group, and this difference was considered statistically significant (p=0.028). Overall, this study does provide limited evidence of a positive association between receiving ADHD medication and employment; however, there are several limitations. Given the pragmatic nature of this study design, it is possible that confounding by indication may have influenced the results, though researchers attempted

to control for as many extraneous factors as possible in their analysis. There are also limitations with respect to applicability and generalizability of the study results. In addition to ADHD, patients enrolled in this study had comorbid substance abuse problems and/or anti-social behaviour, both of which are not seen amongst all adult ADHD patients, but do affect a substantial portion. Additional considerations include: differing duration of follow-up between treated and untreated groups, relatively high amounts of missing data in the untreated group, and limited data regarding the treatment regimen or adherence to medication. For these reasons, caution should be taken in interpreting these results with respect to the Canadian context.

A third study conducted in the United States assessed the functional impairment (including work performance) of adults with ADHD after six months of double-blind treatment with either atomoxetine or placebo.[9] The study population consisted of 410 employed, adult ADHD patients aged 18 to 50 years old from 22 outpatient treatment centres across the United States. Of the 410 participants, 271 received atomoxetine (non-stimulant medication) while the remaining participants received placebo (n=139). The primary functional outcome measure for this study was the Endicott Work Productivity Scale (EWPS), a self-report questionnaire that assesses attendance, lost hours and presenteeism at work. After one month of treatment, the treated group exhibited greater improvement in work performance according to their EWPS score than patients in the untreated group ($p<0.01$). After six months of treatment there were no significant differences between groups. The mean reduction in EWPS score for the treated group was 16.2 (SD=18.4) points and 15.6 (SD=16.0) points for the untreated group. These results suggest that, if any, the association between receiving atomoxetine and improved work performance is marginal. Despite the randomized nature of this study there are some limitations to note. First, there was an extremely high attrition rate; only 104/271 (38.4%) and 68/139 (48.9%) of participants in the treated and untreated groups, respectively, completed the study. Generalizability of the study results is noted as patients with other psychiatric illnesses were excluded. Patients with ADHD are vulnerable to other comorbidities such as substance abuse, anxiety and affective disorders; thus, without including these patients in the present study, results may not be applicable to the adult ADHD population as a whole. A third limitation is that several of the authors have affiliations with industry (Eli Lilly, manufacturer of atomoxetine). For these reasons, caution should be taken in the interpretation of these results and their applicability to the Canadian context.

In conclusion, some literature supporting the claim that adult ADHD has a negative impact on some societal factors, such as work performance and criminality, was identified. Additionally, we found some evidence suggesting that receiving ADHD medication improves work performance and reduced the likelihood of criminal behaviour. As mentioned above, there are several limitations to this evidence base including, small numbers of participants and poor generalizability. There was also little mention of the economic implications of adult ADHD from a broader societal perspective. Based on these findings, we conclude that more research is needed in this area, particularly in the Canadian context, so that we can better understand the economic impact of ADHD and ADHD medications.

Overall Conclusions

Based on the findings from both our systematic review and our *post-hoc* literature review, we have determined that little is known about the economic impact of adult ADHD. There is a

clear need for more research in this area to address questions of cost-effectiveness and economic burden on the health care system.

Appendix A1: Search Strategy

The following is the search strategy used in Medline (Ovid) and Embase.

Embase Classic+Embase (1947 to May 1, 2015), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (1946 to present (May 1, 2015)

1 Attention Deficit Disorder with Hyperactivity/dt
2 (Adderall or amphetamine aspartate or amfetamine aspartate or Obetrol or UNII-H527KAP6L5).tw,kw.
3 ((amphetamine or amfetamine) adj2 (mixed or mixture or salt or salts)).tw,kw.
4 (atomoxetin* or LY 139603 or HSDB 7352 or strattera or tomoxetine or UNII-ASW034S0B8 or UNII-57WVB6I2W0).tw,kw.
5 Bupropion/
6 (bupropion or amfebutamon* or aplenzin or BRN 2101062 or buproprion or budeprion or buproban or elontril or forfivo or UNII-01ZG3TPX31 or wellbutrin).tw,kw.
7 Clonidine/
8 (Apo-Clonidine or clonidine or capresin or caprysin or catapres* or CLON-IR or CLON-XR or Novo-Clonidine or Nu-Clonidine or kapvay or katapres*).tw,kw.
9 Dexmethylphenidate/
10 (dexmethylphenidate or D-MPH or d-threo-methylphenidate or dex methylphenidate or dexmethylphenidate or Focalin or methyl d-phenidate or ritadex or UNII-M32RH9MFGP).tw,kw.
11 Dextroamphetamine/
12 (Dextroamphetamine or Dextroamfetamine or Curban or d-Amphetamine or d-Amfetamine or Dexamphetamine or Dexamfetamine or Dexedrine or dextro-Amphetamine or dextro-Amfetamine or DextroStat or Oxydess).tw,kw.
13 Guanfacine/
14 (Guanfacine or BS-100-141 or Estulic or Lon798 or Tenex or Intuniv or EINECS 249-442-8 or UNII-30OMY4G3MK).tw,kw.
15 (lisdexamfetamine dimesylate or lis-dexamfetamine dimesylate or lisdexamfetamine or elvanse or NRP-104 or NRP104 or SPD-489 or SPD489 or Tyvense or Venvanse or Vyvanse).tw,kw.
16 Methamphetamine/
17 (Methamphetamin* or deoxyephedrine or desoxyephedrine or Desoxyn* or Madrine or metamfetamin* or methylamphetamin* or methyl amphetamine* or methylamfetamin* or methyl amfetamin* or N-methylamphetamin* or N-methylamfetamin*).tw,kw.
18 Methylphenidate/
19 (Methylphenidate* or Attenta or Biphentin* or Calocain* or CCRIS 6258 or Centedrin* or Concerta* or Daytrana* or Dexmethylphenidate* or d-methylphenidate* or d-MPH or EINECS 206-065-3 or EINECS 204-028-6 or Equasym* or EqXL or HSDB 3126 or Medikinet or Meridil* or Metadate* or Methyl phenidate* or Methylin* or MPH or NCI-C56280 or NSC-169868 or OROS-MPH or Quillivant* or Phenidylate* or Rilaline* or Ritalin* or Ritaphen or Rubifen or Tranquilyn or Tsentedrin* or UNII-4B3SC438HI).tw,kw.
20 (Apo-methylphenidate* or Novo-methylphenidate* or PHL-methylphenidate* or PMS-methylphenidate* or Ratio-methylphenidate* or Teva-methylphenidate).tw,kw.

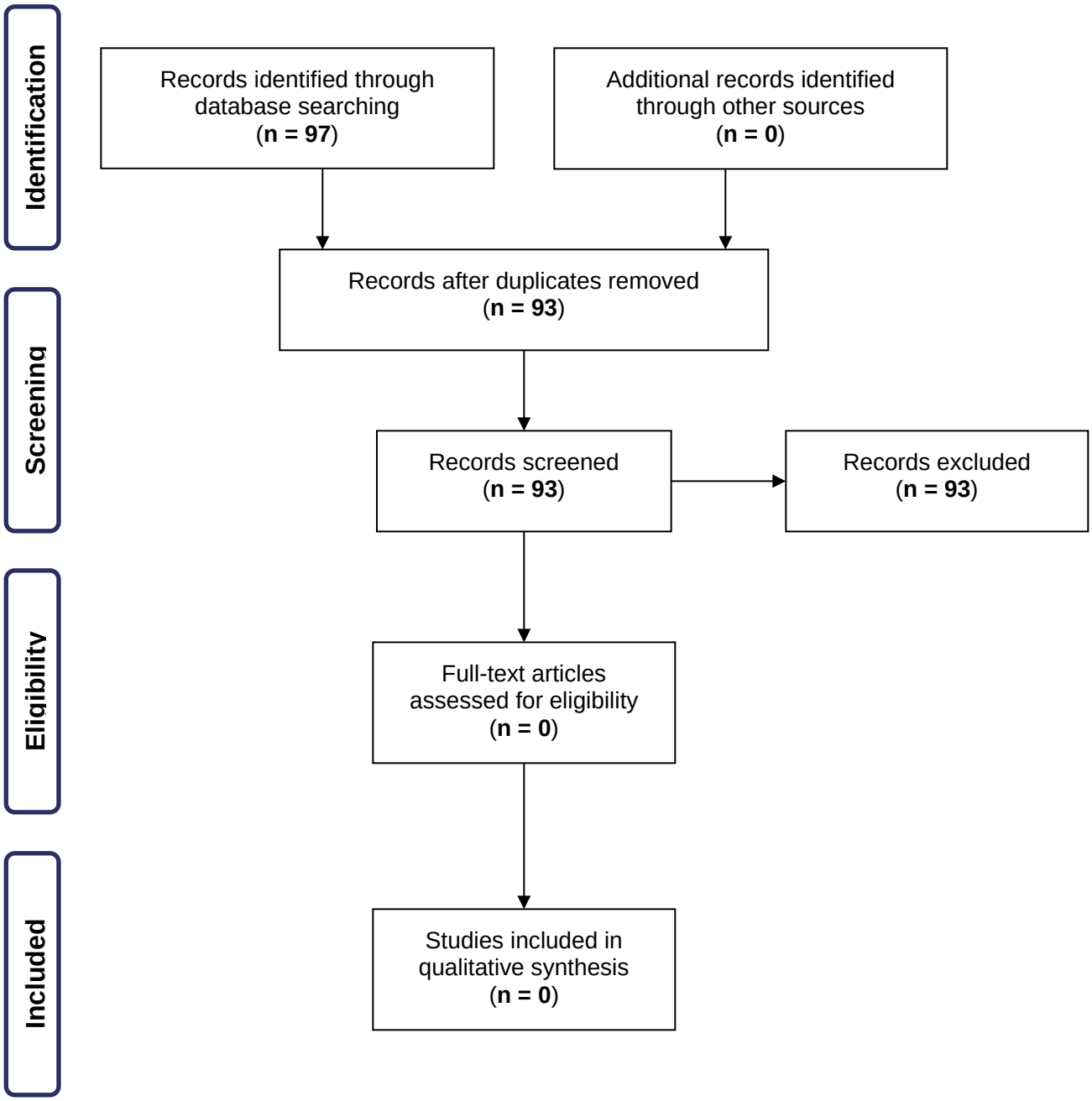
21 (Apo-MPH or Novo-MPH or PHL-MPH or PMS-MPH or Ratio-MPH or Teva-MPH).tw,kw.
22 (modafinil or alertec or benzhydrylsulfinylacetamide or CRL 40476 or modavigil or modiodal or provigil or sparlon or vigil).tw,kw.
23 or/1-22
24 Attention Deficit Disorder with Hyperactivity/
25 attention deficit*.tw,kw.
26 ADHD.tw,kw.
27 hyperkinetic syndrome*.tw,kw.
28 or/24-27
29 23 and 28
30 exp Adult/
31 (adult or adults or adulthood or middle age$1).tw,kw.
32 (older adj2 (age$1 or female$1 or male$1 or patient$1 or person$1 or people$1 or population$1)).tw,kw.
33 (senior$1 or elderly or geriatric* or gerontolog*).tw,kw.
34 or/30-33
35 29 and 34
36 exp Animals/ not (exp Animals/ and Humans/)
37 35 not 36
38 37 use prmz
39 Economics/
40 exp "Costs and Cost Analysis"/
41 Value of Life/
42 exp Economics, Hospital/
43 Economics, Medical/
44 Economics, Nursing/
45 Economics, Pharmaceutical/
46 or/39-45
47 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
48 (expenditure$ not energy).ti,ab.
49 (value adj1 money).ti,ab.
50 budget$.ti,ab.
51 or/47-50
52 46 or 51
53 38 and 52
54 attention deficit disorder/dt [Drug Therapy]
55 amphetamine plus dexamphetamine/
56 (Adderall or amphetamine aspartate or amfetamine aspartate or Obetrol or UNII-H527KAP6L5).tw,kw.
57 ((amphetamine or amfetamine) adj2 (mixed or mixture or salt or salts)).tw,kw.
58 atomoxetine/
59 (atomoxetin* or LY 139603 or HSDB 7352 or strattera or tomoxetine or UNII-ASW034S0B8 or UNII-57WVB6I2W0).tw,kw.
60 amfebutamone/

61 (bupropion or amfebutamon* or aplenzin or BRN 2101062 or buproprion or budeprion or buproban or elontril or forfivo or UNII-01ZG3TPX31 or wellbutrin).tw,kw.
62 clonidine/
63 (Apo-Clonidine or clonidine or capresin or caprysin or catapres* or CLON-IR or CLON-XR or Novo-Clonidine or Nu-Clonidine or kapvay or katapres*).tw,kw.
64 dexmethylphenidate/
65 (dexmethylphenidate or D-MPH or d-threo-methylphenidate or dex methylphenidate or dexmethylphenidate or Focalin or methyl d-phenidate or ritadex or UNII-M32RH9MFGP).tw,kw.
66 dexamphetamine/
67 (Dextroamphetamine or Dextroamfetamine or Curban or d-Amphetamine or d-Amfetamine or Dexamphetamine or Dexamfetamine or Dexedrine or dextro-Amphetamine or dextro-Amfetamine or DextroStat or Oxydess).tw,kw.
68 guanfacine/
69 (Guanfacine or BS-100-141 or Estulic or Lon798 or Tenex or Intuniv or EINECS 249-442-8 or UNII-30OMY4G3MK).tw,kw.
70 lisdexamfetamine/
71 (lisdexamfetamine dimesylate or lis-dexamfetamine dimesylate or lisdexamfetamine or elvanse or NRP-104 or NRP104 or SPD-489 or SPD489 or Tyvense or Venvanse or Vyvanse).tw,kw.
72 methamphetamine/
73 (Methamphetamin* or deoxyephedrine or desoxyephedrine or Desoxyn* or Madrine or metamfetamin* or methylamphetamin* or methyl amphetamine* or methylamfetamin* or methyl amfetamin* or N-methylamphetamin* or N-methylamfetamin*).tw,kw.
74 methylphenidate/
75 (Methylphenidate* or Attenta or Biphentin* or Calocain* or CCRIS 6258 or Centedrin* or Concerta* or Daytrana* or Dexmethylphenidate* or d-methylphenidate* or d-MPH or EINECS 206-065-3 or EINECS 204-028-6 or Equasym* or EqXL or HSDB 3126 or Medikinet or Meridil* or Metadate* or Methyl phenidate* or Methylin* or MPH or NCI-C56280 or NSC-169868 or OROS-MPH or Quillivant* or Phenidylate* or Rilaline* or Ritalin* or Ritaphen or Rubifen or Tranquilyn or Tsentedrin* or UNII-4B3SC438HI).tw,kw.
76 (Apo-methylphenidate* or Novo-methylphenidate* or PHL-methylphenidate* or PMS-methylphenidate* or Ratio-methylphenidate* or Teva-methylphenidate).tw,kw.
77 (Apo-MPH or Novo-MPH or PHL-MPH or PMS-MPH or Ratio-MPH or Teva-MPH).tw,kw.
78 modafinil/
79 (modafinil or alertec or benzhydrylsulfinylacetamide or CRL 40476 or modavigil or modiodal or provigil or sparlon or vigil).tw,kw.
80 or/54-79
81 attention deficit disorder/
82 attention deficit*.tw,kw.
83 ADHD.tw,kw.
84 hyperkinetic syndrome*.tw,kw.
85 or/81-84
86 80 and 85
87 adult/

88 (adult or adults or adulthood or middle age$1).tw,kw.
89 (older adj2 (age$1 or female$1 or male$1 or patient$1 or person$1 or people$1 or population$1)).tw,kw.
90 (senior$1 or elderly or geriatric* or gerontolog*).tw,kw.
91 or/87-90
92 86 and 91
93 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
94 exp humans/ or exp human experimentation/ or exp human experiment/
95 93 not 94
96 92 not 95
97 96 use emez
98 health economics/
99 exp economic evaluation/
100 exp "health care cost"/
101 exp pharmacoeconomics/
102 or/98-101
103 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
104 (expenditure$ not energy).ti,ab.
105 (value adj2 money).ti,ab.
106 budget$.ti,ab.
107 or/103-106
108 102 and 107
109 97 and 108
110 53 or 109
111 remove duplicates from 110

Appendix A2: Results of Search

The following illustrates the selected studies for the review.



Appendix A3: List of Excluded Studies

The following table lists the studies excluded from the review in addition to the rationale for their exclusion.

Study Reference	Reason for exclusion
Lecomte T, Masse M. Methamphetamine - just another stimulant or a more complex problem? Sante Ment Que. 2014;39(2):133-48.	Not an economic evaluation of adult ADHD medication
Gajria K, Lu M, Sikirica V, Greven P, Zhong Y, Qin P, et al. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder - a systematic literature review. Neuropsychiatr Dis Treat. 2014; 10: 1543–1569.	Not an economic evaluation of adult ADHD medication
Benkert D, Krause KH, Wasem J, Aidelsburger P. Effectiveness of pharmaceutical therapy of ADHD (Attention-Deficit/Hyperactivity Disorder) in adults - health technology assessment. GMS Health Technol Assess. 2010;6:Doc13, 2010.	Not an economic evaluation of adult ADHD medication
Matza LS, Paramore C, Prasad M. A review of the economic burden of ADHD. Cost Eff Resour Alloc. 2005 Jun 9;3:5	Not an economic evaluation of adult ADHD medication
Hondebrink L, Rietjens SJ, Hunault CC, Pereira RR, Kelleci N, Yasar G, et al. Methylphenidate intoxications in children and adults: exposure circumstances and evidence-based dose threshold for pre-hospital triage. Clin Toxicol (Phila). 2015 Mar;53(3):168-77.	Not an economic evaluation of adult ADHD medication
Soutullo C, varez-Gomez MJ. Bases for the selection of pharmacological treatment in attention deficit hyperactivity disorder. Rev Neurol. 2013 Feb 22;56 Suppl 1:S119-29	Not an economic evaluation of adult ADHD medication
Kupper T, Haavik J, Drexler H, Ramos-Quiroga JA, Wermelskirchen D, Prutz C, et al. The negative impact of attention-deficit/hyperactivity disorder on occupational health in adults and adolescents. Int Arch Occup Environ Health. 2012 Nov;85(8):837-47.	Not an economic evaluation of adult ADHD medication
Barry CL, Martin A, Busch SH. ADHD medication use following FDA risk warnings. J Ment Health Policy Econ. 2012 Sep;15(3):119-25.	Not an economic evaluation of adult ADHD medication
Steer C, Froelich J, Soutullo CA, Johnson M, Shaw M. Lisdexamfetamine dimesylate: a new therapeutic option for attention-deficit hyperactivity disorder. CNS drugs. 2012 Aug 1;26(8):691-705.	Not an economic evaluation of adult ADHD medication
Caisley H, Muller U. Adherence to medication in adults with attention deficit hyperactivity disorder and pro re nata dosing of psychostimulants: a systematic review. Eur Psychiatry. 2012 Jul;27(5):343-9.	Not an economic evaluation of adult ADHD medication
Carlat D. Evidence-based somatic treatment of depression in	Not an economic

Study Reference	Reason for exclusion
adults. Psychiatr Clin North Am. 2012 Mar;35(1):131-42.	evaluation of adult ADHD medication
Hodgkins P, Shaw M, McCarthy S, Sallee FR. The pharmacology and clinical outcomes of amphetamines to treat ADHD: does composition matter? Cns drugs. 2012 Mar 1;26(3):245-68.	Not an economic evaluation of adult ADHD medication
Rucklidge JJ, Harrison R, Johnstone J. Can micronutrients improve neurocognitive functioning in adults with ADHD and severe mood dysregulation? A pilot study. J Altern Complement Med. 2011 Dec;17(12):1125-31.	Not an economic evaluation of adult ADHD medication
Hodgkins P, Sasane R, Christensen L, Harley C, Liu F. Treatment outcomes with methylphenidate formulations among patients with ADHD: retrospective claims analysis of a managed care population. Curr Med Res Opin. 2011;27 Suppl 2:53-62	Not an economic evaluation of adult ADHD medication
Waschbusch DA, Cunningham CE, Pelham WE, Rimas HL, Greiner AR, Gnagy EM, et al. A discrete choice conjoint experiment to evaluate parent preferences for treatment of young, medication naive children with ADHD. J Clin Child Adolesc Psychol. 2011;40(4):546-61.	Not an economic evaluation of adult ADHD medication
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Study Reference	Reason for exclusion
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Appendix B – Budget Impact Analysis

Research Question

What is the budget impact of alternative policies for reimbursing pharmacotherapies in the treatment of ADHD?

Methods Reimbursement Based Economic Assessment

An applied, policy-oriented economic model focusing on financial impact was developed to facilitate consideration of alternative reimbursement strategies for pharmacotherapies available to treat adult ADHD. Utilization data for both stimulant (long- and short-acting) and non-stimulant medications were provided by the Ontario Public Drug Program (OPDP) from January 1, 2000 to December 31, 2014. More specifically, utilization data were provided for mixed salt amphetamine, dextroamphetamine, methylphenidate (long- and short-acting formulation), lisdexamfetamine, demethyphenidate HCL, dextroamphetamine, and atomoxetine.

The number of users of cognitive enhancers per quarter for the next three years, 2015-2017, were predicted using time series analysis. Four models were used to forecast the number of users of ADHD medications for each drug class.

1. A linear model whereby the number of users was assumed to increase by the same amount each year and also increase with each new ADHD medication covered under OPDP.
2. An exponential model where an exponential relationship between number of users and time and number of ADHD medications covered under OPDP was assumed.
3. A power model that allowed a non-linear relationship between time and number of users, and included the number of ADHD medications covered by OPDP.
4. A constant growth model that assumed a constant percentage increase in the number

of users, with additional coverage of new ADHD medications also leading to a percentage increase.

All of the models considered the following variables: quarter (i.e., January 1-March 31, 2000 was quarter 1, April 1-June 30, 2000 was quarter 3, etc.), and the number of available ADHD medications covered by OPDP. We also had to adjust our predictive models where necessary for short-acting stimulants based on the addition of lisdexamfetamine in 2011 to OPDP coverage, as this substantially impacted the use of short-acting stimulants. Each model was examined for seasonal effects based on absolute and Winters' seasonal effects calculations. For each model, the most suitable combination of independent variables and inclusion of seasonal effects were selected based on the Bayesian information criterion (BIC). We developed prediction models for each age category provided to us by OPDP (<18 years, 18-25 years, 26-35 years, 36-64 years, 65+ years, and all ages). Based on our preliminary results from these models, we decided to collapse all adults into a single group (≥18 years) for comparison with the under 18 group. The final models were chosen based on best fit parameters calculated as part of our model building (see Appendix B1: Model Details for more details). For long-acting stimulants, the power model with no seasonal effects was chosen for the under 18 age group, and the constant growth model with no seasonal effects was chosen for the 18 and over age group. For short acting stimulants, a power model with seasonal effects was chosen for the under 18 age group and an exponential model with seasonal effects was chosen for the 18 and over age group. Finally, for non-stimulant, a power model with no seasonal effects was chosen for the under 18 age group and a linear model with seasonal effects was chosen for the over 18 age group.

Once forecasts for the number of users were obtained for 2015-2017, number of users was then converted to expenditure by multiplying the total number of users per year by average units per user per quarter in the last year and average cost per unit in the last year (Status Quo). Expenditures under alternative reimbursement strategies were estimated. The alternative strategies considered are outlined below Table 1.

Table 1. Alternative reimbursement strategies for ADHD medications covered by OPDP.

	Strategy	Assumptions
1a.	Status quo: no changes. General benefit (GB): short- and long-acting stimulants Exceptional access program (EAP): atomoxetine.	Use current utilization trends to forecast costs for 2015-2017.
1b.	Same as 1a EXCEPT: limited use (LU) – atomoxetine.	Assume 10% of ADHD patients currently on short- or long-acting stimulants will move to atomoxetine. Also assume the price for atomoxetine is reduced to 25% of the brand price.

	Strategy	Assumptions
2a.	GB – short-acting stimulants GB – long-acting stimulants (<18 years) LU/step therapy – long-acting stimulants (18+ years) EAP – atomoxetine	Assume 10% of those currently on long-acting stimulants will move to short-acting stimulants.
2b.	Same as 2a EXCEPT LU – atomoxetine	Assume 10% of short-acting and long-acting stimulant users move to atomoxetine. Also assume the price for atomoxetine is reduced to 25% of the brand price. Assume 10% of those remaining on long-acting stimulants will move to short-acting stimulants.
3a.	Same as 2a EXCEPT GB – extended release methylphenidate (18+ years) LU/step therapy – brand name only long-acting (failed/intolerant generic product)	Assume 10% of users currently on long-acting stimulants move to methylphenidate and assume 10% of remaining move to short-acting stimulants.
3b.	Same as 3a EXCEPT LU – atomoxetine	Assume 10% of users on short- and long-acting stimulants move to atomoxetine. Also assume the price for atomoxetine is reduced to 25% of the brand price.Of remaining long-acting stimulant users, 10% move to methylphenidate. Finally, 10% of the remaining users move to short-acting stimulants.
4	Same as 2a EXCEPT GB – long-acting stimulants (<25 years) LU/step therapy – long-acting stimulants (25+ years)	Assume 10% of long-acting stimulant users, 25 years and older, move to short-acting stimulants.

Findings

Current Usage and Expenditure

For adult ADHD patients (≥18 years), the total average number of users, units, and prescriptions per quarter for ADHD medications in 2014 was 17,482, 2,677,072, and 93,472, respectively. For ADHD patients under age 18, the total average number of users, units, and prescriptions per quarter for ADHD medications in 2014 was 13,529, 1,294,217, and 36,533, respectively. Among children and adults alike, long-acting stimulants account for the majority of ADHD medication usage (54-89%) with extended release methylphenidate being the most popular of the long-acting stimulants. See Table 2 for further information about current usage.

Table 2. Average number of ADHD medication users, units, and prescriptions, per quarter in 2014.

	Users		Units		Prescriptions	
	<18 yrs N (%)	≥18 yrs N (%)	<18 yrs N (%)	≥18 yrs N (%)	<18 yrs N (%)	≥18 yrs N (%)
Total	13529 (100%)	17482 (100%)	1294217 (100%)	2677072 (100%)	36533 (100%)	93472 (100%)
Long-acting stimulants	12007 (89%)	12560 (72%)	1081139 (84%)	1504060 (56%)	32802 (90%)	70447 (75%)
amphetamine mixed salts	1566 (12%)	2066 (12%)	140840 (11%)	243195 (9%)	4392 (12%)	8547 (9%)
dextroamphetamine	99 (1%)	644 (4%)	10745 (1%)	114261 (5%)	231 (1%)	2230 (2%)
methylphenidate	7843 (58%)	7940 (43%)	726960 (56%)	931701 (35%)	21608 (59%)	46598 (50%)
lisdexamfetamine	2499 (18%)	2360 (14%)	202595 (16%)	214904 (8%)	6571 (18%)	13072 (14%)
Short-acting stimulants	1294 (10%)	4778 (27%)	187440 (14%)	1155358 (43%)	2984 (8%)	22062 (24%)
dextroamphetamine	260 (2%)	847 (5%)	33820 (3%)	270598 (10%)	574 (2%)	2923 (3%)
methylphenidate	1034 (8%)	3931 (22%)	169598 (13%)	884760 (33%)	2410 (7%)	19139 (20%)
Non-stimulants	228 (2%)	144 (1%)	25638 (2%)	17654 (1%)	748 (2%)	963 (1%)
atomoxetine	228 (2%)	144 (1%)	25638 (2%)	17654 (1%)	748 (2%)	963 (1%)

OPDP expenditure for ADHD medication among both children and adults has increased significantly since 2000. Among adults spending has risen from $736,000 in 2000 to over $14.5 million in 2014 (Table 3). A similar trend is seen among children with expenditure increasing from $1.5 million to over $10.6 million over the last 15 years (Table 4). In 2014, long-acting stimulants accounted for, by far, the majority of OPDP expenditure for ADHD medications among both children and adults.

Table 3. OPDP expenditure on ADHD medications among those age 18 years and over from January 1, 2000-December 31, 2014.

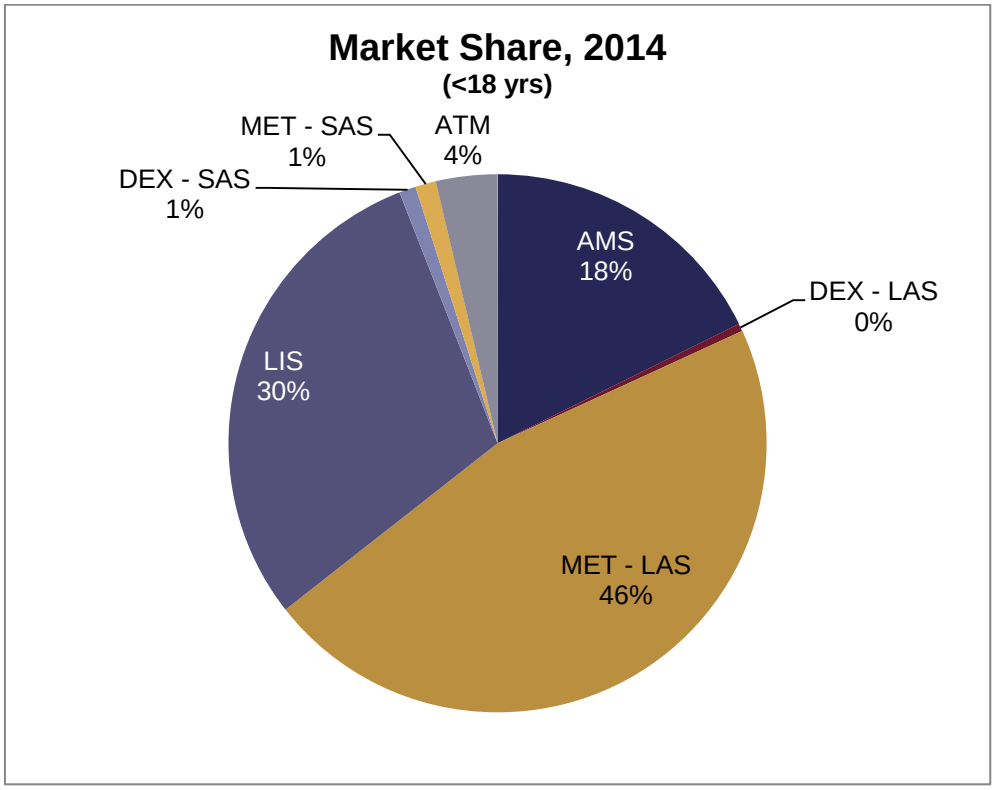
Year	Long-acting stimulants	Short-acting stimulants	Non-stimulants	Total
2000	$251,664.91	$485,000.25	$0.00	$736,665.16
2001	$265,785.70	$540,440.55	$0.00	$806,226.25
2002	$273,512.17	$583,893.08	$0.00	$857,405.25
2003	$352,084.75	$673,596.04	$0.00	$1,025,680.79
2004	$480,280.52	$823,034.09	$0.00	$1,303,314.61
2005	$621,685.43	$1,017,884.18	$0.00	$1,639,569.61
2006	$686,631.04	$1,183,839.48	$14,640.96	$1,885,111.48
2007	$662,999.02	$1,280,649.97	$64,427.72	$2,008,076.71
2008	$830,255.28	$1,470,596.52	$106,860.95	$2,407,712.75
2009	$2,622,411.52	$1,532,888.01	$134,592.93	$4,289,892.46
2010	$4,171,415.97	$1,642,550.97	$161,586.32	$5,975,553.26
2011	$5,562,651.86	$1,926,705.06	$183,333.62	$7,672,690.54
2012	$7,409,453.38	$1,916,294.98	$204,280.54	$9,530,028.90
2013	$9,625,828.88	$2,017,487.10	$259,466.79	$11,902,782.77
2014	$12,489,135.63	$1,822,203.22	$275,239.29	$14,586,578.14

Table 4. OPDP expenditure on ADHD medications among those under age 18 from January 1, 2000-December 31, 2014.

Year	Long-acting stimulants	Short-acting stimulants	Non-stimulants	Total
2000	$547,988.30	$992,883.64	$0.00	$1,540,871.94
2001	$521,401.85	$987,233.78	$0.00	$1,508,635.63
2002	$521,445.55	$1,021,740.06	$0.00	$1,543,185.61
2003	$556,403.41	$1,056,061.73	$0.00	$1,612,465.14
2004	$612,211.03	$1,085,440.87	$0.00	$1,697,651.90
2005	$742,720.82	$1,163,435.09	$1,874.51	$1,908,030.42
2006	$944,685.21	$1,157,764.75	$143,525.54	$2,245,975.50
2007	$1,012,157.36	$1,074,578.29	$283,048.60	$2,369,784.25
2008	$1,116,669.51	$1,029,633.75	$392,182.19	$2,538,485.45
2009	$4,698,775.20	$762,110.34	$387,497.86	$5,848,383.40
2010	$6,442,915.29	$482,432.61	$321,070.10	$7,246,418.00
2011	$7,183,190.48	$378,286.29	$332,630.86	$7,894,107.63
2012	$8,637,522.12	$312,697.85	$340,125.18	$9,290,345.15
2013	$9,448,107.68	$282,802.99	$374,306.30	$10,105,216.97
2014	$10,055,429.15	$239,797.02	$392,965.86	$10,688,192.03

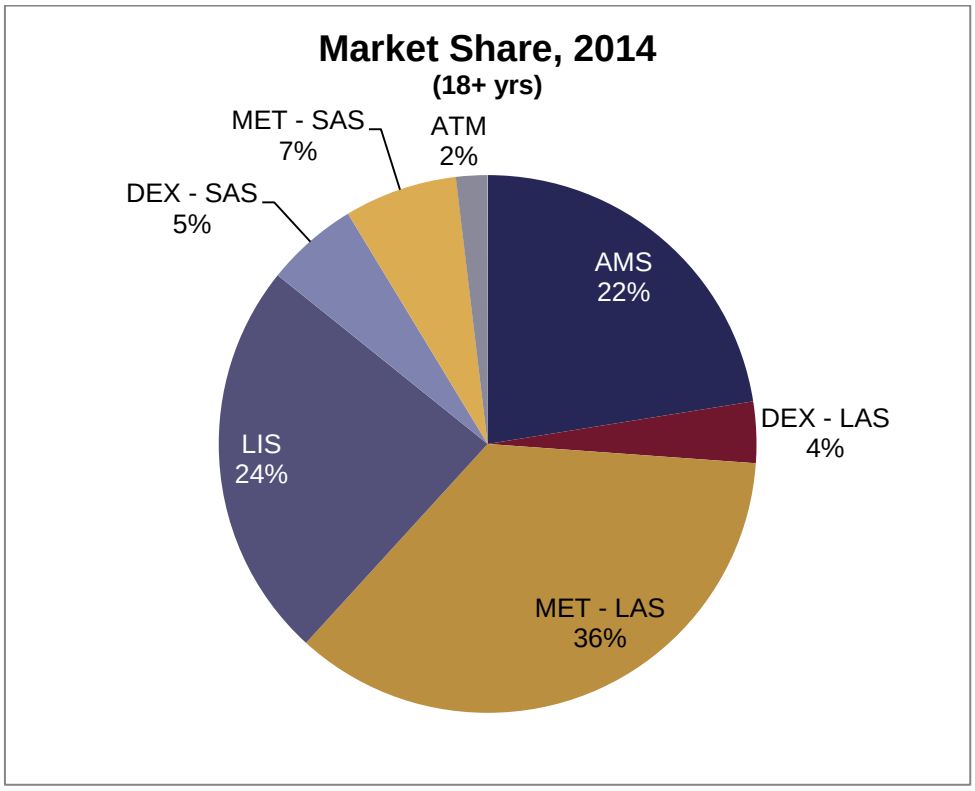
Based on expenditure in 2014, long-acting methylphenidate held the largest market share for patients under age 18 (Figure 1) and patients aged 18 years and older (Figure 2) with 46% and 34%, respectively. Long-acting dextroamphetamine had the smallest market share (<1%) for patients under 18 years old, while atomoxetine had the smallest share (2%) for patients age 18 and older.

Figure 1. Market share of ADHD medications for patients under age 18.



ATM=atomoxetine; AMS=amphetamine mixed salts; DEX-LAS=dextroamphetamine (long-acting); DEX-SAS=dextroamphetamine (short-acting); LIS=lisdexamphetamine; MET-LAS=methylphenidate (long-acting); MET-SAS=methylphenidate (short-acting)

Figure 2. Market share of ADHD medications for patients age 18 and older.

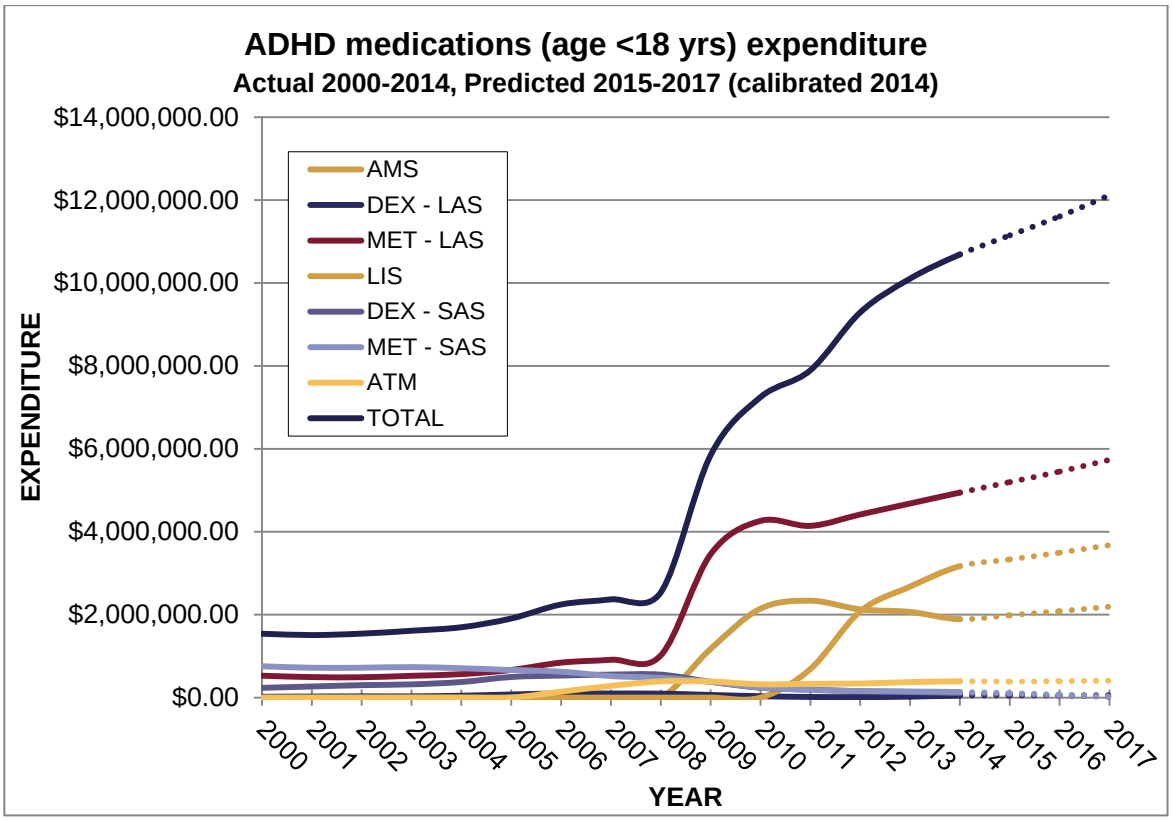


ATM=atomoxetine; AMS=amphetamine mixed salts; DEX-LAS=dextroamphetamine (long-acting); DEX-SAS=dextroamphetamine (short-acting); LIS=lisdexamphetamine; MET-LAS=methylphenidate (long-acting); MET-SAS=methylphenidate (short-acting)

Forecasting expenditure

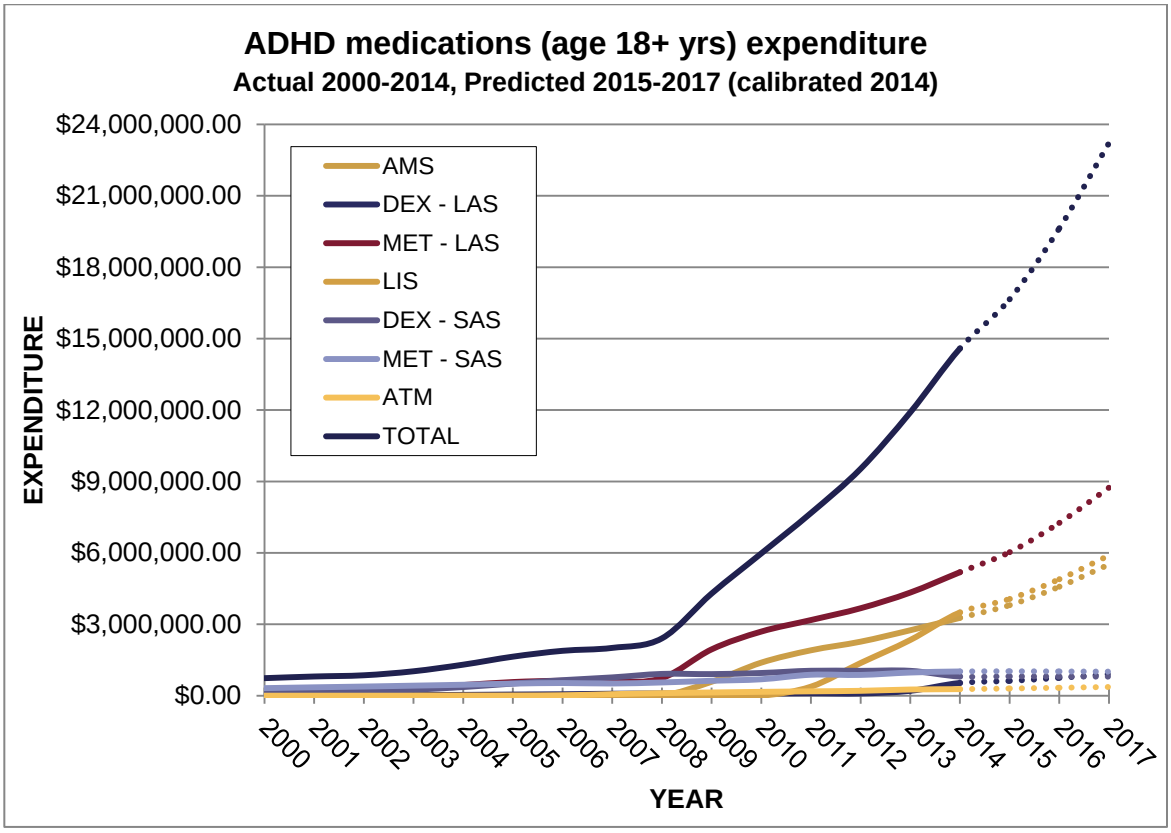
For both children and adults, overall expenditure for ADHD medications is expected to continue to grow over the next three years (Figure 3, Figure 4), with long-acting methylphenidate accounting for the greatest growth. No major increases in expenditure are expected in either age group for short-acting stimulants or non-stimulants over the next three years (Figure 3, Figure 4).

Figure 3. Forecasted ADHD medication expenditure for patients under age 18 (calibrated to actual data from 2014).



ATM=atomoxetine; AMS=amphetamine mixed salts; DEX-LAS=dextroamphetamine (long-acting); DEX-SAS=dextroamphetamine (short-acting); LIS=lisdexamphetamine; MET-LAS=methylphenidate (long-acting); MET-SAS=methylphenidate (short-acting)

Figure 4. Forecasted ADHD medication expenditure for patients age 18 and older (calibrated to actual data from 2014).



ATM=atomoxetine; AMS=amphetamine mixed salts; DEX-LAS=dextroamphetamine (long-acting); DEX-SAS=dextroamphetamine (short-acting); LIS=lisdexamphetamine; MET-LAS=methylphenidate (long-acting); MET-SAS=methylphenidate (short-acting)

Without any changes to current reimbursement for ADHD medications, expenditure is expected to rise to $12.1 million in 2017 for children (<18 years old) and $23.2 million for adults (≥18 years old) (Table 5, Table 6).

Table 5. Forecasted expenditure for ADHD medication for patients under age 18 years.

YEAR	ADHD MEDICATION EXPENDITURE (<18 yrs)							
ACTUAL	**AMS**	**DEX - LAS**	**MET - LAS**	**LIS**	**DEX - SAS**	**MET - SAS**	**ATM**	**TOTAL**
2000	$0.00	$20,045.50	$527,942.80	$0.00	$235,815.50	$757,068.14	$0.00	$1,540,871.94
2001	$0.00	$26,417.16	$494,984.69	$0.00	$267,778.78	$719,455.00	$0.00	$1,508,635.63
2002	$0.00	$29,935.09	$491,510.46	$0.00	$300,917.10	$720,822.96	$0.00	$1,543,185.61
2003	$0.00	$30,285.11	$526,118.30	$0.00	$319,677.58	$736,384.15	$0.00	$1,612,465.14
2004	$0.00	$45,904.67	$566,306.36	$0.00	$376,587.41	$708,853.46	$0.00	$1,697,651.90
2005	$0.00	$75,572.42	$667,148.40	$0.00	$497,676.40	$665,758.69	$1,874.51	$1,908,030.42
2006	$0.00	$100,241.45	$844,443.76	$0.00	$532,373.01	$625,391.74	$143,525.54	$2,245,975.50
2007	$0.00	$99,029.94	$913,127.42	$0.00	$554,944.33	$519,633.96	$283,048.60	$2,369,784.25
2008	$1,597.92	$96,609.82	$1,018,461.77	$0.00	$553,896.29	$475,737.46	$392,182.19	$2,538,485.45
2009	$1,176,417.26	$64,023.07	$3,458,334.87	$0.00	$381,104.45	$381,005.89	$387,497.86	$5,848,383.40
2010	$2,145,999.60	$34,267.92	$4,262,647.77	$0.00	$238,109.77	$244,322.84	$321,070.10	$7,246,418.00
2011	$2,336,635.76	$15,876.11	$4,142,087.76	$688,590.85	$192,654.51	$185,631.78	$332,630.86	$7,894,107.63
2012	$2,127,851.48	$13,104.21	$4,416,871.39	$2,079,695.04	$153,941.93	$158,755.92	$340,125.18	$9,290,345.15
2013	$2,067,085.44	$23,189.64	$4,681,581.30	$2,676,251.30	$135,955.28	$146,847.71	$374,306.30	$10,105,216.97
2014	$1,890,536.03	$49,456.05	$4,945,022.39	$3,170,414.68	$104,808.47	$134,988.55	$392,965.86	$10,688,192.03
PREDICTED								
2015	$1,987,131.18	$51,982.96	$5,197,683.62	$3,332,404.01	$84,704.13	$109,095.07	$385,515.13	$11,148,516.10
2016	$2,084,358.72	$54,526.41	$5,451,999.01	$3,495,453.88	$53,035.97	$68,307.92	$396,984.05	$11,604,665.96
2017	$2,192,572.12	$57,357.25	$5,735,049.78	$3,676,926.93	$20,459.19	$26,350.50	$407,568.42	$12,116,284.19

ATM=atomoxetine; AMS=amphetamine mixed salts; DEX-LAS=dextroamphetamine (long-acting); DEX-SAS=dextroamphetamine (short-acting); LIS=lisdexamphetamine; MET-LAS=methylphenidate (long-acting); MET-SAS=methylphenidate (short-acting)

Table 6. Forecasted expenditure for ADHD medication for patients age 18 years and older.

YEAR	ADHD MEDICATION EXPENDITURE (18+ yrs)							
ACTUAL	**AMS**	**DEX - LAS**	**MET - LAS**	**LIS**	**DEX - SAS**	**MET - SAS**	**ATM**	**TOTAL**
2000	$0.00	$15,445.22	$236,219.69	$0.00	$167,985.21	$317,015.04	$0.00	$736,665.16
2001	$0.00	$16,692.69	$249,093.01	$0.00	$188,435.48	$352,005.07	$0.00	$806,226.25
2002	$0.00	$15,748.81	$257,763.36	$0.00	$200,031.63	$383,861.45	$0.00	$857,405.25
2003	$0.00	$23,869.66	$328,215.09	$0.00	$252,112.27	$421,483.77	$0.00	$1,025,680.79
2004	$0.00	$33,489.33	$446,791.19	$0.00	$363,157.54	$459,876.55	$0.00	$1,303,314.61
2005	$0.00	$48,292.55	$573,392.88	$0.00	$509,799.62	$508,084.56	$0.00	$1,639,569.61
2006	$0.00	$60,738.36	$625,892.68	$0.00	$651,766.85	$532,072.63	$14,640.96	$1,885,111.48
2007	$0.00	$82,661.91	$580,337.11	$0.00	$768,762.84	$511,887.13	$64,427.72	$2,008,076.71
2008	$0.00	$92,680.05	$737,575.23	$0.00	$914,783.40	$555,813.12	$106,860.95	$2,407,712.75
2009	$584,371.26	$93,246.41	$1,944,793.85	$0.00	$906,644.90	$626,243.11	$134,592.93	$4,289,892.46
2010	$1,388,737.62	$89,534.54	$2,693,143.81	$0.00	$953,429.38	$689,121.59	$161,586.32	$5,975,553.26
2011	$1,906,760.84	$99,126.52	$3,177,575.20	$379,189.30	$1,047,442.00	$879,263.06	$183,333.62	$7,672,690.54
2012	$2,269,356.38	$93,738.49	$3,673,767.54	$1,372,590.97	$1,044,008.29	$872,286.69	$204,280.54	$9,530,028.90
2013	$2,748,623.83	$204,702.80	$4,332,442.50	$2,340,059.75	$1,044,414.08	$973,073.02	$259,466.79	$11,902,782.77
2014	$3,271,055.99	$534,529.12	$5,187,202.04	$3,496,348.48	$804,735.21	$1,017,468.01	$275,239.29	$14,586,578.14
PREDICTED								
2015	$3,800,959.77	$621,121.65	$6,027,517.22	$4,062,749.15	$811,432.39	$1,025,935.60	$302,721.18	$16,652,436.95
2016	$4,576,680.79	$747,883.61	$7,257,646.45	$4,891,897.59	$805,604.69	$1,018,567.33	$334,067.48	$19,632,347.94
2017	$5,510,715.25	$900,515.85	$8,738,827.31	$5,890,263.25	$799,818.84	$1,011,251.99	$365,413.79	$23,216,806.29

ATM=atomoxetine; AMS=amphetamine mixed salts; DEX-LAS=dextroamphetamine (long-acting); DEX-SAS=dextroamphetamine (short-acting); LIS=lisdexamphetamine; MET-LAS=methylphenidate (long-acting); MET-SAS=methylphenidate (short-acting)

Impact of Alternative Approaches to Reimbursement

Because this review is focused on adult ADHD patients, some of the alternative reimbursement strategies do not impact ADHD medication expenditure for children (<18 years); however, if a LU listing for atomoxetine were to be implemented for all age groups, expenditure would decrease by 6% in some cases (strategies 1b, 2b, 3b) among children by 2017 (Table 7).

For adults over 18 years with ADHD, all of the alternative reimbursement strategies resulted in a reduction in overall expenditure for ADHD medications (Table 8). Listing atomoxetine as limited use in addition to a general benefit listing for extended release methylphenidate and a limited use listing for brand name only long-acting stimulants with enforced step therapy (strategy 3b) offers the largest reduction in expenditure (-13%) by the end of 2017. Moreover, strategy 2b (LU listing for atomoxetine and long-acting stimulants with enforced step therapy) and strategy 3a (GB for extended release methylphenidate & LU listing/step therapy for brand name only long-acting stimulants) each lead to an 8% decrease in overall ADHD medication expenditure. The remaining strategies result in reductions in expenditure of 3-5%.

Table 7. Forecasted total costs (2017) under each alternative reimbursement strategy for patients under 18 years of age.

AVERAGE COST OF ADHD MEDICATIONS IN 2017						
REIMBURSEMENT STRATEGY	LAS[1]	SAS[2]	NS[3]	TOTAL	NET BUDGET IMPACT	%
#1a Status quo (base case)						
	$11,661,906.09	$46,809.69	$407,568.42	$12,116,284.19	N/A	N/A
#1b LU listing for atomoxetine						
	$10,495,715.48	$42,128.72	$883,084.71	$11,420,928.91	-$695,355.28	-6%
#2a LU listing/step therapy for long-acting stimulants in adults (≥18 years)						
	$11,661,906.09	$46,809.69	$407,568.42	$12,116,284.19	$0.00	0%
#2b. 1b + 2a						
	$10,495,715.48	$42,128.72	$883,084.71	$11,420,928.91	-$695,355.28	-6%
#3a. GB extended release methylphenidate & LU listing/step therapy – brand name only long-acting stimulants (≥ 18 years)						
	$11,661,906.09	$46,809.69	$407,568.42	$12,116,284.19	$0.00	0%
#3b. 1b + 3a						

AVERAGE COST OF ADHD MEDICATIONS IN 2017						
REIMBURSEMENT STRATEGY	LAS[1]	SAS[2]	NS[3]	TOTAL	NET BUDGET IMPACT	%
	$10,495,715.48	$42,128.72	$883,084.71	$11,420,928.91	-$695,355.28	-6%
#4. LU listing/step therapy for long-acting stimulants in adults ≥25 years						
	$11,661,906.09	$46,809.69	$407,568.42	$12,116,284.19	$0.00	0%

[1] LAS = long-acting stimulants, includes amphetamine mixed salts, dextroamphetamine (long-acting), lisdexamfetamine, methylphenidate (long-acting)
[2] SAS = short-acting stimulants, includes dextroamphetamine (short-acting) & methylphenidate (short-acting)
[3] NS = non-stimulants, includes atomoxetine

Table 8. Forecasted total costs (2017) under each alternative reimbursement strategy for patients 18 years and older.

AVERAGE COST OF ADHD MEDICATIONS IN 2017						
REIMBURSEMENT STRATEGY	**LAS[1]**	**SAS[2]**	**NS[3]**	**TOTAL**	**NET BUDGET IMPACT**	**%**
#1a Status quo (base case)						
	$21,040,321.67	$1,811,070.83	$365,413.79	$23,216,806.29	N/A	N/A
#1b LU listing for atomoxetine						
	$18,936,289.50	$1,629,963.75	$1,620,211.44	$22,186,464.69	-$1,030,341.60	-5%
#2a LU listing/step therapy for long-acting stimulants in adults (≥18 years)						
	$18,936,289.50	$3,090,722.81	$365,413.79	$22,392,426.10	-$824,380.19	-4%
#2b. 1b + 2a						
	$17,042,660.55	$2,781,650.53	$1,620,211.44	$21,444,522.52	-$1,772,283.76	-8%
#3a. GB generic extended release methylphenidate & LU listing/step therapy – brand name only long-acting stimulants (≥ 18 years)						
	$18,141,707.87	$2,962,757.61	$365,413.79	$21,469,879.27	-$1,746,927.02	-8%
#3b. 1b + 3a						
	$16,327,537.08	$2,847,588.93	$1,343,643.19	$20,518,769.20	-$2,698,037.09	-13%
#4. LU listing/step therapy for long-acting stimulants in adults ≥25 years						
	$19,493,640.31	$2,756,221.72	$365,413.79	$22,615,275.81	-$601,530.47	-3%

[1] LAS = long-acting stimulants, includes amphetamine mixed salts, dextroamphetamine (long-acting), lisdexamfetamine, methylphenidate (long-acting)
[2] SAS = short-acting stimulants, includes dextroamphetamine (short-acting) & methylphenidate (short-acting)
[3] NS = non-stimulants, includes atomoxetine

Overall Conclusions

In conclusion, without any changes to current reimbursement for ADHD medications, expenditure is expected to increase to $12.1 million for children (<18 years) and $23.2 million for adults (≥18 years). Listing atomoxetine as limited use in addition to a general benefit listing for extended release methylphenidate and a limited use listing for brand name only long-acting stimulants with enforced step therapy (strategy 3b) would generate the greatest reduction (-13%) in overall expenditure for adult ADHD medications by the end of 2017. Strategy 2b (LU listing for atomoxetine and long-acting stimulants with enforced step therapy)

and strategy 3a (GB for extended release methylphenidate & LU listing/step therapy for brand name only long-acting stimulants) would each lead to a 8% decrease in overall adult ADHD medication expenditure. Strategies 1b, 2a and 4 would also result in reductions in overall expenditure for adult ADHD medication from 3-5%.

Appendix B1: Model Details

Table 9. Model details for long-acting stimulants for ADHD patients under 18 years.

	CONSTANT	QUARTER	NO. DRUGS IN CLASS
LINEAR MODEL			
Coefficient	4004.428652	106.58	-6125.77281
Std. error	195.2084171	39.27	297.1131713
BIC	4231.111048		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
EXPONENTIAL MODEL			
Coefficient	1.870407932	1.04	570.5305251
Std. error	0.044089608	0.01	0.067105729
BIC	4260.715049		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
POWER MODEL			
Coefficient	3519.994688	1.57	-4814.84673
Std. error	304.0715047	0.48	579.4865437
BIC	4219.779391		
	CONSTANT	**NEW TRT AVAILABLE**	
CONSTANT GROWTH MODEL			
Coefficient	0.48098917	0.015367793	
Std. error	0.09623955	0.009093783	
BIC	4249.964053		

Table 10. Model details for long-acting stimulants for ADHD patients 18 years and older.

	CONSTANT	QUARTER	NO. DRUGS IN CLASS
LINEAR MODEL			
Coefficient	3211.850559	211.87	-6436.43639
Std. error	289.1285592	58.16	440.0624953
BIC	4299.339219		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
EXPONENTIAL MODEL			
Coefficient	1.46389862	1.19	218.4389041
Std. error	0.026231306	0.01	0.039924849

BIC	4202.126049		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
POWER MODEL			
Coefficient	2290.474188	0.00	-3454.13744
Std. error	130.8747325	0.00	292.6802186
BIC	4183.997943		
	CONSTANT	**NEW TRT AVAILABLE**	
CONSTANT GROWTH MODEL			
Coefficient	0.277666581	0.047524857	
Std. error	0.054247066	0.005125866	
BIC	4131.517042		

Table 11. Model details for short-acting stimulants for ADHD patients under 18 years.

	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
LINEAR MODEL			
Coefficient	-999.4610695	-225.41	8457.145899
Std. error	83.01651352	16.70	126.3536684
BIC	4140.29435		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
EXPONENTIAL MODEL			
Coefficient	0.64865784	0.9577622	15806.1946
Std. error	0.024574066	0.0049430	0.037402479
BIC	4156.675421		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
POWER MODEL			
Coefficient	-738.6024331	-72.02	7633.337328
Std. error	102.5052875	5.45	168.4039592
BIC	4132.770495		
	CONSTANT	**NEW TRT AVAILABLE**	
CONSTANT GROWTH MODEL			
Coefficient	-0.098035385	-0.023592463	
Std. error	0.040772477	0.003852637	
BIC	4207.813634		

Table 12. Model details for short-acting stimulants for ADHD patients 18 years and older.

	CONSTANT	2012	Q*2012	QUARTER	NO. DRUGS IN CLASS
LINEAR MODEL					
Coefficient	245.183607	3381.64	-281.148527	225.8171123	1205.809029
Std. error	36.95095584	242.50	18.32814539	4.7486376	65.19249439
BIC	4192.146676				
	CONSTANT	**2012**	**Q*2012**	**QUARTER**	**NO. DRUGS IN CLASS**
EXPONENTIAL MODEL					
Coefficient	0.997976068	2.89	0.915313735	1.084675088	1853.270578
Std. error	0.008109691	0.05	0.00402251	0.001042192	0.014307912
BIC	4237.649763				
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**		
POWER MODEL					
Coefficient	45.1683326	154.98	1767.347533		
Std. error	61.60916331	8.26	95.8698529		
BIC	4076.879265				
	2012	**NEW TRT AVAILABLE**	**CONSTANT**		
CONSTANT GROWTH MODEL					
Coefficient	-0.02139877	0.046509094	0.02		
Std. error	0.003156756	0.015625147	0.00		
BIC	3970.45101				

Table 13. Model details for non-stimulants stimulants for ADHD patients under 18 years.

	CONSTANT	QUARTER	NO. DRUGS IN CLASS
LINEAR MODEL			
Coefficient	0	14.32849503	114.2662338
Std. error	0	1.840840895	10.04587373
BIC	1546.424903		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
EXPONENTIAL MODEL			
Coefficient	1	1.099908814	111.2357087
Std. error	0	0.015127004	0.082551389

BIC	1544.229442		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
POWER MODEL			
Coefficient	0	390.8957525	-286.999794
Std. error	0	35.02664474	42.35728363
BIC	1508.641656		
	CONSTANT	**NEW TRT AVAILABLE**	
CONSTANT GROWTH MODEL			
Coefficient	0	0.047163403	
Std. error	0	0.016062648	
BIC	1582.758164		

Table 14. Model details for non-stimulants stimulants for ADHD patients 18 years and older.

	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
LINEAR MODEL			
Coefficient	0	16.37132353	-3.97590798
Std. error	0	0.337952053	1.795577349
BIC	1511.297804		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
EXPONENTIAL MODEL			
Coefficient	1	1.328141476	15.65356808
Std. error	0	0.018909055	0.100465938
BIC	1422.575511		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
POWER MODEL			
Coefficient	0	3.529485713	20.32193471
Std. error	0	0.101781323	1.903872445
BIC	1370.903231		
	CONSTANT	**NEW TRT AVAILABLE**	
CONSTANT GROWTH MODEL			
Coefficient	0	0.09791442	
Std. error	0	0.017570396	
BIC	1454.356251		

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