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Medication for Attention-Deficit/Hyperactivity Disorder and Risk for Suicide Attempts

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is a risk factor for suicidal behavior, but the effect of ADHD medication on suicidal behavior remains unclear. This study aimed to examine the associations between medication treatment for ADHD and risk of suicide attempts.

Methods: We identified a large cohort of patients with ADHD (N=3,874,728, 47.8% female) using data from commercial healthcare claims 2005-2014 in the US. We used population-level and within-individual analyses to compare risk of suicide attempts during months when individuals received prescribed stimulant or non-stimulant medication relative to months when they did not receive medication.

Results: In both population-level and within-individual analyses, ADHD medication was associated with lower odds of suicide attempts (odds ratio [OR] =0.69, 95% CI: 0.66- 0.73, and OR=0.61, 95% CI: 0.57-0.66, respectively). Similar reductions were found in children to middle-aged adults and in clinically relevant subgroups, including ADHD patients with pre-existing depression or substance use disorder. The reduction was mainly seen for stimulant medication (OR=0.72, 95% CI: 0.66-0.77); non-stimulant medication was not associated with statistically significant changes in risk of suicide attempts (OR=0.94, 95% CI: 0.74-1.19). Sensitivity analyses assessing the influence of different exposure definitions, different outcome definitions, subsets of the cohort, and different analytic approaches provided comparable results.

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Conclusions: Stimulant medication was associated with a reduced risk of suicide attempts in patients with ADHD, and non-stimulant medication is unlikely to increase the risk of suicide attempts.

Keywords

ADHD; ADHD medication; suicide attempt; cohort study; real-world evidence; stimulants

INTRODUCTION

Suicide and suicide attempt (i.e., suicidal behavior) are serious public health problems. About 800,000 people around the world die due to suicide annually, and research estimates that for each person who dies by suicide, more than 20 others attempt suicide (1). Although suicide rates have fallen globally, the rates have increased in the United States from 1999 to 2016 (2). Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder, affecting 5–7% of school-age children (3). ADHD symptoms persist into adulthood for approximately half of individuals diagnosed in childhood, and research suggests that both childhood and adult ADHD are associated with elevated risk for suicidal behavior (4–7). In order to reduce suicide morbidity and mortality, the National Action Alliance for Suicide Prevention outlined a prioritized research agenda highlighting the importance of studying whether treatment for psychiatric problems can prevent suicidal behavior (8).

Stimulant medications are the first-line pharmacological treatment for ADHD (9). Stimulants are the most commonly prescribed psychotropic medications in children, and their use among adults has increased markedly in recent years (10), with 6.6% of US adults using prescription stimulants annually (11). Non-stimulant medications (e.g., atomoxetine and guanfacine) are also available to treat ADHD. Both stimulant and non-stimulant medications are effective in reducing symptoms of ADHD in children and adults (9). However, the potential impact of ADHD medications on suicidal behavior remains unclear (12, 13). In 2005, the FDA implemented a black box warning regarding an elevated risk of suicidal ideation in children and adolescents being treated with atomoxetine (14). A meta-analysis of randomized controlled trials (RCTs) found that suicidal ideation, although uncommon, was significantly more frequent in pediatric ADHD patients treated with atomoxetine compared to placebo, but there was no significant difference for suicidal behaviors (15).

Given that the external validity of RCTs is limited (e.g., individuals with suicidal behavior are often excluded from trials), real-world evidence for the effect of ADHD medications on suicidal behavior is needed (16, 17). A few studies using prescription databases from Europe and Asia have found null or protective effects of stimulant medications on risk of suicidal behavior (18–21), but evidence from large-scale US studies is lacking. Only one comparative study between atomoxetine and stimulants is available (22), but it provided no direct estimate of the effects of these medications on risk of suicidal behavior. In addition, several clinically relevant questions are yet to be explored. First, most of the previous studies were limited to young ADHD patients, and the association in adult patients warrants further investigation. Second, there are currently few guidelines regarding the prescription of

ADHD medication among ADHD patients with psychiatric comorbidities (e.g., depression, substance use disorder) (8), which are high-risk groups for suicidal behavior (23). Understanding the effects of ADHD medication in individuals with comorbid disorders would help inform clinical practice.

In this study, we followed a large sample of commercially insured patients with ADHD in the US to examine the hypothesis that ADHD medication is associated with reduced risk for suicide attempts. We tested this hypothesis by using a within-individual comparison design and explored potential differences in the associations across age groups, types of medication, and comorbidities. We also conducted a series of sensitivity analyses to assess the robustness of the findings.

METHODS AND MATERIALS

Study population

We used data from the Truven Health MarketScan® Commercial Claims and Encounters databases (MarketScan), which includes inpatient, outpatient, and filled prescription claims from more than 100 insurers in the US. Only fully paid and adjudicated claims were included to ensure quality of coding (24). From 2005 to 2014, there are approximately 146 million unique enrollee observations, encompassing employees and their spouses and dependents who are covered by employer-sponsored commercial health insurance. The data are representative of the largest segment of health care users in the US, an estimated 49% of the population (24). We identified all ADHD patients aged 5 years or older, defined as individuals who received an ADHD diagnosis (codes 314 in the International Classification of Diseases, Ninth Edition [ICD-9]) or ADHD medication (see below) between January 1, 2005 and December 31, 2014. We followed ADHD patients from their index date (i.e., first inpatient or outpatient diagnosis or filled prescription) until the first disenrollment (i.e., end of medical or drug insurance coverage) or December 31, 2014, whichever occurred first. Analysis of MarketScan is considered exempt from human participants research by the University of Chicago institutional review board because all records are de-identified.

Exposure

We identified ADHD medication from filled prescription claims using national drug codes for the following generic names. Stimulant medications included amphetamine salt combination, dexamethylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate, methamphetamine hydrochloride, methylphenidate, and methylphenidate hydrochloride. We also included atomoxetine hydrochloride, a non-stimulant medication for ADHD. Prescription claims without valid fill dates or days' supply (180 days) were excluded.

Outcome

We defined follow-up months as having an outcome event if study participants had at least one emergency room visit, ambulance ride, or inpatient hospitalization for suicide attempt (ICD-9 codes: E95). This operationalization was consistent with that used in prior analyses

of MarketScan data and was selected in order to capture time-specific claims to avoid misclassifying recurring treatment visits as events (25, 26).

Statistical analyses

To examine the association between ADHD and risk of suicide attempts, we compared the risk of at least one suicide attempt between ADHD patients and non-ADHD controls. We matched ADHD patients and controls (no ADHD diagnosis or ADHD medication) 1:1 on sex, calendar year of first enrollment, age of first enrollment in MarketScan, and length of enrollment. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using conditional logistic regression.

To explore the association between ADHD medication and suicide attempts, we created a monthly person-time dataset in ADHD patients and compared the risk of suicide attempts during months in which patients received or did not receive ADHD medication (25, 26). We permitted suicide attempt events to occur more than one time during follow-up. We defined a patient as medicated during a given month if a prescription was filled in that month or if there was a carryover from a prior month (i.e., days' supply extended into that month). If a prescription was filled in the month with an outcome event, the medication was considered present only if the prescription was filled prior to the outcome event. This reclassification occurred in a small number of instances ($n=111$, $<0.01\%$ of included months).

We conducted two sets of analyses. First, we applied a population-level model to compare the risk of outcome events between medicated months and un-medicated months. ORs were estimated using discrete-time logistic regression, adjusting for time-varying covariates (age, calendar year, time since last event, any antidepressant medication [see Supplementary Table 1 for included antidepressants], and any psychological treatment in a given month), and with cluster-robust standard errors accounting for the correlations among months within individuals. Second, to reduce confounding by indication (i.e., factors that differ between patients who did and did not receive ADHD medication) (16, 17), we performed within-individual comparisons using conditional logistic regression models, with each individual entered as a separate stratum. This model compared the risk of outcome events during months when an individual received ADHD medication relative to months when the same individual did not receive ADHD medication. The design, therefore, controlled for confounding by unmeasured factors that are constant within each individual during the follow-up (e.g., genetic predisposition and early environments). In order to account for time-varying factors, we included the following measured covariates: time since last event, any antidepressant medication, and any psychological treatment. We did not include years of age and calendar year, as the small changes in these variables were unlikely to influence the within-individual ORs. We fitted the conditional logistic models to the entire dataset, as well as stratified by sex.

We further explored the within-individual associations between ADHD medication and suicide attempts in clinically relevant subgroups. The first analysis examined the associations by age groups to assess if the associations varied among patients of different ages. Second, because stimulant and non-stimulant medications differ in their pharmacological mechanism and treatment efficacy (9), we conducted separate analyses in

patients who ever received stimulant or non-stimulant, respectively. Mixed users are allowed in both analyses, and the estimate for stimulant medication is adjusted for any concomitant non-stimulant, and vice versa. The third and fourth analyses examined the association between ADHD medication and suicide attempts in patients aged 13 years with and without a prior diagnosis of depression or substance use disorder (26), respectively. The last analysis explored how duration of treatment influenced risk of suicide attempts. In a sub-sample of patients with at least two years of follow-up, we examined the association between duration of ADHD medication exposure (i.e., cumulative months of medication during the prior two years) and risk of suicide attempts, while controlling for concurrent ADHD medication (26).

We conducted six sensitivity analyses to examine whether the results were altered by different cohort selection or outcome definitions. The first analysis examined the association in a cohort with incident diagnoses of ADHD (i.e., patients who had no diagnosis of ADHD or prescription of ADHD medication for at least one year before the diagnosis), which permitted evaluation of associations among patients who were new to ADHD treatment. The second analysis censored individuals at first outcome event in the incident diagnosis cohort, which precluded bias due to reverse causation. The third and fourth analyses excluded individuals who received other psychotropic medications or psychological treatment, respectively, in order to test whether the results were explained by other treatments. Fifth, research has documented that the rate of suicide attempts is elevated in the period immediately before and after the start of ADHD medication treatment (21). To test whether ADHD medication was associated with the elevated risk in this high-risk period, we compared the risk of suicide attempts during the first three months of treatment with that during three months preceding treatment initiation in patients with their first prescription of ADHD medication within the incident diagnosis cohort. The sixth analysis examined the association between ADHD medication and depression events, which is a more prevalent outcome that is associated with suicidal behavior. Depression events were defined as emergency room visits, ambulance rides, or inpatient hospitalizations for depression (ICD-9 codes: 296.2, 296.3, 300.4, 311).

All analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Table 1 presents summary statistics for patients with ADHD. We identified 3,874,728 patients with ADHD (47.8% female), among whom 1,852,406 (84.0%) male and 1,447,536 (86.8%) female patients received at least one prescription of ADHD medication. During the follow-up periods, 2288 male patients (0.1%) and 3576 (0.2%) female patients had at least one suicide attempt. Compared with non-ADHD controls, ADHD patients had higher risk of any suicide attempt (OR=4.70, 95% CI, 4.37-5.05 for males; OR=4.92, 95% CI, 4.65-5.22 for females; Supplementary Table 2).

Associations between ADHD medication and suicide attempts

In population-level analyses, months with ADHD medication were associated with a 31% lower risk of suicide attempt in ADHD patients relative to un-medicated months (OR=0.69,

95% CI: 0.66- 0.73, Table 2). The within-individual comparison found similar results: ADHD patients were at 39% lower risk of suicide attempts during medicated months compared to un-medicated months (OR=0.61, 95% CI: 0.57-0.66), while also adjusting for the time-varying covariates. This model is based on 5849 individuals (2281 male and 3568 female) with at least one suicide attempt event and switch in medication status or other covariates. The associations were similar in male (OR=0.64, 95% CI: 0.57- 0.73) and female ADHD patients (OR=0.59, 95% CI: 0.54-0.65). Supplementary Table 3 presents covariate parameter estimates.

Subgroup analyses

Subgroup analyses showed that ADHD medication was associated with reduced risks of suicide attempts in all age groups, from children to middle-aged adults (ORs ranged from 0.44 to 0.69, Table 3). When examining different types of ADHD medication, stimulant medication was associated with a similar reduction of risk for suicide attempt (OR=0.72, 95% CI: 0.66-0.77) as in the main analyses, whereas the association with non-stimulant (OR=0.94, 95% CI: 0.74-1.19) was not statistically significant. When considering comorbid conditions, we found that ADHD medication was associated with reduced risks of suicide attempts in ADHD patients with (OR=0.65, 95% CI: 0.57-0.74) and without a prior diagnosis of depression (OR=0.59, 95% CI: 0.53-0.65) and the test for interaction was non-significant ($p=0.89$). A similar pattern of results was found in patients with (OR=0.75, 95% CI: 0.60-0.93) and without a prior diagnosis of substance use disorder (OR=0.59, 95% CI: 0.55-0.64, test for interaction $p=0.32$). Regarding duration of treatment, one-year increase in duration of ADHD medication was associated with 28% reduced risk of suicide attempts (OR=0.72, 95% CI: 0.61-0.85).

Sensitivity analyses

Sensitivity analyses for the association between ADHD medication and suicide attempts in patients with incident diagnoses of ADHD and in the first-event analysis provided comparable results with the main analyses (Table 4). When examining only individuals without other psychotropic medications or psychological treatment, the associations were similar as the main analyses. Among patients with their first prescription of ADHD medication, we observed higher rates of suicide attempt events during the periods three months before and after the start of treatment compared to the other periods (Supplementary Figure 1). When comparing the risk of suicide attempts during the first three months of treatment with that during three months preceding treatment initiation, the association was not statistically significant (OR=0.92, 95% CI: 0.74-1.15). For depression events, the risk was 28% lower during medicated than un-medicated months (OR=0.72, 95% CI: 0.71-0.73).

DISCUSSION

In this large cohort study of patients with ADHD, we found that the use of ADHD medication was associated with a reduced risk of suicide attempts when comparing medicated months to un-medicated months within individuals, while controlling for time-varying factors (e.g., antidepressant and psychological treatment). Similar reductions were found across all age groups and in ADHD patients with prior depression or substance use

disorder. The reduction was mainly seen for stimulant medication, whereas non-stimulant medication was associated with a minor and statistically non-significant reduction in risk of suicide attempts.

To our knowledge, this study is the largest to date to examine the association between ADHD medication and risk of suicide attempts. In line with previous studies (18–21), we found no evidence that either stimulant medication or non-stimulant medication was associated with an increased risk of suicide attempts. Use of stimulant medication, however, was associated with a 28% lower concurrent risk of suicide attempt, compared with 19% and 22% (not statistically significant) reductions in previous studies from Sweden and Hong Kong (18, 21), respectively. These results support a growing body of pharmacoepidemiological research demonstrating that stimulant medication is associated with lower risks for adverse behavioral outcomes (e.g., injury, motor vehicle accident, and criminality) (17). Our results also suggest longer duration of ADHD medication treatment was associated lower risk of suicide attempts. If these results reflect causal relationships, the protective effects may be mediated by the improvement of ADHD symptoms, such as increased executive functioning (27). At the same time, continued treatment may lead to lower risks of depression or substance use disorder, which may alternatively, or additionally, mediate the risk of suicidal behaviors in ADHD patients (6). In keeping with the latter explanation, we also found ADHD medication was associated with a lower risk of depression events.

The finding that individuals with ADHD had a substantially increased risk of suicide attempts compared with individuals without ADHD highlights the importance of suicide prevention in this at-risk group. Our results suggest that the reduction of suicide attempts associated with ADHD medication was not limited to young patients with ADHD but also extended to middle-aged adults. The awareness of ADHD in adults has rapidly increased and influenced clinical practice in recent years (28). With an estimated prevalence of about 3% (29), ADHD is one of the most common mental health problems in adults. Considering the prevalence of ADHD and its strong link with suicide, successful treatments for ADHD could make a substantial contribution to the prevention and reduction of suicidal behavior. Moreover, patients with ADHD have high rates of psychiatric comorbidities, including depression and substance use disorder, which are the most over-represented mental health disorders among individuals who attempt suicide (30). We found that ADHD medication was associated with reduced risks of suicide attempts in ADHD patients both with and without comorbid depression or substance use disorder, and the associations were independent of concomitant treatment with antidepressants and psychological therapy. Nevertheless, the combination of multiple therapies in real-life care is complex, and future research should investigate whether polypharmacy and multimodal treatment improves outcomes.

We found that rates of suicide attempt were particularly high during the periods before and after initiation of ADHD medication, which was in line with a previous study from Hong Kong (21). Comparing the risk during the first three months of treatment with that during three months preceding treatment initiation revealed a small and non-significant reduction (OR=0.92). One possible explanation is that the observed increased risk of suicide attempts

after treatment initiation is likely not due to ADHD medication but factors (e.g., mood change) that precede it. Another possibility is some of the claims of suicide attempts after treatment initiation may reflect continued treatment of previous events rather than new events. Nevertheless, neither of the explanations suggest the elevated risk of suicide attempts after treatment initiation is due to ADHD medication, and additional research is needed to understand the triggers for high rates of suicide attempts before initiation of ADHD medication, which will provide important information for treatment decision-making.

This study has several strengths and limitations. We investigated a large sample from the US, which has the highest prevalence of ADHD medication use among developed countries (10). Information on the exposure (i.e., filled prescriptions) was independent of the outcome and free from recall bias. Most importantly, we used a within-individual design, which adjusts for all confounders that are stable during the follow-up. However, because of the observational nature of the data, we could not account for all potential confounders. For example, time-varying factors (e.g., life events, episodes of depression, and other treatments) that motivate individuals to use or stop ADHD medication may simultaneously influence the risk of suicide attempt. As an attempt to reduce time-varying confounding, we have adjusted antidepressants and psychological treatment in all the analyses and performed the sensitivity analyses in individuals without other psychotropic medications or psychological treatment. The results suggest that the association between ADHD medication and suicide attempts were unlikely to be fully explained by other treatments or general treatment engagement. Nevertheless, we cannot prove causal effects of treatment from the study. Further studies with other samples and designs are needed to triangulate the findings.

Several additional limitations have to be considered. First, the use of ADHD medication was measured by filled prescriptions. If some patients did not take the medication as indicated, it would introduce misclassification of exposure. Therefore, our results should be interpreted as analogous to “intention-to-treat” in RCTs (26). Second, we do not have information on the indication of ADHD medication prescription. Some individuals may receive these medications for off-label uses, although the results were not substantially different in the overall cohort and in the incident ADHD diagnosis cohort. Third, the coding for ADHD or ADHD medications in MarketScan has not been formally validated. If the misclassifications were non-differential, it would reduce the effect estimates towards null, meaning that our results are likely to be conservative estimates of the actual effects of medication on suicidality. Fourth, although we used emergency room visits, ambulance rides, or inpatient hospitalizations to define outcome events, misclassification is inevitable. We also did not have access to suicide attempt events that did not result in contact with the medical system. Fifth, findings of this study are based on data for patients with commercial health insurance. Generalizations to other patient groups (e.g., publically insured, uninsured) should be made with caution (31). Finally, the current study focused on suicidal behavior (and depression) and did not include other clinically relevant issues—such as negative side effects (e.g., problems with sleep and appetite) or problems with stimulant medication diversion or misuse—that physicians, patients, and their families must consider (11).

In conclusion, in a large US sample of patients with ADHD, we found that stimulant medication was associated with a reduced risk of suicide attempts, and we found no

evidence of an increased risk associated with non-stimulant medication. In light of the high risk of suicide in patients with ADHD, it will be useful to consider these associations in conjunction with other risks and benefits of ADHD medication when making treatment decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

Dr. Gibbons has served as an expert witness in cases involving the U.S. Department of Justice and Wyeth, Pfizer, and GlaxoSmithKline. Dr. Larsson has served as a speaker for Evolan Pharma and Shire and has received research grants from Shire; all outside the submitted work. All other authors report no biomedical financial interests or potential conflicts of interest.

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Table 1.

Summary statistics of included ADHD patients.

	Male		Female	
	N	%	N	%
No. of patients	2,206,469	-	1,668,259	-
At least one prescription of ADHD medication	1,852,406	84.0	1,447,536	86.8
At least one switch of medication status	1,267,928	57.5	960,848	57.6
At least one suicide attempt event	2288	0.1	3576	0.2
	Median	IQR	Median	IQR
Age at start of follow-up	16	10-27	24	15-40
Follow-up months	16	8-34	15	8-31

IQR: Interquartile range.

Table 2.

Associations between ADHD medication and suicide attempts.

	Patients (n)	Suicide attempt events (n)	Population-level OR (95% CI)	Within-individual OR (95% CI)
All	3,874,728	6453	0.69 (0.66-0.73)	0.61 (0.57-0.66)
Male	2,206,469	2481	0.70 (0.64-0.76)	0.64 (0.57-0.72)
Female	1,668,259	3972	0.70 (0.65-0.74)	0.59 (0.54-0.65)

Table 3.

Associations between ADHD medication and suicide attempts in clinically relevant subgroups.

	Patients (n)	Suicide attempt events (n)	Within-individual OR (95% CI)
Age group 5-12	1,136,345	770	0.51 (0.41-0.62)
Age group 13-17	658,811	2539	0.67 (0.59-0.75)
Age group 18-25	699,037	1356	0.69 (0.58-0.82)
Age group 26-35	502,524	608	0.67 (0.52-0.87)
Age group 36-45	416,469	624	0.48 (0.37-0.61)
Age group 46+	461,542	556	0.44 (0.33-0.57)
Effect of stimulant medication in patients who ever received stimulant medication	3,123,260	5121	0.72 (0.66-0.77)
Effect of non-stimulant medication in patients who ever received non-stimulant medication	359,752	942	0.94 (0.74-1.19)
Patients who were at least 13 years old with a prior diagnosis of depression	525,009	2681	0.65 (0.57-0.74)
Patients who were at least 13 years old without a prior diagnosis of depression	2,468,878	3663	0.59 (0.53-0.65)
Patients who were at least 13 years old with a prior diagnosis of substance use disorder	91,750	810	0.75 (0.60-0.93)
Patients who were at least 13 years old without a prior diagnosis of substance use disorder	2,902,137	5534	0.59 (0.55-0.64)
Effect of duration of ADHD medication treatment in patients with at least two years of follow-up	1,249,914	1988	0.72 (0.61-0.85) *

* OR reflects the relative difference in odds associated with one-year increase in months of ADHD medication received in the prior two years.

Table 4.

Sensitivity analyses for the associations between ADHD medication and suicide attempts.

Cohort	Outcome	Patients (n)	Outcome events (n)	Within-individual OR (95% CI)
Incident diagnosis cohort	Suicide attempt events	801,838	1323	0.82 (0.68-0.98)
Incident diagnosis cohort and first event only	First event of suicide attempt	800,554	1103	0.57 (0.46-0.71)
Individuals with no other psychotropic medications	Suicide attempt events	1,956,518	468	0.50 (0.36-0.68)
Individuals with no psychological treatment	Suicide attempt events	2,713,023	1433	0.54 (0.46-0.64)
3 months before and after start of ADHD medication	Suicide attempt events	528,281	331	0.92 (0.74-1.15)
Full cohort	Depression events	3,874,728	191,017	0.72 (0.71-0.73)

KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources .	Include any additional information or notes if necessary.
Antibody				
Bacterial or Viral Strain				
Biological Sample				
Cell Line				
Chemical Compound or Drug				
Commercial Assay Or Kit				
Deposited Data; Public Database				
Genetic Reagent				
Organism/Strain				
Peptide, Recombinant Protein				
Recombinant DNA				
Sequence-Based Reagent				
Software; Algorithm	SAS 9.4	SAS Institute Inc., Cary, NC	RRID:SCR_008567	
Transfected Construct				
Other	De-identified patient claims data	Truven Health MarketScan® Commercial Claims and Encounters databases		