Published in final edited form as:
Pharmacoepidemiol Drug Saf. 2015 February ; 24(2): 208–214. doi:10.1002/pds.3713.

Antidepressant Treatment and Suicide Attempts and Self-inflicted Injury in Children and Adolescents

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Abstract

Purpose—In 2004 FDA placed a black box warning on antidepressants for risk of suicidal thoughts and behavior in children and adolescents. The purpose of this paper is to examine the risk of suicide attempt and self-inflicted injury in depressed children ages 5–17 treated with antidepressants in two large observational datasets taking account time-varying confounding.

Methods—We analyzed two large U.S. medical claims databases (MarketScan and LifeLink) containing 221,028 youth (ages 5–17) with new episodes of depression, with and without antidepressant treatment during the period of 2004–2009. Subjects were followed for up to 180 days. Marginal structural models were used to adjust for time-dependent confounding.

Results—For both datasets, significantly increased risk of suicide attempts and self-inflicted injury were seen during antidepressant treatment episodes in the unadjusted and simple covariate adjusted analyses. Marginal structural models revealed that the majority of the association is produced by dynamic confounding in the treatment selection process, and revealed odds ratios close to 1.0, which were consistent with chance expectations.

Conclusions—The imbalance in both static and dynamic characteristics of patients in terms of the treatment selection process lead to the appearance of an association between antidepressant treatment and suicide attempts and self-inflicted injury. Use of MSM to adjust for dynamic treatment selection adjusts for this imbalance and may explain why some previous observational

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studies have found positive associations between antidepressant treatment and suicide and related behaviors in youth.

Keywords

Antidepressants; children and adolescents; suicide attempts; self-inflicted injury; marginal structural models; time-varying confounding; pharmacoepidemiology

Introduction

In 2004, the U.S. Food and Drug Administration (FDA) raised concerns about the effect of antidepressants on risk of suicide in youth, leading to a black box warning for the entire class[1]. In a meta-analysis of 25 randomized clinical trials (RCTs) of newer antidepressants (serotonin specific reuptake inhibitors – SSRIs and serotonin norepinephrine reuptake inhibitors – SNRIs) there was close to a doubling of the rate of spontaneously reported suicidal thoughts and behavior in treated (4%) versus placebo (2%) patients[2]. A subsequent expanded meta-analysis found a non-significant difference of 0.9%[3]. Prospective assessments showed no evidence of an effect, and in community practice, a suicide attempt is more likely to *precede* initiation of an SSRI antidepressant in adolescents than to follow it[4–5].

Observational studies have also been conducted. Valuck[6] examined data from 24,119 adolescents with a first diagnosis of major depression and with at least six months of follow-up data. Treatment with SSRI's, other antidepressants, or combinations of antidepressants resulted in no significant increased risk in suicide attempts. Similar results were found by Simon[4–5]. In contrast, Olfson[7] conducted a case-control study in depressed children and found significant association for both suicide attempts (n=263) and completion (n=8) in children with antidepressant treatment. Tiihonen[8] found current antidepressant use to be associated with increased risk of suicide attempts but decreased risk of suicide completion in youth that had ever used an antidepressant. More recently, a research synthesis of all double blind placebo controlled RCTs of fluoxetine (an SSRI) in youth found no effect on suicidal thoughts or behavior[9–10]. Psychological autopsy studies have found that depression makes a greater contribution to suicide in midlife and the elderly, and conversely, impulsive aggression makes a greater contribution in youth[11–12].

There are several difficulties with using the data from RCTs to draw causal inferences regarding the relationship between antidepressant treatment and suicide. First, the patients at greatest risk (suicidal youth) have generally been excluded from these studies. Second, the majority of events are suicidal thoughts with questionable relation to suicide[13]. Third, the suicidal events are generally spontaneously reported and are not methodically studied as pre-specified endpoints; in studies that have used both spontaneous and systematic collection of events, rates are much higher with the latter approach[14]. Fourth, patients randomized to active medication will have more side-effects in general, leading to increased contact with study staff and greater opportunity to report suicidal thoughts and behavior (i.e., ascertainment bias[15]).

Similarly, there are problems with using data from observational studies to draw causal inferences. First, there is confounding by indication in which patients who take antidepressants are generally more severely ill and therefore at greater suicide risk[15,16]. A suicide attempt or self-inflicted injury is often the event that causes initiation of antidepressant treatment[4–5]. Second, the endpoints are based on medical claims and many attempts and self-inflicted injuries are unreported. Third, traditional regression approaches are inadequate for time varying confounders. Fourth, in medical claims data, depressive severity is not directly measured.

In this paper, we explore the relationship between antidepressant treatment and suicide attempt and self-inflicted injury in parallel in two large U.S. databases (LifeLink and MarketScan) using statistical methods that minimize biased inferences from observational data. We use the method of marginal structural models (MSM)[17] to adjust for the time-dependency of confounders in these longitudinal datasets, and then use a discrete-time survival analysis[18–20] to model the effect of treatment on time to suicide attempt or self-inflicted injury. The fundamental idea of MSM is that there are two dynamic models, one for the treatment selection process and the other for the dynamic effect of treatment on the outcome of interest. The first model is used to derive weights which when applied to the second stage model create a pseudo-population which is similar to what would be observed if the treatment assignment were sequentially randomized; thereby eliminating the confounding between characteristics of the individuals which change over time and can affect both the likelihood of future treatment and the outcome of treatment. Conceptually, MSM is similar to a propensity score[21] which takes on time-specific values and is used as a weight in a second stage analysis rather than used to match treated and control subjects.

Methods

The Sample

Two different large-scale U.S. medical claims databases were used in parallel; MarketScan (www.marketscan.com) and LifeLink (formerly PharMetrics) (www.imshealth.com). Each datasets covers the lives of approximately 50 million people and aggregate information from private insurance companies. The datasets contain complete longitudinal information on clinical utilization in inpatient and outpatient settings and all filled prescriptions. Identical specifications were used for both datasets. We selected all data during the period of 2004 through 2009 for patients with a new diagnosis of depression (ICD-9: 296.2*, 296.3*, 300.4 or 311) in patients ages 5–17. The index date was the date of the depression diagnostic claim. Patients who, during the 6 months prior to study entry, had insurance coverage, no diagnosis of depression, bipolar disorder or schizophrenia, and any antidepressant or antipsychotic medication claims were included. Subjects were followed for up to 180 days.

Variables

The primary outcome measure was suicide attempt and self-inflicted injury (E950–E958 and late effects of self-inflicted injury E959). We note that while intent is difficult to establish ICD9-CM codes are specific about suicide. In fact, the heading for ICD9-CM codes E950 to

E959 is “Suicide and self-inflicted injury.” The clarifying notes state: “injuries in suicide and attempted suicide” and “self-inflicted injuries specified as intentional.” [22]

Medication use was determined using prescription claims data (day’s supply) of antidepressants (SSRIs, SNRIs, tricyclic antidepressants (TCAs), other antidepressants and bupropion), antiepileptics, anxiolytics, antihistamines, antipsychotics (conventional and atypical), analgesics, antimanics, and sedatives. Data on psychotherapy visits and psychiatric hospitalizations were also available. Comorbid conditions were also available in terms of ADHD, anxiety, bipolar disorder, seizures, and psychotic and conduct disorders. We did not include any comorbidity index as a covariate because comorbidity indices have been validated in adult samples as predictors of short-term mortality and are therefore inappropriate for youth.

Statistical Methods

The medical claims data were used to create a monthly person-time dataset[20], with 6 monthly observation periods from the index depression episode date. A patient who was available during all 6 months of follow-up and did not make a suicide attempt or self-inflicted injury would have 6 monthly observations with an event code of 0 for all 6 records. A patient who had his/her coverage revoked after 3 months and did not make a suicide attempt or self-inflicted injury would have 3 monthly observations with an event code of 0 for all 3 records. A patient who made a suicide attempt or self-inflicted injury in month 4 would have a total of 4 records with event codes of 0 for the first 3 months and a code of 1 on the 4^{th} month. A drug was considered present during a given month if a prescription was filled in that month or a carryover from a prior month was filled (i.e., day’s supply extended into the next month). If a prescription was filled in the month of a suicide attempt or self-inflicted injury, the drug was considered present if the prescription was filled prior to the attempt or self-inflicted injury. Prior suicide attempt and self-inflicted injury was included as an important covariate in the model and was assessed during the six month period prior to the index date. A suicide attempt or self-inflicted injury on the same day as the index date was treated as a prior suicide attempt or self-inflicted injury.

The statistical analysis was comprised of two stages. In the first stage, a logistic regression model was used to predict antidepressant usage on each of the 6 months conditional on fixed covariates (demographics and prior suicide attempt and self-inflicted injury) and time-varying covariates (comorbid conditions, concomitant medications (listed above), psychiatric hospitalizations and psychotherapy above). The predicted probability of treatment at time-point t was computed as the continued product of probabilities from baseline to time-point t. The inverses of these estimated probabilities were then used as weights $W(t)$ in the second stage analysis that related actual treatment (dynamically determined on a month by month basis) to suicide attempt and self-inflicted injury using a discrete time survival model[18–19]. In practice, $W(t)$ is highly variable and fails to be normally distributed. To overcome this problem, Robins[17] suggested use of the stabilized weight:

$$SW(t)=\prod_{k=0}^{t}\frac{f\{A(k)|\overline{A}(k-1),V\}}{f\{A(k)|\overline{A}(k-1),\overline{L}(k)\}},$$

where *L* is the set of all baseline and time-varying covariates, *V* is a subset of *L* consisting of only the baseline covariates (i.e. time invariant effects), *A(k)* is the actual treatment assignment at time *k*, and $\bar{A}(k)$ is the treatment history. The standardized weights should have mean close to 1.0. The net result is that using MSM we are able to control for the effects of time-dependent confounders that are affected by prior treatment. At each time-point the weight is the inverse of the probability of receiving antidepressant treatment given all factors that affect antidepressant prescription. Robins[23] showed that this method creates a pseudo-population that resembles data from a sequentially randomized experiment, under the assumption that all of the factors that determine treatment are observed. As such, the method does not necessarily remove the biases inherent in an observational study, but rather brings an observational study result as close as possible to what might have resulted from an RCT.

There is variability in the completeness of E-codes by state and there are some states that do not mandate the reporting of E-codes[24]. Our datasets, however, come from claims submitted to insurance companies for reimbursement, which do include E-codes for all states. In 2006, 0.24% of all claims have at least one E-code present in states with mandates versus 0.20% in states without mandates. To examine the effect of mandates on the results of our MSM analysis we recomputed the MSM for claims originating in the 18 states with mandates for E-code reporting in emergency department data systems (reducing the sample size from 55,284 subjects to 20,706) from the MarketScan data where state information was available.

Results

Table 1 presents a comparison of the MarketScan and LifeLink databases in terms of the covariates used in the MSM. With the exception of prior suicide attempt and self-inflicted injury rates, the two databases are generally similar.

Dynamic Predictors of Antidepressant Treatment

Table 2 presents the results of the 1st stage treatment selection model. In general, the predictors of treatment were quite similar between the two datasets. The major predictors of increased likelihood of receiving antidepressant treatment were age and receiving other CNS medications (antileptics, antipsychotics, anxiolytics, and sedative/hypnotics). Patients with comorbid anxiety disorder were also at increased likelihood of receiving antidepressant treatment. By contrast, patients diagnosed with bipolar disorder were less likely to receive antidepressant treatment.

MarketScan Data

A total of 55,284 subjects met criteria for the study. The average age was 14.3 years. 58.0% were female. The overall annualized suicide attempt and self-inflicted injury rate was 12*(173/338922)*100 = 0.61% (0.53% off treatment versus 1.03% on treatment). The

average standardized weight was 1.05 (standard deviation (SD) = 0.66). The overall unweighted and unadjusted analysis revealed increased risk of suicide attempt and self-inflicted injury with treatment (odds ratio (OR) = 1.99, 95% confidence interval (CI) = 1.39, 2.85). The unweighted covariate adjusted analysis decreased the risk estimate slightly, but remained significant (OR=1.84, 95% CI = 1.29, 2.64). The weighted MSM analysis revealed a non-significant relationship between antidepressant treatment and suicide attempt and self-inflicted injury (OR=1.21, 95% CI = 0.79, 1.88).

LifeLink (PharMetrics) Data

A total of 165,744 subjects met criteria for the study. The average age was 14.1 years. 56.0% were female. The overall annualized suicide attempt and self-inflicted injury rate was 12*(1172/910271)*100 = 1.55% (1.30% off treatment versus 2.54% on treatment). The average standardized weight was 1.05 (SD = 0.55). The overall unweighted and unadjusted analysis revealed increased risk of suicide attempt and self-inflicted injury with treatment (OR=1.94, 95% CI = 1.72, 2.20). The unweighted covariate adjusted analysis decreased the risk estimate but remained significant at (OR=1.66 95% CI = 1.47, 1.87). The weighted MSM analysis revealed a non-significant relationship between antidepressant treatment and suicide attempt and self-inflicted injury (OR=1.05, 95% CI = 0.92, 1.19).

Restriction to SSRIs

Results were quite similar when the analysis was restricted to SSRIs. For the MarketScan data, the unadjusted OR=2.17 (95% CI = 1.50, 3.15), whereas the weighted MSM analysis yielded OR=1.25 (95% CI = 0.79, 1.97). For the LifeLink data, the unadjusted OR=2.05 (95% CI = 1.81, 2.33) whereas the weighted MSM analysis yielded OR=1.12 (95% CI = 0.98, 1.29).

Restriction to States that Mandate use of E-codes

When analysis was restricted to the 18 states that mandate E-code reporting, the crude OR in these states (unweighted and unadjusted) was OR = 2.84, 95% CI (1.54, 5.23), which is larger than the overall OR of 1.99, 95% CI (1.39, 2.85). The weighted MSM estimate is reduced to OR=1.52 (0.73 – 3.19) versus OR=1.21 (0.79, 1.88) for the entire cohort. Proportionally, the reduction in odds ratio with MSM adjustment is similar (47% reduction in mandated states versus 39% in all states).

Discussion

Results of our study revealed that the simple unadjusted and unweighted analysis showed significantly increased risk of suicide attempt and self-inflicted injury when patients were receiving antidepressant treatment for both databases. In both databases, addition of potentially confounding covariates to the model decreased the magnitude of this relationship, but it remained statistically significant. MSM revealed a non-significant relationship between antidepressant treatment and suicide attempt and self-inflicted injury in both databases, with point estimates of 1.05 and 1.21 for LifeLink and MarketScan respectively. These findings suggest that imbalance in both static and dynamic characteristics of patients in terms of the treatment selection process lead to the appearance

of a significant association between antidepressant treatment and suicide attempt and self-inflicted injury. The MSM estimated treatment effects translate to number needed to harm of 1429 and 909 respectively. The question is whether we want to deny treatment to the roughly 1000 patients who have a positive benefit to harm balance (and may become suicidal because of a poorly treated disorder) to avoid harm to one patient who may or may not become suicidal because of treatment. Similar results were obtained when the analysis was restricted to treatment with SSRIs only (point estimates of 1.12 and 1.25 for LifeLink and MarketScan respectively). Our use of MSM combined with good temporal resolution of these data allowed us to adjust for the association between suicidal risk and initiation of antidepressant treatment, and provide a more realistic estimate of any possible relationship between antidepressant treatment and suicide attempt and self-inflicted injury.

There are several limitations of this study. First, suicide attempt and self-inflicted injury may be under-reported in that doctors may treat a suicide attempt or self-inflicted injury but classify it under an unrelated ICD-9 code. However, as noted by Bowie and Shafer[22], "These codes [E950–E959] are used only if the condition is truly deemed a suicide or self-inflicted injury. Use of these codes on an insurance claim can have a devastating impact on how the claim is handled and can have far-reaching effects for a person who tries to obtain insurance in the future." Second, while we have endeavored to include as many observed confounders as possible, there are likely other unmeasured confounders which may remain unbalanced. Third, just because a prescription has been filled, does not mean that the medication was actually taken and/or taken at the time of the prescription fill. Fourth, we do not have data on completed suicide or mortality during follow-up, and unless the fatal suicide attempt or self-inflicted injury led to hospitalization or treatment, it would go undetected in the medical claims data.

MSM has been used previously in drug safety studies to examine the effectiveness of beta blockers[25], angiotensin receptor blockers on mortality in patients with chronic heart failure[26], paracalcitral and survival in hemodialysis patients[27], the effect of aspirin on cardiovascular mortality[28], estrogen and progesterone on coronary heart disease[29], the effect of antidepressants on viral suppression in homeless HIV patients. Valenstein[30] explored several different statistical strategies including MSM in comparing the effects of different antidepressants on completed suicide in adult veterans and found generally similar results across the different antidepressants.

A curious result is that the rate of suicide attempt and self-inflicted injury was almost double for both treated and untreated occasions in the LifeLink database than in the MarketScan database. An even larger discrepancy was seen for suicide attempt and self-inflicted injury in the 6 months prior to the new index episode. In an attempt to better understand this difference, we examined the regional representations from where the patients were drawn from and discovered that they are in fact quite different. The LifeLink database is characterized by a larger Midwest and Northeast representation (52.5% and 21.3%) versus the South (12.39%) and West (13.81%). By contrast, the MarketScan database has just the opposite coverage, with greatest representation in the south (39.76%) and west (22.53%) relative to the LifeLink data, and less representation in the Midwest (30.24%) and Northeast (7.37%) than the LifeLink database. These differences in regional sampling may account for

factors that increase the overall risk of suicide attempt and self-inflicted injury, for example African Americans have a greater proportional representation in the south and have lower suicide rates than whites[16]. It should be noted that the difference in suicide attempt and self-inflicted injury rates between treated and untreated time-intervals was remarkably similar between the two datasets as was the results of the MSM analysis. State mandates do not account for the difference in overall suicide attempt and self-inflicted injury rates between the two databases (states with mandates 0.47% (0.37% off treatment versus 1.00% on treatment) versus and 0.70% (0.63% off treatment versus 1.05% on treatment) in states without mandates. Further study of regional differences in suicide rates and factors that may influence differential rates of suicide related claims in different medical claims databases should be a high priority in pharmacoepidemiology.

In conclusion, we find that both unadjusted and adjusted traditional time-to-event models find a statistically significant association between antidepressant treatment and suicidal behavior in children and adolescents. The use of MSM reveals that the majority of this effect and its statistical significance are produced by treatment selection effects in which dynamic characteristics of patients and prior treatment influence the likelihood of both future treatment and suicide attempt and self-inflicted injury. If there is a direct effect of antidepressant treatment on suicide attempt and self-inflicted injury rates in youth, it is much smaller in magnitude than has been previously suggested.

Acknowledgments

This work was supported by NIMH grant MH8012201 (RDG) and AHRQ grants 1U18HS016973 (RDG) and T32HS000084 (MCP). We are indebted to Dr. Bruce Lambert from the University of Illinois at Chicago for comments on an earlier draft. Dr. Gibbons has been an expert witness in suicide cases for the US Department of Justice, Wyeth and Pfizer.

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Key points

- In 2004 FDA placed a black box warning on antidepressants for risk of suicidal thoughts and behavior in children and adolescents based on clinical trial results, although some studies have questioned the causal link between antidepressant use and suicide.
- Large claim datasets reflect actual clinical practice but causal links are obscured by confounding by indication and time-varying effects of variables that affect both future antidepressant treatment and suicide attempts and self-inflicted injury.
- Marginal structural models (MSM) have been developed to take into account time-varying confounding in both observational and clinical trials with dynamic treatment assignment.
- We use two large claim datasets and find that after taking into account the time-varying effect of confounders the apparent link between antidepressant use and suicide attempts and self-inflicted injury is diminished and not statistically significant.
- If there is a direct effect of antidepressant treatment on suicide attempt and self-inflicted injury rates in youth, it is much smaller in magnitude than those from previous studies.

Table 1

Distribution of Covariates used in MSM

Covariates	MarketScan Mean or %	LifeLink Mean or %
Demographics		
Age, mean	14.3	14.1
Female	58.0	56.4
Comorbid Conditions		
Prior Suicide Attempts* (ICD-9: E950–E959, X60–X89, Y87.0)	0.2	1.3
ADHD (ICD-9: 314.0x)	7.7	13.3
Anxiety Spectrum Disorder (ICD-9: 300.0x)	7.2	10
Bipolar Disorder (ICD-9: 296.4x, 296.5x, 296.6x, 296.7x, 296.8x)	3.9	5.6
Psychotic Disorder (ICD-9: 293.xx, 296.9, 297.xx, 298.xx, 299.xx)	5.6	4.3
Seizure Disorder (ICD-9: 345.8x, 345.9x, 780.39)	0.6	0.9
Conduct Disorder (ICD-9: 312.xx)	1.8	3.9
Medication Use		
Antihistamines	1.5	2.4
Antipsychotics	2.7	2.0
Antiepileptics	2.0	2.3
Anxiolytics	1.0	0.8
Lithium	0.2	0.2
Narcotic Analgesics	1.3	1.3
Sedative/Hypnotics	0.4	0.4
Health Service Use		
Psychiatric Hospitalization	3.6	1.9
Psychotherapy visit	41.9	37.4

* includes self-inflicted injury

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2016 February 01.

Table 2

Dynamic Predictors of Antidepressant Treatment

	MarketScan			LifeLink		
Variable	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Month 0	0.71	0.69–0.74	<.0001	0.88	0.86–0.89	<.0001
Month 1	1.50	1.46–1.54	<.0001	1.32	1.30–1.33	<.0001
Month 2	1.30	1.27–1.34	<.0001	1.23	1.22–1.24	<.0001
Month 3	1.20	1.17–1.24	<.0001	1.15	1.13–1.16	<.0001
Month 4	1.12	1.09–1.15	<.0001	1.07	1.06–1.08	<.0001
Sex (Male)	1.06	1.02–1.09	0.002	1.21	1.18–1.23	<.0001
Age	1.63	1.51–1.75	<.0001	1.31	1.26–1.36	<.0001
Age^2	0.99	0.98–0.99	<.0001	0.99	0.99–1.00	<.0001
Prior Suicide Attempts*	1.07	0.77–1.50	0.681	1.02	0.93–1.11	0.707
ADHD	1.07	1.01–1.13	0.014	1.25	1.22–1.29	<.0001
Anxiety	1.58	1.50–1.66	<.0001	1.83	1.78–1.89	<.0001
Bipolar	0.86	0.80–0.93	0.000	0.33	0.31–0.35	<.0001
Conduct Disorder	1.09	0.98–1.21	0.116	1.10	1.05–1.15	<.0001
Psychotic Disorder	1.21	1.14–1.29	<.0001	1.19	1.14–1.24	<.0001
Seizure	1.17	0.99–1.38	0.062	0.91	0.84–0.98	0.015
Narcotic Analgesics	1.07	0.99–1.16	0.081	1.05	1.02–1.08	0.002
Antiepileptics	2.28	2.10–2.47	<.0001	1.80	1.71–1.90	<.0001
Antihistamine	1.41	1.30–1.52	<.0001	1.31	1.27–1.35	<.0001
Lithium	1.19	0.87–1.63	0.269	1.42	1.20–1.67	<.0001
Antipsychotics	4.17	3.90–4.46	<.0001	2.42	2.30–2.56	<.0001
Anxiolytics	2.28	2.07–2.50	<.0001	1.52	1.44–1.60	<.0001
Sedative/Hypnotics	2.86	2.48–3.29	<.0001	1.66	1.53–1.80	<.0001
Psychiatric Hospitalization	0.70	0.65–0.75	<.0001	1.15	1.12–1.18	<.0001
Psychotherapy Visit	1.30	1.27–1.33	<.0001	1.12	1.11–1.13	<.0001

Note: Month 5 is the reference

* includes self-inflicted injury