Original Investigation

Antidepressant Dose, Age, and the Risk of Deliberate Self-harm

Matthew Miller, MD, ScD; Sonja A. Swanson, ScM; Deborah Azrael, PhD; Virginia Pate, PhD, PhD; Til Stürmer, MD, ScD

IMPORTANCE A comprehensive meta-analysis of randomized trial data suggests that suicidal behavior is twice as likely when children and young adults are randomized to antidepressants compared with when they are randomized to placebo. Drug-related risk was not elevated for adults older than 24 years. To our knowledge, no study to date has examined whether the risk of suicidal behavior is related to antidepressant dose, and if so, whether risk depends on a patient's age.

OBJECTIVE To assess the risk of deliberate self-harm by antidepressant dose, by age group.

DESIGN, SETTING, AND PARTICIPANTS This was a propensity score–matched cohort study using population-based health care utilization data from 162 625 US residents with depression ages 10 to 64 years who initiated antidepressant therapy with selective serotonin reuptake inhibitors at modal or at higher than modal doses from January 1, 1998, through December 31, 2010.

MAIN OUTCOMES AND MEASURES *International Classification of Diseases, Ninth Revision (ICD-9)* external cause of injury codes E950.x-E958.x (deliberate self-harm).

RESULTS The rate of deliberate self-harm among children and adults 24 years of age or younger who initiated high-dose therapy was approximately twice as high as among matched patients initiating modal-dose therapy (hazard ratio [HR], 2.2 [95% CI, 1.6-3.0]), corresponding to approximately 1 additional event for every 150 such patients treated with high-dose (instead of modal-dose) therapy. For adults 25 to 64 years of age, the absolute risk of suicidal behavior was far lower and the effective risk difference null (HR, 1.2 [95% CI, 0.8-1.9]).

CONCLUSIONS AND RELEVANCE Children and young adults initiating therapy with antidepressants at high-therapeutic (rather than modal-therapeutic) doses seem to be at heightened risk of deliberate self-harm. Considered in light of recent meta-analyses concluding that the efficacy of antidepressant therapy for youth seems to be modest, and separate evidence that antidepressant dose is generally unrelated to therapeutic efficacy, our findings offer clinicians an additional incentive to avoid initiating pharmacotherapy at high-therapeutic doses and to closely monitor patients starting antidepressants, especially youth, for several months.

Invited Commentary page 909

Supplemental content at jamainternalmedicine.com

CME Quiz at jamanetworkcme.com

Author Affiliations: Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts (Miller, Azrael); Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts (Swanson); Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill (Pate, Stürmer).

Corresponding Author: Matthew Miller, MD, ScD, Department of Health Policy and Management, Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115 (mmiller@hsph.harvard.edu).

JAMA Intern Med. 2014;174(6):899-909. doi:10.1001/jamainternmed.2014.1053
Published online April 28, 2014.

The US Food and Drug Administration's (FDA) meta-analysis of antidepressant trials found that children randomized to receive antidepressants had twice the rate of suicidal ideation and behavior compared with children who received placebo.[1] Meta-analysis of adult placebo-controlled trials found that participants 18 to 24 years of age randomized to receive antidepressants were at elevated risk of suicidal thoughts and behavior, those 25 to 64 years of age were at equal risk, and those 65 years or older were at lower risk.[2]

Nonrandomized studies can address some of the limitations of existing randomized antidepressant trials, including their short duration, the small number of suicide-related events observed, the homogeneity of participants, and the different antidepressant types and doses administered across trials. Nonrandomized studies, however, require careful consideration of confounding, especially with respect to the indication for using antidepressants in the first place.[3-8] To minimize such confounding, rigorous observational studies have focused on treatment initiation[9] and avoided nonuser comparison groups.[10,11] In addition, because suicide attempts may lead clinicians to prescribe antidepressants, careful research has eschewed before vs after study designs and instead focused on whether deliberate self-harm (DSH) differs across antidepressant classes and agents. In general, these studies have reported either no evidence of differential risk across class or agent, or small and inconsistent differences.[12-19]

Patients exposed to higher doses of antidepressants tend to experience more frequent and severe adverse effects, including putatively suicidogenic ones, such as akathisia,[20-27] compared with patients prescribed lower doses.[28,29] Despite this dose-related phenomenon and scant evidence that higher doses are more effective in alleviating depressive symptoms,[28,29] neither the FDA meta-analyses nor any observational study to date has examined whether the risk of suicidal behavior is related to antidepressant dose. The current study takes up this question among a cohort of initiators of antidepressant therapy and addresses as well whether dose-related risk is modified by a patient's age.

Methods

Patients and Data Source

The current cohort study involved 162 625 patients 10 to 64 years of age with a depression diagnosis who initiated therapy with selective serotonin reuptake inhibitors (SSRIs) from January 1, 1998, through December 31, 2010. Initiation was defined as filling an SSRI antidepressant prescription without evidence of prescriptions fills for any class of antidepressants in the preceding 12 months. Analyses focus on the first treatment episode. Eligibility required evidence of depression as indicated by an *International Classification of Diseases, Ninth Revision (ICD-9)* code for depression recorded during the 12 months prior to antidepressant initiation (**Table 1** and **Table 2**). To allow uniform assessment and selection of all patients, participants were required to be actively enrolled in a contributing health plan for the 15 months prior to initiation (ie, 12 months for baseline covariate assessment + 2 months [ie, a 60-day grace period] + 30 days [ie, the usual days' supply]). The cohort study was based on observational health care utilization data. Informed consent was not obtained for persons in the data set. The study was exempted by the Harvard School of Public Health institutional review board.

The PharMetrics Claims Database used in this study comprises commercial health plan information obtained from managed care plans throughout the United States. The database includes medical and pharmaceutical claims for over 61 million unique patients from over 98 health plans, and includes *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) inpatient and outpatient diagnoses, Current Procedural Terminology 4 and Healthcare Common Procedure Coding System procedure codes, and both retail and mail-order records of all reimbursed dispensed prescriptions. Our analyses focus on persons younger than 65 years, the age group for which our data are nationally representative of the commercially insured and for which we had sufficient sample size.

Antidepressant Medication Exposure

We restricted analyses to new initiators of therapy with antidepressants, rather than prevalent users, because such a design allows us to detect adverse events that follow soon after therapy with a drug is started, assess risks over time, and control for selection bias with baseline patient characteristics that are not influenced by effects of antidepressant treatment. Incident user designs also mitigate potential bias owing to a patient's drug exposure history influencing current treatment assignment. To further minimize potential confounding by the class of antidepressants prescribed and the use of unusual agents, analyses were restricted to patients initiating therapy with the most commonly prescribed SSRIs (citalopram hydrobromide, sertraline hydrochloride, and fluoxetine hydrochloride), which together constitute 67% of all SSRI therapy initiated.

Patients were assigned to 1 of 3 empirically derived dose categories (modal dose, higher than modal, lower than modal) based on the distribution of doses prescribed among antidepressant initiators. In the 10- to 24-year cohort there were 32 504 in the modal dose category, 7117 in the higher than modal dose category, and 14 542 in the below modal dose category; in the 25- to 64-year-old cohort there were 99 316 in the modal dose category, 23 668 in the higher than modal dose categoy, and 20 065 in the lower than modal dose category. The modal daily dose for citalopram hydrobromide, sertraline hydrochloride, and fluoxetine hydrochloride were, respectively, 20 mg/d, 50 mg/d, and 20 mg/d. Participants who received doses below our empirically derived modal dose often received doses considered below the minimal effective dose for depression[30-32]; to minimize potential confounding, analyses were restricted to participants who received modal dose or doses higher than the modal dose. Patients receiving index doses in excess of the recommended maximum therapeutic dose constituted less than 2% of all patients (112 in the 10- to 24-year-cohort and 677 in the 25- to 64-year-old cohort) and, for similar reasons, were excluded from analysis; maximum daily doses for citalopram hydrobromide, sertraline

Table 1. Baseline Characteristics of the Study Cohort, by Dose, Ages 10 to 24 Years

Baseline Characteristic[a]	Cohort, No. (%)			
	Prematched[b]		Propensity Score–Matched	
	Modal Dose (n = 32 504)	High Dose (n = 7117)	Modal Dose (n = 13 948)	High Dose (n = 7108)
Age, y				
10-15	6346 (19.5)	1423 (20.0)	2964 (21.3)	1421 (20.0)
16-19	14 995 (46.1)	3182 (44.7)	6104 (43.8)	3179 (44.7)
20-24	11 163 (34.3)	2512 (35.3)	4880 (35.0)	2508 (35.3)
Male sex	10 949 (33.7)	2704 (38.0)	5054 (36.2)	2698 (38.0)
Severity level of depression diagnosis[c]				
Tier 1: Primary inpatient diagnosis ≤30 d preindex	1296 (4.0)	315 (4.4)	601 (4.3)	315 (4.4)
Tier 2: Primary inpatient diagnosis 31-360 d preindex	202 (0.6)	74 (1.0)	128 (0.9)	72 (1.0)
Tier 3: Nonprimary inpatient diagnosis ≤360 d preindex	616 (1.9)	194 (2.7)	364 (2.6)	191 (2.7)
Tier 4: ≥2 Outpatient diagnoses ≤360 d preindex	17 707 (54.5)	4425 (62.2)	8670 (62.2)	4421 (62.2)
Tier 5: 1 Inpatient diagnosis ≤360 d preindex	12 683 (39.0)	2109 (29.6)	4185 (30.0)	2109 (29.7)
Anxiety disorders	6808 (20.9)	1841 (25.9)	3501 (25.1)	1836 (25.8)
Deliberate self-harm	451 (1.4)	106 (1.5)	183 (1.3)	104 (1.5)
Primary inpatient depression diagnosis	1498 (4.6)	389 (5.5)	729 (5.2)	387 (5.4)
No depression diagnosis within 30 d of index date	3892 (12.0)	1327 (18.6)	2389 (17.1)	1318 (18.5)
Suicidal ideation ≤30 d prior to anxiety disorder initiation (2006 forward only)	522 (2.6)	113 (2.9)	254 (3.1)	113 (2.9)
Attention-deficit/hyperactivity disorder	3218 (9.9)	856 (12.0)	1577 (11.3)	854 (12)
Cognitive impairment or dementia	10 (0.0)	3 (0.0)	6 (0.0)	3 (0.0)
Personality disorder	288 (0.9)	74 (1.0)	145 (1.0)	74 (1.0)
Substance abuse	2787 (8.6)	655 (9.2)	1243 (8.9)	652 (9.2)
Use of any opiate	7239 (22.3)	1486 (20.9)	2908 (20.8)	1484 (20.9)
Distinct drug prescriptions filled, No.				
1 (antidepressant only)	5082 (15.6)	1349 (19.0)	2557 (18.3)	1346 (18.9)
2-3	9967 (30.7)	2229 (31.3)	4428 (31.7)	2226 (31.3)
4-5	7379 (22.7)	1546 (21.7)	3056 (21.9)	1546 (21.8)
6-9	7212 (22.2)	1400 (19.7)	2763 (19.8)	1399 (19.7)
≥10	2864 (8.8)	593 (8.3)	1144 (8.2)	591 (8.3)
≥1 Psychiatric hospitalizations	1554 (4.8)	418 (5.9)	774 (5.5)	413 (5.8)
Outpatient visits, No.				
0-4	7308 (22.5)	1447 (20.3)	2818 (20.2)	1447 (20.4)
5-9	9635 (29.6)	2021 (28.4)	4010 (28.7)	2021 (28.4)
10-19	9904 (30.5)	2236 (31.4)	4461 (32.0)	2235 (31.4)
20-39	4715 (14.5)	1134 (15.9)	2165 (15.5)	1132 (15.9)
≥40	942 (2.9)	279 (3.9)	494 (3.5)	273 (3.8)
Hospitalizations				
≥1 for substance abuse	205 (0.6)	59 (0.8)	114 (0.8)	59 (0.8)
≥1 for other reasons	2148 (6.6)	468 (6.6)	922 (6.6)	467 (6.6)
Cancer				
Lung	2 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
Colorectal	3 (0.0)	0	0	0
Other malignant neoplasm	153 (0.5)	45 (0.6)	80 (0.6)	45 (0.6)
Cardiac arrhythmias	554 (1.7)	148 (2.1)	261 (1.9)	148 (2.1)
Congestive heart failure	20 (0.1)	5 (0.1)	10 (0.1)	5 (0.1)
Arthritis	70 (0.2)	8 (0.1)	16 (0.1)	8 (0.1)
Cerebrovascular disease	72 (0.2)	19 (0.3)	37 (0.3)	19 (0.3)
Cluster headaches or migraines	1168 (3.6)	237 (3.3)	469 (3.4)	236 (3.3)
Diabetes mellitus	386 (1.2)	91 (1.3)	173 (1.2)	90 (1.3)
Disorders of the eye	17 (0.1)	1 (0.0)	2 (0.0)	1 (0.0)

(continued)

Table 1. Baseline Characteristics of the Study Cohort, by Dose, Ages 10 to 24 Years (continued)

Baseline Characteristic[a]	Cohort, No. (%)			
	Prematched[b]		Propensity Score–Matched	
	Modal Dose (n = 32 504)	High Dose (n = 7117)	Modal Dose (n = 13 948)	High Dose (n = 7108)
Gait or balance disorder	108 (0.3)	18 (0.3)	37 (0.3)	18 (0.3)
Postural hypotension	57 (0.2)	22 (0.3)	40 (0.3)	22 (0.3)
Hyperparathyroidism	5 (0.0)	0	0	0
Osteoarthritis	112 (0.3)	37 (0.5)	64 (0.5)	35 (0.5)
Osteoporosis	12 (0.0)	5 (0.1)	8 (0.1)	4 (0.1)
Parkinson disease	1	0	0	0
Seizures	216 (0.7)	63 (0.9)	118 (0.8)	61 (0.9)
Urinary incontinence	163 (0.5)	36 (0.5)	73 (0.5)	35 (0.5)
Physician prescriber type				
General practitioner or internist	14 430 (44.4)	2358 (33.1)	4694 (33.7)	2358 (33.2)
Psychiatrist	6735 (20.7)	2108 (29.6)	3970 (28.5)	2101 (29.6)
Other	11 339 (34.9)	2651 (37.3)	5284 (37.8)	2649 (37.2)
SSRI				
Citalopram hydrobromide	9500 (29.2)	1586 (22.3)	3238 (23.2)	1586 (22.3)
Fluoxetine hydrochloride	11 005 (33.9)	1203 (16.9)	2307 (16.5)	1203 (16.9)
Sertraline hydrochloride	11 999 (36.9)	4328 (60.8)	8403 (60.2)	4319 (60.8)

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

[a] For our younger-aged cohorts, the strongest predictors of initiating therapy with high- rather than modal-dose antidepressants (when all factors in Table 1 and Table 2 are simultaneously adjusted) include having been admitted to a psychiatric hospital in the year prior to starting antidepressant therapy, having an internist (rather than a psychiatrist or other health professional) prescribe the initial antidepressant, taking no prescription medications other than the antidepressant initiated, and being prescribed sertraline rather than either fluoxetine or citalopram (see eTable 1 and eTable 2 in Supplement).

[b] From January 1, 1998, through December 31, 2010, 624 171 patients initiated therapy with 1 of the study antidepressants; 607 538 initiated monotherapy. Of the 222 896 patients with baseline depression and no prior antidepressant use in the washout period, 202 605 were 10 to 64 years of age. Of these, 167 092 initiated therapy at or above the modal dose (166 253 within the therapeutic range (ie, excluding patients with subtherapeutic doses), and 162 605 did so without baseline bipolar disorder or schizophrenia (162 605 within the therapeutic range).

[c] *International Classification of Diseases, Ninth Revision* codes 296.2x, 296.3x, 298.0x, 300.4x, 309.0x, 309.1x, 311.xx, 293.83, 296.90, 309.28.

hydrochloride, and fluoxetine hydrochloride were, respectively, 40 mg/d, 200 mg/d, and 80 mg/d. Patients initiating therapy with more than 1 drug or with more than 1 dosing regimen were also excluded from analyses.

Follow-up and Study End Point

Exposure status was assigned based on the initiated medication. Study follow-up began on the day after initiation of the first antidepressant therapy. When a dispensing occurred before the previous prescription should have run out, use of the new prescription was assumed to have begun the day after the end of the old prescription. Primary analyses used a 60-day grace period (≤60 days beyond the provided days' supply can elapse before censoring).

Patients were censored the date they switched agents, added other antidepressant agents, changed dose, 360 days after the index date, ended enrollment in their health insurance plan, engaged in DSH, or the end of the study period, whichever came first.

The first occurrence of DSH was our outcome of interest, and it was defined as a medical claim with an *ICD-9* external cause of injury code (e-code) (E950.x-E958.x).

Patient Characteristics

Baseline patient characteristics included age, sex, medical comorbidities, treatment history, and concomitant medication use in the 12 months prior to initiation of antidepressant therapy. Psychiatric risk factors included the number of acute psychiatric hospitalizations, the number of acute hospitalizations for substance abuse, psychiatric comorbidity, and prior DSH. A hierarchy of depression was constructed as a function of the proximity of the most recent depression diagnosis to antidepressant initiation and whether the diagnosis was rendered during an inpatient stay or an outpatient visit.

Statistical Analysis

Patients were divided into 2 age groups guided by the age-related risk of suicidal behavior identified in the FDA's meta-analyses (ages 10-24 years vs 25-64 years). We estimated propensity scores for treatment initiation of high vs modal dose for each age group separately based on the patient characteristics described in the previous subsection (age is modeled as a continuous variable within each cohort). Up to 2 patients receiving a modal dose were matched to every patient receiving a high dose using an adaptation of a published propensity score algorithm.[33] Thus, the research question we addressed is what would have happened, with respect to future DSH, if people who initiated high-dose therapy had instead initiated with modal-dose therapy.

Crude rates of DSH were calculated over the 1-year exposure period (ie, subject to censoring as described herein). Crude rates were also reported for 3 time periods after initiating

Table 2. Baseline Characteristics of the Study Cohort, by Dose, Ages 25 to 64 Years

Baseline Characteristic[a]	Cohort, No. (%)			
	Prematched[b]		Propensity Score–Matched	
	Modal Dose (n = 99 316)	High Dose (n = 23 668)	Modal Dose (n = 45 002)	High Dose (n = 23 637)
Age, y				
25-40	42 808 (43.1)	9622 (40.7)	18 619 (41.4)	9618 (40.7)
41-55	41 538 (41.8)	10 156 (42.9)	19 260 (42.8)	10 143 (42.9)
≥56	14 970 (15.1)	3890 (16.4)	7123 (15.8)	3876 (16.4)
Male sex	32 547 (32.8)	8381 (35.4)	15 672 (34.8)	8365 (35.4)
Severity level of depression diagnosis[c]				
Tier 1: Primary inpatient diagnosis ≤30 d preindex	836 (0.8)	321 (1.4)	563 (1.3)	321 (1.4)
Tier 2: Primary inpatient diagnosis 31-360 d preindex	126 (0.1)	80 (0.3)	102 (0.2)	77 (0.3)
Tier 3: Nonprimary inpatient diagnosis ≤360 d preindex	2105 (2.1)	736 (3.1)	1290 (2.9)	735 (3.1)
Tier 4: ≥2 Outpatient diagnoses ≤360 d preindex	48 237 (48.6)	13 610 (57.5)	25 532 (56.7)	13 585 (57.5)
Tier 5: 1 Outpatient diagnosis ≤360 d preindex	48 012 (48.3)	8921 (37.7)	17 515 (38.9)	8919 (37.7)
Anxiety disorders	20 844 (21.0)	5731 (24.2)	10 764 (23.9)	5719 (24.2)
Deliberate self-harm	217 (0.2)	68 (0.3)	119 (0.3)	68 (0.3)
Primary inpatient depression diagnosis	962 (1.0)	401 (1.7)	665 (1.5)	398 (1.7)
No depression diagnosis within 30 d of index date	15 710 (15.8)	6680 (28.2)	11 499 (25.6)	6649 (28.1)
Suicidal ideation ≤30 d prior to anxiety disorder initiation (2006 forward only)	406 (0.6)	115 (0.8)	244 (0.9)	115 (0.8)
Cognitive impairment or dementia	70 (0.1)	30 (0.1)	43 (0.1)	29 (0.1)
Personality disorder	462 (0.5)	184 (0.8)	299 (0.7)	178 (0.8)
Substance abuse	8853 (8.9)	2343 (9.9)	4265 (9.5)	2336 (9.9)
Use of any opiate	32 512 (32.7)	7422 (31.4)	14 469 (32.2)	7417 (31.4)
Distinct drug prescriptions filled, No.				
1 (antidepressant only)	9018 (9.1)	2892 (12.2)	5096 (11.3)	2877 (12.2)
2-3	23 047 (23.2)	5972 (25.2)	10 963 (24.4)	5963 (25.2)
4-5	20 807 (21.0)	4676 (19.8)	9117 (20.3)	4671 (19.8)
6-9	26 773 (27.0)	5828 (24.6)	11 395 (25.3)	5826 (24.6)
≥10	19 671 (19.8)	4300 (18.2)	8431 (18.7)	4300 (18.2)
≥ 1 Psychiatric hospitalizations	1025 (1.0)	419 (1.8)	698 (1.6)	416 (1.8)
Outpatient visits, No.				
0-4	18 846 (19.0)	4217 (17.8)	8087 (18.0)	4213 (17.8)
5-9	24 715 (24.9)	5479 (23.1)	10 549 (23.4)	5477 (23.2)
10-19	29 477 (29.7)	6890 (29.1)	13 130 (29.2)	6885 (29.1)
20-39	19 340 (19.5)	4982 (21.0)	9378 (20.8)	4971 (21.0)
≥40	6938 (7.0)	2100 (8.9)	3858 (8.6)	2091 (8.8)
Hospitalizations, No.				
≥ 1 for substance abuse	483 (0.5)	165 (0.7)	300 (0.7)	165 (0.7)
≥ 1 for other reasons	11 034 (11.1)	2720 (11.5)	5171 (11.5)	2716 (11.5)
Cancer				
Lung	203 (0.2)	50 (0.2)	96 (0.2)	50 (0.2)
Breast	125 (0.1)	25 (0.1)	46 (0.1)	25 (0.1)
Colorectal	218 (0.2)	53 (0.2)	103 (0.2)	53 (0.2)
Prostate	272 (0.3)	62 (0.3)	126 (0.3)	62 (0.3)
Other malignant neoplasm	3155 (3.2)	803 (3.4)	1485 (3.3)	799 (3.4)
Attention-deficit/hyperactivity disorder	1259 (1.3)	474 (2.0)	781 (1.7)	467 (2.0)
Cardiac arrhythmias	3591 (3.6)	946 (4.0)	1760 (3.9)	944 (4.0)
Congestive heart failure	962 (1.0)	311 (1.3)	531 (1.2)	311 (1.3)
Arthritis	856 (0.9)	250 (1.1)	462 (1.0)	248 (1.0)
Cerebrovascular disease	1859 (1.9)	525 (2.2)	953 (2.1)	524 (2.2)
Diabetes mellitus	7514 (7.6)	2077 (8.5)	3640 (8.1)	1997 (8.5)

(continued)

Table 2. Baseline Characteristics of the Study Cohort, by Dose, Ages 25 to 64 Years (continued)

Baseline Characteristic[a]	Cohort, No. (%)			
	Prematched[b]		Propensity Score–Matched	
	Modal Dose (n = 99 316)	High Dose (n = 23 668)	Modal Dose (n = 45 002)	High Dose (n = 23 637)
Cluster headaches or migraines	4283 (4.3)	1164 (4.9)	2117 (4.7)	1161 (4.9)
Disorders of the eye	117 (0.1)	29 (0.1)	57 (0.1)	29 (0.1)
Gait or balance disorder	964 (1.0)	291 (1.2)	501 (1.1)	290 (1.2)
Postural hypotension	184 (0.2)	47 (0.2)	87 (0.2)	46 (0.2)
Hyperparathyroidism	141 (0.1)	34 (0.1)	70 (0.2)	34 (0.1)
Osteoarthritis	6004 (6.0)	1695 (7.2)	3034 (6.7)	1689 (7.1)
Osteoporosis	1479 (1.5)	365 (1.5)	689 (1.5)	365 (1.5)
Parkinson disease	94 (0.1)	17 (0.1)	36 (0.1)	17 (0.1)
Seizures	650 (0.7)	211 (0.9)	365 (0.8)	210 (0.9)
Urinary incontinence	1002 (1.0)	300 (1.3)	562 (1.2)	299 (1.3)
Physician prescriber type				
General practitioner or internist	59 059 (59.5)	11 501 (48.6)	22 791 (50.6)	11 500 (48.7)
Psychiatrist	11 012 (11.1)	4902 (20.7)	8132 (18.1)	4872 (20.6)
Other	29245 (29.4)	7265 (30.7)	14079 (31.3)	7265 (30.7)
SSRI				
Citalopram hydrobromide	37 172 (37.4)	6465 (27.3)	13 063 (29.0)	6465 (27.4)
Fluoxetine hydrochloride	27 061 (27.2)	3742 (15.8)	6834 (15.2)	3742 (15.8)
Sertraline hydrochloride	35 083 (35.3)	13 461 (56.9)	25 105 (55.8)	13 430 (56.8)

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

[a] For the older-aged cohorts, the strongest predictors of being initiated with high- rather than modal-dose antidepressants include having an internist (rather than a psychiatrist or other health professional) prescribe the initial antidepressant, not taking prescription medications other than the antidepressant initiated, and being prescribed sertraline rather than either fluoxetine or citalopram (see eTable 2 in Supplement).

[b] From January 1, 1998, through December 31, 2010, 624 171 patients initiated therapy with 1 of the study antidepressants; 607 538 initiated monotherapy. Of the 222 896 patients with baseline depression and no prior antidepressant use in the washout period, 202 605 were 10 to 64 years of age. Of these, 167 092 initiated therapy at or above the modal dose (166 253 within the therapeutic range (ie, excluding patients with subtherapeutic doses), and 162 605 did so without baseline bipolar disorder or schizophrenia (162 605 within the therapeutic range).

[c] *International Classification of Diseases, Ninth Revision* (codes 296.2x, 296.3x, 298.0x, 300.4x, 309.0x, 309.1x, 311.xx, 293.83, 296.90, 309.28.

therapy: days 1 to 30, days 31-90, and days 91-360. Exact methods were used to calculate 95% confidence intervals. Modified Poisson regression using an identity link was used to estimate the 90-day risk differences; Cox models were used to estimate hazard ratios (HRs).

Sensitivity analyses examined how robust our findings were to a range of grace periods. Additional subgroup analyses restricted participants to those without a prior suicide attempt and to those who had not received antidepressants in the 3 years prior to their index date. In mid-2005 a new diagnostic billing code for suicidal ideation became available. We used this historical development to assess the extent to which our primary analyses may have been confounded by this well-established predictor of DSH by examining the extent to which matched cohorts based on propensity score algorithms that did not incorporate suicidal ideation achieved balance on suicidal ideation and the extent to which adjusting for suicidal ideation as a covariate in Cox models attenuated the risk of suicide attempts associated with higher dose.

Bias analyses assessed the strength of residual confounding that would need to be present to fully explain associations found in our primary analyses.[34,35] Specifically, we estimated the strength of a single dichotomous unmeasured confounder that would be necessary to nullify the estimated 90-day risk difference. Bias in the risk difference is dependent on 2 factors: how predictive the hypothetical confounder is of attempts, and how imbalanced the confounder is across high- vs modal-dose treatment groups (both assessed on the additive scale). A priori, we expected depression severity (eg, prior inpatient stays or psychiatric comorbidities) and a history of suicidality (eg, prior ideation or attempts) to be the strongest potential confounders. Accordingly, we present the magnitude of confounding introduced by these measured confounders in the prematched cohort along with the bias analyses.

Results

Baseline patient characteristics in age-group-stratified, propensity score–matched cohorts of high- vs modal-dose users were well balanced across dose categories (Table 1 and Table 2). For example, the age and sex distributions among high- vs modal-dose initiators were almost identical, and the distribution of our constructed tiers of depression severity differed little across dose categories. Suicidal ideation was also closely balanced across dose cohorts within each age stratum even though it did not contribute to the matching algorithm. Approximately half of all patients (45%) with a depression diagnosis who initiated high-dose SSRIs therapy (30 785) filled prescrip-

Table 3. Rate of Deliberate Self-harm (DSH)[a] per 1000 Person-years, by Dose and Age Group Over the First Year After Initiating Therapy, and by Time Since Initiating Therapy

Dose	Patients Initiating Therapy, No.	DSH Events	Person-years ×1000	DSH Rate (per 1000 Person-years)	DSH Rate (95% CI) by Time Since Index Date (No. of Events), d		
					0-30	31-90	91-360
Age 10-24 y							
High	7116	74	2 351.10	31.5 (24.9-39.3)	51.8 (35.4-73.4) (n = 29 patients)	36.8 (25.6-51.2) (n = 32 patients)	14.1 (7.9-23.4) (n = 13 patients)
Modal	14 189	68	4 628.50	14.7 (11.5-18.5)	20.9 (13.6-30.8) (n = 23 patients)	19.0 (13.3-26.4) (n = 33 patients)	6.7 (3.7-11.3) (n = 12 patients)
Age 25-64 y							
High	23 637	32	9 855.74	3.2 (2.3-4.5)	4.2 (2.0-8.0) (n = 8 patients)	2.8 (1.4-5.2) (n = 9 patients)	3.1 (1.8-5.0) (n = 15 patients)
Modal	45 002	49	17 672.36	2.8 (2.1-3.6)	7.5 (5.1-10.8) (n = 27 patients)	2.2 (1.2-3.6) (n = 13 patients)	1.1 (0.5-2.0) (n = 9 patients)

[a] Acts of self-harm of undetermined intent are not included in analyses (and constitute 19% of self-harm events that occurred during treatment among antidepressant initiators in our cohort). Most DSH claims in our analyses (88%) resulted from visits to emergency departments or hospital admissions.

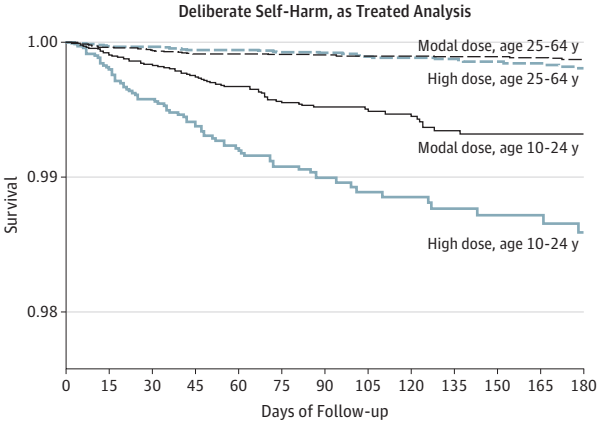
tions written by internists or general practitioners (13 859) (Table 1 and Table 2). Among patients younger than 25 years, internists and/or general practitioners wrote one-third (33%) of all initial high-dose prescriptions; psychiatrists and/or psychologists wrote 30% of all such prescriptions (Table 1). Among patients 25 to 64 years of age, internists and/or general practitioners wrote 49% of all such high-dose prescriptions; psychiatrists and/or psychologists wrote 21% of such prescriptions (Table 2). Roughly one-third (32%) of all high-dose antidepressant initiators received prescription written by other types of physicians (31% among patients aged 25 to 64 years [Table 2], 37% among patients aged ≤24 years [Table 1]; 10% of the latter physicians were pediatricians [data not shown]).

In our matched cohorts, 142 participants ages 10 to 24 years (68 modal-dose initiators, 74 high-dose initiators) engaged in DSH within 1 year of treatment initiation; the corresponding rates of DSH for the modal- vs high-dose initiators were 14.7 (95% CI, 11.5-18.5) and 31.5 (95% CI, 24.9-39.3) events per 1000 person-years, respectively. For participants ages 25 to 64 years, there were 81 such acts (49 in modal-dose initiators, 32 in high-dose initiators), corresponding to rates of 2.8 (95% CI, 2.1-3.6) and 3.2 (95% CI, 2.3-4.5) events per 1000 person-years for the modal- vs high-dose participants, respectively (**Table 3**). Although the hazards were proportional throughout the 1-year follow-up period, most of the events occurred in the first 3 months after initiation (Table 3, **Figure 1**).

Propensity score–matched analyses produced HRs that were substantially higher in the 10- to 24-year-old cohorts than in the older cohorts (**Table 4**): among 10- to 24-year-olds the rate of DSH among high-dose participants was approximately double that among modal-dose participants (HR, 2.2; 95% CI, 1.6-3.0); for participants 25 to 64 years of age, the HR was considerably lower (HR, 1.2; 95% CI, 0.8-1.9). The age group by dose interaction achieved statistical significance (P = .04) (data not shown).

Findings for the young cohort were robust to several different model specifications, including analyses that varied the grace period from 7 to 360 days, excluded participants without a DSH history prior to their index prescription. and among patients who were treatment naïve for at least 3 years (Table 4). The DSH HRs for high vs modal dose among those initiating

Figure 1. Probability of Remaining Free of Deliberate Self-harm and Time Since Initiating High- vs Modal-Dose Antidepressant Therapy, by Age Group



therapy in 2006 or later were found to be consistent with those found for the entire study period. Moreover, DSH HRs among this population were virtually identical regardless of whether Cox models adjusted for suicidal ideation (because suicidal ideation, while strongly predictive of the outcome, was not strongly related to dose) (Table 4).

In our primary analysis of the 10- to 24-year-old cohort, for every 1000 patients initiating high-dose therapy there were approximately 7 (7.3) more DSH events over the first 90 days of treatment among high-dose initiators compared with modal-dose initiators (95% CI, 3.6-11.1) (Table 4). The corresponding number needed to harm was 136. For the older cohort, the risk difference was effectively zero. Not all acts of DSH are e-coded in claims data (eg, some overdose by drug events are known to occur but lack e-codes, leading to underestimates of both intentional and unintentional overdose event rates). Although this is likely to be nondifferential with respect to our exposure of interest and therefore is unlikely to bias estimates appreciably because event rates are underestimated, the number needed to harm we derived is likely a conservative estimate (ie, an upper bound on the true number needed to harm).

Table 4. Deliberate Self-harm (DSH) Comparing Propensity Score–Matched Participants Initiating High-Dose vs Modal-Dose Antidepressant Therapy[a]

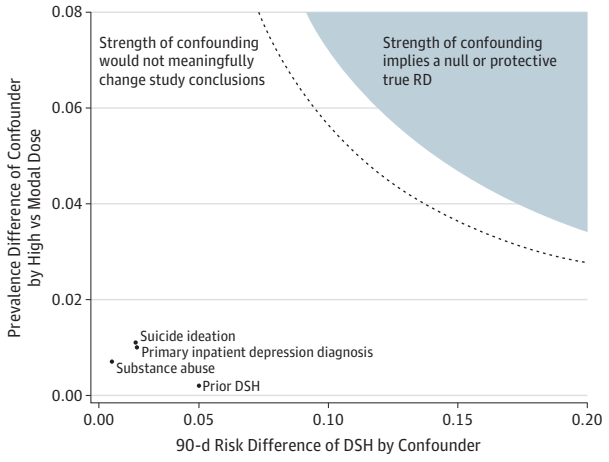
Analysis	(95% CI) 1-Year HR	(95% CI) 90-d Risk Difference per 1000 Persons	No. Needed to Harm
10- to 24-Year-Old Cohort			
Duration of grace period, d			
60[b]	2.2 (1.6 to 3.0)	7.3 (3.6 to 11.1)	136.2
7	2.1 (1.4 to 3.2)	18.2 (7.2 to 29.1)	55.0
14	2.0 (1.4 to 3.0)	15.8 (6.7 to 24.9)	63.2
30	2.3 (1.6 to 3.2)	12.7 (6.7 to 18.8)	78.4
90	2.1 (1.5 to 2.8)	6.9 (3.3 to 10.5)	145.0
180	2.0 (1.5 to 2.7)	6.9 (3.3 to 10.5)	145.0
360	1.7 (1.3 to 2.2)	6.9 (3.3 to 10.5)	145.0
First treatment carried forward	1.4 (1.1 to 1.8)	5.8 (2.9 to 8.7)	171.8
No history of baseline DSH	2.1 (1.5 to 3.0)	7.3 (3.7 to 10.9)	137.4
3-y treatment naive	1.7 (1.0 to 2.8)	6.5 (0.1 to 12.8)	154.8
2006-2010 data only: no SI adjustment	1.8 (1.2 to 2.6)	8.4 (2.8 to 14.1)	118.5
2006-2010 data only: adjusting for SI	1.8 (1.2 to 2.6)	8.9 (3.3 to 14.5)	112.6
25- to 64-Year-Old Cohort			
Duration of grace period, d			
60[b]	1.2 (0.8 to 1.9)	−0.2 (−0.8 to 0.4)	NS
7	1.0 (0.6 to 1.8)	−0.3 (−1.7 to 1.1)	NS
14	0.9 (0.5 to 1.5)	−0.6 (−1.9 to 0.6)	NS
30	1.0 (0.6 to 1.7)	−0.6 (−1.4 to 0.3)	NS
90	1.2 (0.8 to 1.9)	−0.2 (−0.8 to 0.3)	NS
180	1.3 (0.9 to 2.0)	−0.2 (−0.8 to 0.3)	NS
360	1.4 (0.9 to 2.0)	−0.2 (−0.8 to 0.3)	NS
First treatment carried forward	1.4 (1.0 to 1.9)	−0.1 (−0.7 to 0.5)	NS
No history of baseline DSH	1.1 (0.7 to 1.8)	−0.3 (−0.9 to 0.3)	NS
3-y treatment naive	2.1 (0.9 to 4.8)	0.7 (−0.4 to 1.7)	NS
2006-2010 data only: no SI adjustment	1.3 (0.8 to 2.3)	−0.1 (−1.0 to 0.7)	NS
2006-2010 data only: adjusting for suicidal ideation	1.3 (0.8 to 2.2)	−0.0 (−0.9 to 0.8)	NS

Abbreviations: DSH, deliberate self-harm; NS, not significant clinically or statistically; SI, suicidal ideation.

[a] Hazard ratios (HRs) for deliberate self-harm (DSH) during 1-year of follow-up comparing propensity score–matched participants initiating high-dose vs modal-dose antidepressant therapy, risk differences per 1000 persons over the first 90 days of therapy, and corresponding number of patients needed to be treated to result in 1 additional suicide attempt

[b] Primary analysis. Sensitivity analyses of our unmatched cohort produced HRs similar to those from our (propensity score) matched analyses, not only when models adjusted for (ie, included a covariate for) the propensity to be treated with high-dose therapy, but also in crude and age- and sex-adjusted models. For example, crude, age- and sex-adjusted, and propensity score–adjusted HRs (95% CIs) of our unmatched 10- to 24-year-old cohorts were, respectively, 1.72 (95% CI, 1.32-2.25), 1.77 (95% CI, 1.36-2.32), and 1.87 (95% CI, 1.42-2.46) (not shown).

Figure 2. Bias Analysis for 10- to 24-Year-Old Cohort



DSH indicates deliberate self-harm; RD, risk difference. The dotted line indicates the strength of confounding implied if true RD is 2 attempts per 1000. The shaded area indicates the strength of confounding implied if the true risk difference is null or protective.

Figure 2 depicts how strong a risk factor and how imbalanced a hypothetical unmeasured confounder would need to be in order to nullify our 90-day risk difference in the younger cohort. As can be seen, a putative confounder that would nullify our findings (or even reduce the risk difference to what we considered a clinically meaningful difference of 2 events per 1000 patients) would need to be both far more predictive of subsequent DSH than our most highly predictive covariates (history of DSH, suicidal ideation, substance abuse, or inpatient hospitalization for depression) and also an order of magnitude more imbalanced across dose levels than our most imbalanced prematched covariate. It is important to note that such an unmeasured confounder would need to be this strong in the *matched* cohort; that is, it would need to be very strongly associated with dose and subsequent DSH even after adjustment for all the measured confounders accounted for in the propensity score–matching process.

Discussion

To our knowledge, the current investigation is the first prospective cohort study to examine the relation between dose

of antidepressants and the risk of DSH. We found that the rate of DSH for children and young adults was approximately twice as large among patients initiating high-dose therapy compared with those initiating modal-dose therapy. Given the high baseline rates of DSH among these patients, we expect approximately 1 additional DSH event for every 136 patients 10 to 24 years of age who are treated with high-dose therapy (instead of modal-dose therapy). For the older cohorts, the absolute risk of DSH was far lower, and the difference in risk between the cohorts was effectively null.

Several possible mechanisms linking antidepressant use to suicidal behavior have been suggested,[20,23-26,36-39] including an early energizing effect that allows patients with depression to act on suicidal impulses, suicidogenic adverse effects (eg, akathisia, insomnia, panic attacks), episode-shifting effects (from depressive to manic episodes), and paradoxical worsening of depression. Although our study does not address the mechanisms whereby higher doses might lead to higher suicide risk, if depression-independent suicidogenic effects increase with dose, as has been observed for akathesia,[28] but antidepressive effects are insensitive to doses within a broad therapeutic range, as seems to be the case,[29,40-45] higher doses might produce a net tendency toward suicidal behavior.

To the extent that depression-independent suicidogenic effects of antidepressants exist, older adults may be less susceptible, on balance, if the antidepressive efficacy of antidepressants is superior for older adults compared with children and younger adults.[46,47] Our finding that dose-related suicide risk seems to be more pronounced among children and young adults might also reflect an age-related susceptibility to suicidogenic effects of antidepressants independent of depression severity, as was observed in randomized trials with placebo controls.[1]

The elevated risk of DSH we observe among youth receiving therapy with high-dose antidepressants compared with those receiving therapy with a modal dose might also be due to more frequent and severe drug discontinuation syndromes among patients receiving high-dose therapy.[48] Although we censor at known discontinuation of therapy, it is still possible that differential nonadherence and/or differential severity of withdrawal reactions due to nonadherence contributed to our findings. This form of nondifferential adherence would, however, bias findings to the null, as would poorer adherence that was related to untoward adverse effects, which in general tend to be more common among high-dose users, suggesting that our estimate of the risk of DSH associated with high-dose therapy is conservative. The robustness of our findings to grace periods as disparate as 1 week to 1 year also militates against withdrawal reactions playing a major role. Finally, the half-lives of our SSRIs are relatively long (range, 16-35 hours),[49] making severe withdrawal reactions less likely.

To examine the extent to which confounding not explicitly modeled in our propensity score adjustment may account for our results, we applied our primary matching algorithm, which did not include a covariate for baseline suicidal ideation, to data from 2006 through 2010. Baseline suicidal ideation, while a potent predictor of subsequent DSH (as expected), was not associated with dose (even across unmatched cohorts), suggesting that other potential but unaccounted-for risk factors for DSH might also be reasonably balanced across our cohorts defined by dose. Although it is still possible that unmeasured confounding accounts for the dose-response relationship we observed, it is not obvious what other factors might have led to meaningful confounding of our results. Indeed, such an unmeasured confounder would have to possess a very strong association with both dose and suicidal behavior—and also remain largely uncorrelated with risk factors we explicitly accounted for in analyses. Estimates from our bias analysis suggest that any such unmeasured confounder would need to be both more predictive of subsequent DSH than the most highly predictive risk factor in our data set (history of DSH) and also an order of magnitude more imbalanced across dose levels than our most imbalanced covariate.

When interpreting findings from the current study, one should bear in mind several additional caveats. First, as in all analyses relying on claims databases, we have limited ability to adjust for the severity of psychiatric illness. We do, however, use propensity score techniques to adjust for psychiatric comorbidity and comedication and for a proxy of depression severity involving whether a patient's depression diagnosis occurred during an inpatient admission for depression, whether the diagnosis was a primary or secondary diagnosis, and whether the diagnosis occurred within the month prior to their index date or more remotely. Propensity scores offer an advantage in studies of rare outcomes (eg, DSH) because propensity scores model the relation of covariates and their interactions with the drug exposure (which is relatively frequent) and not directly with the study outcome (which is often rare), thereby mitigating the risk of overfitting in a traditional outcome model.[50,51] As is the case for all observational studies, however, our ability to adjust fully for underlying suicide risk at baseline depends on our ability to accurately classify baseline confounders—and is compromised to the extent that measurement and reporting of conditions coded on insurance claims are misclassified.[52] Second, we used administrative data and therefore did not measure antidepressant adherence directly. Using automated prescription data may, however, more accurately measure use than studies that rely on data from self-report surveys.[53-55] A related point is that we define drug exposure in our primary analysis in a way that seeks to capture how patients fill their medications (ie, analyses are "as treated") but in so doing admit possible selection bias owing to censoring.[56] Nevertheless, our findings were robust to analyses in which exposure was defined using "first treatment carried forward," which is not subject to immeasurable time bias or other selection biases due to censoring, but rather likely bias findings toward the null (especially over extended follow-up periods). Finally, it should be noted that although our study provides strong evidence against initiating adolescents and young adults with depression using high-dose antidepressant therapy, it does not address whether initiating antidepressant therapy with the most commonly prescribed (modal) dose increases or decreases the risk of DSH relative to no pharmacological treatment, or, for that matter, if our findings apply to patients with other indications. While the ques-

tion "Does prescribing antidepressants increase or decrease suicide risk?" is a question of great clinical importance (and controversy), we decided against using untreated patients as the reference group to minimize the potential for confounding by indication.

Conclusions

In our study, approximately half of all patients initiating high-dose antidepressant therapy filled prescriptions written by internists or general practitioners. This statistic, coupled with the acknowledgment that treatment decisions should be made on the basis of expected benefits and harms, underscores the relevance of our findings to clinicians caring for patients in both specialty and nonspecialty settings. Considered in light of recent meta-analyses concluding that the efficacy of antidepressant therapy for youth seems to be modest,[46,47] and separate evidence that dose is generally unrelated to the therapeutic efficacy of antidepressants,[29,40-45] our findings offer clinicians an additional incentive to avoid initiating pharmacotherapy at high-therapeutic doses and to monitor all patients starting antidepressants, especially youth, for several months and regardless of history of DSH.

ARTICLE INFORMATION

Accepted for Publication: November 18, 2013.

Published Online: April 28, 2014. doi:10.1001/jamainternmed.2014.1053.

Author Contributions: Dr Miller had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Miller, Azrael, Pate, Stürmer.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Miller, Swanson, Azrael.
Critical revision of the manuscript for important intellectual content: Azrael, Pate, Stürmer.
Statistical analysis: Swanson, Azrael, Pate, Stürmer.
Obtained funding: Miller.
Administrative, technical, or material support: Miller, Pate.
Study supervision: Miller, Stürmer.

Conflict of Interest Disclosures: Dr Stürmer does not accept personal compensation of any kind from any pharmaceutical company, although he receives salary support from the Center for Pharmacoepidemiology and from unrestricted research grants from pharmaceutical companies (GlaxoSmithKline, Merck, Sanofi) to the department of epidemiology, University of North Carolina at Chapel Hill. No other disclosures are reported.

Funding/Support: Drs Miller, Azrael, Pate, and Stürmer received support for this work from an investigator-initiated research grant (RO1MH085021) from the National Institute of Mental Health (principal investigator, Dr Miller). Dr Stürmer receives investigator-initiated research funding and support as principal investigator (grant R01 AG023178) from the National Institute on Aging at the National Institutes of Health. He also receives research funding as principal investigator of the UNC-DEcIDE Center from the Agency for Healthcare Research and Quality.

Role of the Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry*. 2006;63(3):332-339.

2. Stone M, Laughren T, Jones ML, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ*. 2009;339:b2880.

3. Psaty BM, Siscovick DS. Minimizing bias due to confounding by indication in comparative effectiveness research: the importance of restriction. *JAMA*. 2010;304(8):897-898.

4. Bosco JL, Silliman RA, Thwin SS, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol*. 2010;63(1):64-74.

5. Patten SB. Confounding by severity and indication in observational studies of antidepressant effectiveness. *Can J Clin Pharmacol*. 2008;15(2):e367-e371.

6. Didham RC, McConnell DW, Blair HJ, Reith DM. Suicide and self-harm following prescription of SSRIs and other antidepressants: confounding by indication. *Br J Clin Pharmacol*. 2005;60(5):519-525.

7. Psaty BM, Koepsell TD, Lin D, et al. Assessment and control for confounding by indication in observational studies. *J Am Geriatr Soc*. 1999;47(6):749-754.

8. Walker AM. Confounding by indication. *Epidemiology*. 1996;7(4):335-336.

9. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol*. 2003;158(9):915-920.

10. Brookhart MA, Stürmer T, Glynn RJ, Rassen J, Schneeweiss S. Confounding control in healthcare database research: challenges and potential approaches. *Med Care*. 2010;48(6)(suppl):S114-S120.

11. Stürmer T, Jonsson Funk M, Poole C, Brookhart MA. Nonexperimental comparative effectiveness research using linked healthcare databases. *Epidemiology*. 2011;22(3):298-301.

12. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA*. 2004;292(3):338-343.

13. Martinez C, Assimes TL, Mines D, Dell'aniello S, Suissa S. Use of venlafaxine compared with other antidepressants and the risk of sudden cardiac death or near death: a nested case-control study. *BMJ*. 2010;340:c249.

14. Martinez C, Rietbrock S, Wise L, et al. Antidepressant treatment and the risk of fatal and non-fatal self-harm in first episode depression: nested case-control study. *BMJ*. 2005;330(7488):389.

15. Rubino A, Roskell N, Tennis P, Mines D, Weich S, Andrews E. Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study. *BMJ*. 2007;334(7587):242.

16. Schneeweiss S, Patrick AR, Solomon DH, et al. Comparative safety of antidepressant agents for children and adolescents regarding suicidal acts. *Pediatrics*. 2010;125(5):876-888.

17. Schneeweiss S, Patrick AR, Solomon DH, et al. Variation in the risk of suicide attempts and completed suicides by antidepressant agent in adults: a propensity score-adjusted analysis of 9 years' data. *Arch Gen Psychiatry*. 2010;67(5):497-506.

18. Valenstein M, Kim HM, Ganoczy D, et al. Antidepressant agents and suicide death among US Department of Veterans Affairs patients in depression treatment. *J Clin Psychopharmacol*. 2012;32(3):346-353.

19. Valuck RJ, Libby AM, Sills MR, Giese AA, Allen RR. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. *CNS Drugs*. 2004;18(15):1119-1132.

20. Baldassano CF, Truman CJ, Nierenberg A, Ghaemi SN, Sachs GS. Akathisia: a review and case report following paroxetine treatment. *Compr Psychiatry*. 1996;37(2):122-124.

21. Hansen L, Wilkinson DG. Drug induced akathisia, suicidal ideation and its treatment in the elderly. *Int J Geriatr Psychiatry*. 2001;16(2):231-233.

22. Healy D, Whitaker C. Antidepressants and suicide: risk-benefit conundrums. *J Psychiatry Neurosci*. 2003;28(5):331-337.

23. Kasantikul D. Drug-induced akathisia and suicidal tendencies in psychotic patients. *J Med Assoc Thai*. 1998;81(7):551-554.

24. Lipinski JF Jr, Mallya G, Zimmerman P, Pope HG Jr. Fluoxetine-induced akathisia: clinical and theoretical implications. *J Clin Psychiatry*. 1989;50(9):339-342.

25. Power AC, Cowen PJ. Fluoxetine and suicidal behaviour: some clinical and theoretical aspects of a controversy. *Br J Psychiatry*. 1992;161:735-741.

26. Teicher MH, Glod CA, Cole JO. Antidepressant drugs and the emergence of suicidal tendencies. *Drug Saf*. 1993;8(3):186-212.

27. Hamilton MS, Opler LA. Akathisia, suicidality, and fluoxetine. *J Clin Psychiatry*. 1992;53(11):401-406.

28. Hansen L. Fluoxetine dose-increment related akathisia in depression: implications for clinical care, recognition and management of selective serotonin reuptake inhibitor-induced akathisia. *J Psychopharmacol*. 2003;17(4):451-452.

29. Adli M, Baethge C, Heinz A, Langlitz N, Bauer M. Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? a systematic review. *Eur Arch Psychiatry Clin Neurosci*. 2005;255(6):387-400.

30. Benkert O, Szegedi A, Wetzel H. Minimum effective dose for antidepressants: an obligatory requirement for antidepressant drug evaluation? *Int Clin Psychopharmacol*. 1996;11(3):177-185.

31. Dipiro JT, Talbert RL, Matzke GL, Yee GC, Wells BG, Posey ML. *Pharmacotherapy: A Pathophysiologic Approach*. 5th ed. New York, NY: McGraw-Hill Medical; 2008.

32. Taylor D, Paton C, Kerwin R. *Prescribing Guidelines*. 10th ed. London, England: Informa Healthcare; 2010.

33. Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques, 2001. http://www2.sas.com/proceedings/sugi26/p214-26.pdf. Accessed October 1, 2012.

34. VanderWeele TJ. Unmeasured confounding and hazard scales: sensitivity analysis for total, direct, and indirect effects. *Eur J Epidemiol*. 2013;28(2):113-117.

35. Vanderweele TJ, Arah OA. Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. *Epidemiology*. 2011;22(1):42-52.

36. Healy D. Lines of evidence on the risks of suicide with selective serotonin reuptake inhibitors. *Psychother Psychosom*. 2003;72(2):71-79.

37. Maris RW. Suicide. *Lancet*. 2002;360(9329):319-326.

38. Nutt DJ. Death and dependence: current controversies over the selective serotonin reuptake inhibitors. *J Psychopharmacol*. 2003;17(4):355-364.

39. Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. *J Clin Psychiatry*. 1991;52(12):491-493.

40. Bech P, Tanghøj P, Andersen HF, Overø K. Citalopram dose-response revisited using an alternative psychometric approach to evaluate clinical effects of four fixed citalopram doses compared to placebo in patients with major depression. *Psychopharmacology (Berl)*. 2002;163(1):20-25.

41. Bollini P, Pampallona S, Tibaldi G, Kupelnick B, Munizza C. Effectiveness of antidepressants: meta-analysis of dose-effect relationships in randomised clinical trials. *Br J Psychiatry*. 1999;174:297-303.

42. Hansen RA, Moore CG, Dusetzina SB, Leinwand BI, Gartlehner G, Gaynes BN. Controlling for drug dose in systematic review and meta-analysis: a case study of the effect of antidepressant dose. *Med Decis Making*. 2009;29(1):91-103.

43. Kelly MW, Perry PJ, Holstad SG, Garvey MJ. Serum fluoxetine and norfluoxetine concentrations and antidepressant response. *Ther Drug Monit*. 1989;11(2):165-170.

44. Ruhé HG, Booij J, v Weert HC, et al. Evidence why paroxetine dose escalation is not effective in major depressive disorder: a randomized controlled trial with assessment of serotonin transporter occupancy. *Neuropsychopharmacology*. 2009;34(4):999-1010.

45. Ruhé HG, Huyser J, Swinkels JA, Schene AH. Dose escalation for insufficient response to standard-dose selective serotonin reuptake inhibitors in major depressive disorder: systematic review. *Br J Psychiatry*. 2006;189:309-316.

46. Tsapakis EM, Soldani F, Tondo L, Baldessarini RJ. Efficacy of antidepressants in juvenile depression: meta-analysis. *Br J Psychiatry*. 2008;193(1):10-17.

47. Jureidini JN, Doecke CJ, Mansfield PR, Haby MM, Menkes DB, Tonkin AL. Efficacy and safety of antidepressants for children and adolescents. *BMJ*. 2004;328(7444):879-883.

48. Weiss JJ, Gorman JM. Antidepressant adherence and suicide risk in depressed youth. *Am J Psychiatry*. 2005;162(9):1756-1757.

49. Smith EG. Association between antidepressant half-life and the risk of suicidal ideation or behavior among children and adolescents: confirmatory analysis and research implications. *J Affect Disord*. 2009;114(1-3):143-148.

50. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: analytic strategies using propensity scores. *Ann Intern Med*. 2002;137(8):693-695.

51. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-2281.

52. Grobbee DE, Hoes AW. Confounding and indication for treatment in evaluation of drug treatment for hypertension. *BMJ*. 1997;315(7116):1151-1154.

53. Piper JM, Ray WA, Griffin MR. Effects of Medicaid eligibility expansion on prenatal care and pregnancy outcome in Tennessee. *JAMA*. 1990;264(17):2219-2223.

54. Strom BL, Carson JL. Use of automated databases for pharmacoepidemiology research. *Epidemiol Rev*. 1990;12:87-107.

55. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol*. 1995;142(10):1103-1112.

56. Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. *Am J Epidemiol*. 2008;168(3):329-335.

Invited Commentary

Initial Dose of Antidepressant and Suicidal Behavior in Youth
Start Low, Go Slow

David A. Brent, MD; Robert Gibbons, PhD

In this methodologically exemplar pharmacoepidemiological study by Miller et al,[1] data on patients with depression were assessed for prospective risk for deliberate self-harm (DSH; ie, suicide attempt) according to whether the patients had been initiated on therapy with the modal dose vs higher than modal dose of antidepressant. Using propensity-matched analysis, initiation at a higher than modal dose of antidepressant resulted in a 2-fold increased risk of deliberate self-harm in patients aged 10 to 24 years, especially in the first 3 months of treatment, while there was no such effect found in those aged 25 to 64 years.

Related article page 899

One of the many strengths of this study was that the outcome was actual suicidal behavior rather than the more commonly used outcome "suicidal events," which includes worsening in suicidal ideation, such as "thoughts of death" as well as actual suicidal behavior. These analyses examined unselected patients at much higher risk for suicidal behavior than the carefully screened participants in clinical trials. The prospective risk for suicidal behavior was assessed in patients treated for the same indication, namely, depression. These patients were new initiators of selective serotonin reuptake inhibitor (SSRI) therapy who had not been treated with an antidepressant in the past year. The use of propensity score matching allowed for contrasts between groups that were well