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Emergency Department Visits by Adults for Psychiatric Medication Adverse Events

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Abstract

IMPORTANCE—In 2011, an estimated 26.8 million US adults used prescription medications for mental illness.

OBJECTIVE—To estimate the numbers and rates of adverse drug event (ADE) emergency department (ED) visits involving psychiatric medications among US adults between January 1, 2009, and December 31, 2011.

DESIGN AND SETTING—Descriptive analyses of active, nationally representative surveillance of ADE ED visits using the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance system and of drug prescribing during outpatient visits using the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey.

PARTICIPANTS—Medical records from national probability samples of ED and outpatient visits by adults 19 years or older were reviewed and analyzed.

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Study concept and design: Hampton, Daubresse, Alexander, Budnitz.

Acquisition, analysis, or interpretation of data: Hampton, Chang.

Drafting of the manuscript: Hampton.

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Conflict of Interest Disclosures: Dr Alexander reported being an ad hoc member of the Food and Drug Administration's Drug Safety and Risk Management Advisory Committee, serving as a paid consultant to IMS Health, and participating on an IMS Health scientific advisory board. This arrangement has been reviewed and approved by The Johns Hopkins University in accord with its conflict of interest policies. No other disclosures were reported.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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EXPOSURES—Antidepressants, antipsychotics, lithium salts, sedatives and anxiolytics, and stimulants.

MAIN OUTCOMES AND MEASURES—National estimates of ADE ED visits resulting from therapeutic psychiatric medication use and of psychiatric medication ADE ED visits per 10 000 outpatient visits at which psychiatric medications were prescribed.

RESULTS—From 2009 through 2011, there were an estimated 89 094 (95% CI, 68 641–109 548) psychiatric medication ADE ED visits annually, with 19.3% (95% CI, 16.3%–22.2%) resulting in hospitalization and 49.4% (95% CI, 46.5%–52.4%) involving patients aged 19 to 44 years. Sedatives and anxiolytics, antidepressants, antipsychotics, lithium salts, and stimulants were implicated in an estimated 30 707 (95% CI, 23 406–38 008), 25 377 (95% CI, 19 051–31 704), 21 578 (95% CI, 16 599–26 557), 3620 (95% CI, 2311–4928), and 2779 (95% CI, 1764–3794) respective ADE ED visits annually. Antipsychotics and lithium salts were implicated in 11.7 (95% CI, 10.1–13.2) and 16.4 (95% CI, 13.0–19.9) ADE ED visits per 10 000 outpatient prescription visits, respectively, compared with 3.6 (95% CI, 3.2–4.1) for sedatives and anxiolytics, 2.9 (95% CI, 2.3–3.5) for stimulants, and 2.4 (95% CI, 2.1–2.7) for antidepressants. The commonly used sedative zolpidem tartrate was implicated in 11.5% (95% CI, 9.5%–13.4%) of all adult psychiatric medication ADE ED visits and in 21.0% (95% CI, 16.3%–25.7%) of visits involving adults 65 years or older, in both cases significantly more than any other psychiatric medication.

CONCLUSIONS AND RELEVANCE—Psychiatric medications are implicated in many ADEs treated in US EDs. Efforts to reduce ADEs should include adults of all ages but might prioritize medications causing high numbers and rates of ED visits.

In 2011, an estimated 26.8 million US adults, 11.5% of the adult population, used prescription medications to treat mental illness.[1] Psychiatric medications, namely, antidepressants, antipsychotics, lithium salts, sedatives and anxiolytics, and stimulants, have an important role in the management of mental illness,[2] but they can also cause significant adverse effects.[3–6] Given the wide range of treatments available for multiple mental illnesses,[7–9] providers must weigh the benefits and risks of psychiatric medications in deciding whether to prescribe one and, if so, which one.

Public health surveillance can help quantify the adverse effects of medications as they are used outside of strictly controlled clinical trials and can help monitor that quantity of adverse drug events (ADEs) over time. Data on the frequency of psychiatric medication ADEs in the United States are limited[10,11] but could be used to focus efforts to reduce ADEs, as well as to provide a baseline for assessing the effect of such efforts. We used nationally representative public health surveillance data to estimate the numbers and rates of emergency department (ED) visits and hospitalizations for ADEs resulting from therapeutic use of psychiatric medications among adults 19 years or older between January 1, 2009, and December 31, 2011.

Methods

Data Sources

Data collection, management, quality assurance, and analyses were determined to be public health surveillance activities by the Centers for Disease Control and Prevention and Food and Drug Administration (FDA) human participants oversight bodies and did not require human participant review, institutional review board approval, or individual patient consent. We estimated the number of annual ADE ED visits in the United States and its territories using data from 63 hospitals that participate in the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, a nationally representative probability sample of hospitals with a minimum of 6 beds and a 24-hour ED. The NEISS-CADES project is a collaboration of the Centers for Disease Control and Prevention, the FDA, and the US Consumer Product Safety Commission, which has previously been described in detail.[11,12] In brief, trained abstractors review the clinical diagnoses and supporting information in the medical records of each ED visit to ascertain ADEs identified by treating clinicians. Abstractors report up to 2 medications implicated in each ADE, up to 10 concomitant medications listed in the medical record, and ADE narrative descriptions. Details of ADEs, including their manifestations and physician diagnoses, are further coded with the use of the Medical Dictionary for Regulatory Activities (MedDRA, version 9.1; International Federation of Pharmaceutical Manufacturers and Associations).

To estimate the use of specific medications, we used publicly available data from the National Ambulatory Medical Care Survey (NAMCS) of office-based clinicians and the National Hospital Ambulatory Medical Care Survey (NHAMCS) of non-federal, noninstitutional hospitals' outpatient departments and EDs.[13] We used National Center for Health Statistics bridged-race population estimates, which are based on US census data, to determine the numbers of US adult men, adult women, and adults, between 2009 and 2011, aged 19 to 44 years, 45 to 64 years, and 65 years or older.[14]

Case Criteria

We defined a case as an ED visit by a patient 19 years or older during the period January 1, 2009, through December 31, 2011, for a problem that was attributed to the therapeutic use of a medication or a medication-specific adverse effect and which did not result in the patient's death in or before arrival at the ED. We considered medications to be psychiatric (eTable 1 in the Supplement) if they met the following criteria: (1) they were classified as an antidepressant, antipsychotic, sedative and anxiolytic, stimulant, or other central nervous system medication in the modified Department of Veterans Affairs National Drug File used by the NEISS-CADES; (2) they were classified as an antidepressant, antipsychotic, central nervous system stimulant, or anxiolytic, sedative, or hypnotic in the National Center for Health Statistics Ambulatory Care Drug Database System[15]; (3) they were marketed during the study period (2009–2011)[16,17]; (4) they were available only by prescription[17]; and (5) they were available in a noninjectable dose form.[16,17] The ADE ED visits that did not involve medications meeting all of these criteria were considered to be due to nonpsychiatric medication use. We used the classification scheme by Burgyone et al[18] to determine whether

patients who made ADE ED visits were using antiparkinsonian drugs. We categorized ADEs by mechanism as allergic reactions (ie, immunologically mediated effects), adverse reactions (ie, undesirable pharmacological or idiosyncratic effects at recommended dosages), secondary effects (ie, medication delivery–related effects such as choking), or unintentional therapeutic overdoses (ie, excess doses or supratherapeutic drug effects from therapeutic use of a medication). We also categorized adverse effects (eTable 2 in the Supplement). Because ADE ED visits may include multiple adverse effects that collectively may fall under multiple adverse effect categories, the total number of adverse effects may be greater than the total number of ADE ED visits. We excluded from all analyses ED visits resulting from intentional self-harm, documented drug abuse, therapeutic failures, nonadherence, or drug withdrawal.

We used data from the 2009 and 2010 NAMCS and NHAMCS surveys to identify outpatient prescription visits for adults 19 years or older during which psychiatric medications were ordered, prescribed, or continued. Both surveys recorded up to 8 prescription or over-the-counter medications, vaccines, and dietary supplements ordered or continued for each visit.

Statistical Analysis

Each NEISS-CADES, NAMCS, and NHAMCS case receives a sample weight based on the inverse probability of selection. The NEISS-CADES case sample weights are modified for non-response and are poststratified to adjust for the number of annual ED visits at different types of hospitals, while the NAMCS and NHAMCS case sample weights are adjusted for nonresponse and undergo weight smoothing. We calculated national estimates of ADE ED visits and outpatient prescription visits, as well as their corresponding 95% CIs, with the SUR-VEYMEANS procedure (SAS, version 9.3; SAS Institute Inc) to account for the sample weights and complex sample designs. To obtain annual estimates, we divided the NEISS-CADES estimates of ADE ED visits from 2009 through 2011 and their corresponding 95% CIs by 3 and divided the NAMCS and NHAMCS estimates of outpatient prescription visits in 2009 and 2010 and their corresponding 95% CIs by 2. We considered estimates based on small numbers of cases (<20 cases for the NEISS-CADES and <30 cases for the NAMCS and NHAMCS) and estimates having a coefficient of variation greater than 30% to be statistically unreliable and noted them as such in the tables.[11,19]

To estimate rates of ADE ED visits relative to outpatient medication use, we divided the estimated number of ADE ED visits caused by specific medications by the estimated number of outpatient visits at which the medications of interest were ordered or continued. The 95% CI for each rate incorporated variance estimates for both numerator and denominator components.[20] Because we calculated these components from separate surveillance systems, we treated them as independent (ie, as having zero covariance). We calculated annual ADE ED visit incidence rates or visits per 100 000 population for 2009 through 2011 using national estimates of ADE ED visits and National Center for Health Statistics bridged-race population estimates.

Results

From 2009 through 2011, there were an estimated 89 094 (95% CI, 68 641–109 548) annual ED visits due to ADEs from therapeutic use of psychiatric medications involving adult patients 19 years or older (Table 1), accounting for 9.6% (95% CI, 8.3%–11.0%) of all adult ADE ED visits. Patients were admitted, held for observation, or transferred to another acute care facility after 19.3% (95% CI, 16.3%–22.2%) of psychiatric medication ADE ED visits, a hospitalization rate similar to the 25.3% (95% CI, 20.6%–29.9%) rate for nonpsychiatric medication ADE ED visits. Almost half (49.4%) of psychiatric medication ADE ED visits involved adult patients aged 19 to 44 years, while 17.3% of visits involved adult patients 65 years or older. The population rates for annual psychiatric medication ADE ED visits were similar across age groups, with 40.6 (95% CI, 31.2–49.9) visits per 100 000 adults aged 19 to 44 years, 36.4 (95% CI, 27.2–45.6) visitsper100 000 adults aged 45 to 64 years, and 38.0 (95%CI, 28.8–47.1) visits per 100 000 adults 65 years or older. Most psychiatric medication ADE ED visits involved women (61.9%), with 46.4 (95% CI, 36.0–56.8) visits per 100 000 adult women compared with 30.3 (95% CI, 23.0–37.6) visits per 100 000 adult men.

ADE ED Visits by Psychiatric Medication Category and Class

Annually, sedatives and anxiolytics were implicated in an estimated 30 707 (95% CI, 23 406–38 008) ED visits, antidepressants in an estimated 25 377 (95% CI, 19 051–31 704) ED visits, antipsychotics in an estimated 21 578 (95% CI, 16 599–26 557) ED visits, lithium salts in an estimated 3620 (95% CI, 2311–4928) ED visits, and stimulants in an estimated 2779 (95% CI, 1764–3794) ED visits (Table 2). When the estimated number of outpatient prescription visits was taken into account, lithium salts and antipsychotics (16.4 and 11.7 ED visits per 10 000 out-patient prescription visits, respectively) were implicated in ED visits at a rate higher than other psychiatric medication categories. Antipsychotics were implicated at a 3.3-fold higher rate than sedatives and anxiolytics (3.6 ED visits per 10 000 out-patient prescription visits), a 4.0-fold higher rate than stimulants (2.9 ED visits per 10 000 outpatient prescription visits), and a 4.9-fold higher rate than antidepressants (2.4 ED visits per 10 000 outpatient prescription visits).

Typical antipsychotics (26.1 ED visits per 10 000 outpatient prescription visits) were implicated in ED visits at a 2.9-fold higher rate than atypical antipsychotics (9.1 ED visits per 10 000 outpatient prescription visits) (Table 2). However, typical antipsychotics other than haloperidol were implicated in ED visits at a rate of 13.1 (95% CI, 10.4–15.8) ED visits per 10 000 outpatient prescription visits, which is much closer to that of atypical antipsychotics. All antipsychotic classes were implicated in ADE ED visits at higher rates than any of the sedative and anxiolytic, antidepressant, or stimulant classes. Nonbenzodiazepine sedatives and anxiolytics (4.2 ED visits per 10 000 outpatient prescription visits) had the highest rate of ADE ED visits among the sedative and anxiolytic, antidepressant, or stimulant classes, but typical antipsychotics, typical antipsychotics other than haloperidol, and atypical antipsychotics had rates of ADE ED visits that were 6.2-fold higher, 3.1-fold higher, and 2.2-fold higher, respectively, than the corresponding rates of nonbenzodiazepine sedatives and anxiolytics. In 26.0% (95% CI, 18.2%–33.8%) of typical antipsychotic ADE ED visits and 17.7% (95% CI, 14.3%–21.1%) of atypical antipsychotic

ADE ED visits, the patients involved were documented to also be taking antiparkinsonian medications. Long-acting and short-acting benzodiazepines were similarly likely to cause ADE ED visits, and the proportion of ADE ED visits that resulted in hospitalization was also similar for long-acting and short-acting benzodiazepines.

ADE ED Visits by Patient Age and Sex

Antipsychotics (31.3%) and antidepressants (30.5%) were the leading causes of psychiatric medication ADE ED visits by adult patients aged 19 to 44 years, but sedatives and anxiolytics caused the most psychiatric medication ADE ED visits by patients aged 45 to 64 years (38.1%) and patients 65 years or older (55.2%) (Table 3). Regardless of the age group of the patients involved, antipsychotics and lithium salts had the highest rates of ADE ED visits relative to the number of outpatient visits at which they were prescribed.

Antidepressants were the leading cause of psychiatric medication ADE ED visits by female patients aged 19 to 44 years (36.2% [95% CI, 32.5%–40.0%]), while antipsychotics were the leading cause of psychiatric medication ADE ED visits by male patients aged 19 to 44 years (40.1% [95% CI, 34.4%–45.9%]) (eTable 3 in the Supplement). Sedatives and anxiolytics caused the most psychiatric medication ADE ED visits by both male and female patients aged 45 to 64 years, as well as by both male and female patients 65 years or older. Regardless of patient sex, antipsychotics and lithium salts had the highest rates of ADE ED visits relative to the number of outpatient visits at which they were prescribed.

Within medication categories, rates of antipsychotic, sedative and anxiolytic, and antidepressant ADE ED visits per 10 000 outpatient prescription visits were highest when the patients involved were aged 19 to 44 years (Table 3) regardless of the patients' sex (eTable 3 in the Supplement). However, psychiatric medication ADE ED visits were less likely to result in hospitalization if the patients involved were aged 19 to 44 years (10.8% [95% CI, 8.9%–12.6%]) compared with those aged 45 to 64 years (25.7% [95% CI, 21.7%–29.7%]) or 65 years or older (31.3% [95% CI, 24.0%–38.7%]).

ADE ED Visits Due to Specific Psychiatric Medications

Ten specific medications, alone or in combination with other medications, were implicated in 57.5% (95% CI, 55.4%–59.7%) of all estimated adult psychiatric medication ADE ED visits (Table 4). Although zolpidem tartrate caused significantly fewer ED visits per outpatient prescription visit than lithium, quetiapine fumarate, haloperidol, or risperidone, it was implicated in 11.5% of adult psychiatric medication ADE ED visits, significantly more than any other drug. The proportion of visits due to zolpidem was highest among visits by adults 65 years or older (21.0% [95% CI, 16.3%–25.7%]) compared with 12.2% (95% CI, 9.9%–14.4%) of visits in which the patients were adults aged 45 to 64 years and 7.6% (95% CI, 5.7%–9.6%) of visits in which the patients were adults aged 19 to 44 years. Zolpidem (5.5 visits) was implicated in more ADE ED visits per 10 000 outpatient prescription visits than the benzodiazepines alprazolam (2.7 visits), lorazepam (3.1 visits), and clonazepam (3.3 visits) or the antidepressant citalopram hydrobromide (3.0 visits), but the antipsychotic haloperidol (43.3 visits) was implicated in the most ADE ED visits per 10 000 out-patient

prescription visits. The ED visits for lithium ADEs were most likely to result in hospitalizations, with 50.6% (95% CI, 40.5%–60.7%) of such visits doing so.

Adverse Drug Effects

Specific adverse effects were documented in an estimated 88.3% (95% CI, 86.1%–90.5%) of psychiatric medication ADE ED visits. Two or more types of adverse effects were identified in 33.9% (95% CI, 28.1%–39.8%) of all psychiatric medication ADE ED visits. Among ADE ED visits in which sedatives and anxiolytics were implicated either alone or in combination with other medications, altered mental status (eg, delirium) and disturbances in consciousness (eg, somnolence) were the most common adverse effects (Table 5). Sedatives and anxiolytics in general and zolpidem in particular were implicated in 74.9% (95% CI, 69.3%–80.6%) and 32.1% (95% CI, 25.1%–39.0%), respectively, of all psychiatric medication ED visits for falls or head injuries. Sensory abnormalities (eg, vertigo) and hypersensitivity reactions (eg, rash or urticaria) were common among antidepressant ADE ED visits. Movement disorders and spasticities (eg, dystonia, trismus, and extrapyramidal disorders) were the most common adverse effects among antipsychotic ADE ED visits. For every 10 000 outpatient visits at which they were prescribed, haloperidol, typical antipsychotics other than haloperidol, and atypical antipsychotics caused 26.9 (95% CI, 21.1–32.6), 5.1 (95% CI, 3.6–6.5), and 2.0 (95% CI, 1.6–2.3) ADE ED visits, respectively, for movement disorders or spasticities. An abnormal drug level was the most common adverse effect for ADE ED visits in which lithium salts were implicated. Among ED visits for stimulant ADEs, sensory abnormalities and cardiovascular manifestations such as palpitations were the most common adverse effects.

Discussion

Based on active, population-representative public health surveillance data, ADEs from adult therapeutic use of psychiatric medications led to almost 90 000 estimated US ED visits annually from 2009 through 2011, with almost half involving adults aged 19 to 44 years and with 1 in 5 visits resulting in hospitalization. Antipsychotics and lithium salts were implicated in significantly more ED visits relative to the number of outpatient visits at which they were prescribed than other psychiatric medications. Almost three-fifths of psychiatric medication ADE ED visits were due to 10 drugs, with zolpidem alone accounting for more than 1 in 5 visits among adults 65 years or older. These findings suggest several opportunities to reduce harms from the adverse effects of psychiatric medications.

Antipsychotics caused more than 21 000 estimated adult ADE ED visits annually and more adult ED visits for psychiatric medication ADEs relative to their use in outpatient practice than sedatives and anxiolytics, antidepressants, or stimulants. Movement disorders and spasticities were the most common antipsychotic ADE manifestations, occurring more frequently with haloperidol, which has also been associated with higher mortality rates among the elderly,[21,22] than with other antipsychotics relative to their use in outpatient practice. Even the atypical antipsychotics, which were significantly less likely to cause ADE ED visits than the typical antipsychotics, led to twice as many ADE ED visits per 10 000 outpatient prescription visits as any class of the antidepressants, sedatives and anxiolytics, or

stimulants. Because 60% of atypical antipsychotic prescribing and 64% of typical antipsychotic prescribing have been identified as off-label prescribing (ie, for indications other than those approved by the FDA),[23] it is likely that many of these ADE ED visits resulted from off-label use. In addition, well over half of the off-label use of antipsychotics may be based on inadequate evidence of likely patient benefit.[23] Concerns about antipsychotics' risks and their possible overuse have prompted the leaders of the American Psychiatric Association to urge providers to prescribe antipsychotics cautiously and only after exploring the feasibility of using alternate treatments.[24] Avoiding antipsychotics in favor of other options less likely to cause ADEs could be particularly appropriate when considering treatment of major depressive disorder, insomnia, or anxiety disorders because the FDA has not approved the use of any antipsychotic for the first-line treatment of major depressive disorder, the use of any antipsychotic for the treatment of insomnia, or the use of any atypical antipsychotic for the treatment of anxiety disorders.[25]

Perhaps surprisingly, zolpidem was implicated in more ADE ED visits than any other psychiatric medication and caused a markedly high number of ADE ED visits relative to the number of outpatient visits at which it was prescribed, particularly compared with antidepressants and benzodiazepines. However, data from the Drug Abuse Warning Network[26] have shown that ED visits for zolpidem ADEs increased 220% from 2005 to 2010, and previous studies[27,28] have indicated that zolpidem use is associated with a substantial risk of falls. While the FDA's recent efforts to modify recommended dosing regimens hold promise for reducing zolpidem ADEs,[29] clinicians can also reduce zolpidem ADEs by prescribing zolpidem for insomnia, its sole FDA-approved indication,[29] only after considering other treatments such as sleep hygiene education, stimulus control, sleep restriction, relaxation training, and cognitive behavior therapy.[9,30]

The unexpected finding that rates of antipsychotic, sedative and anxiolytic, and antidepressant ADE ED visits per 10 000outpatientprescriptionvisitswerehighestamongadults aged 19 to 44 years indicates that ADEs should be an important consideration in the choice of psychiatric treatments among younger adults. Likely causes for the high rates among younger adults include a greater proclivity to seek ED care or ability to access ED care among younger adults,[10,31] a greater propensity to attribute younger adults' problems to ADEs by ED medical providers (perhaps due to younger adults usually having fewer comorbidities),[32] and less frequent outpatient visits among younger adults.[31] Polypharmacy involving all types of medications is a less likely cause because younger adults are less likely to be using 3 or more medications than older adults.[31] Focused research on age-related differences in ADEs may identify specific causes of younger adults' high rates of psychiatric medication ADE ED visits.

Limitations of the NEISS-CADES have likely resulted in conservative estimates of annual ADEs from psychiatric medications. First, the NEISS-CADES relies both on patients seeking care in EDs and on ED medical providers identifying and documenting ADEs, which may introduce a bias toward the detection of acute, known drug adverse effects for which ED testing is available, or effects that can be readily distinguished from problems caused by patients' comorbidities. Chronic problems from medication use such as the metabolic disorders associated with antipsychotics[4] are unlikely to be identified by the

NEISS-CADES. Second, visits resulting from medication abuse or use for self-harm are excluded, although both medication abuse and self-harm are substantial public health concerns.[33,34] Third, medications primarily used to treat other conditions but sometimes used to treat psychiatric conditions (eg, anticonvulsants) were excluded from the analysis. On the other hand, some medications often used for treating psychiatric conditions (eg, amphetamines and benzodiazepines) may also be used to treat other conditions, but the NEISS-CADES does not collect information on the specific indication for each medication implicated in an ADE or on whether or not the medication was used on label or off label. The NEISS-CADES also does not collect unique patient identifiers, information on a patient's comorbid conditions, consistent information on psychiatric medication dosage, or information on the specialty of the physician who prescribed the medications that caused an ADE ED visit.

While the NAMCS and NHAMCS data are commonly used to estimate outpatient medication use and provide results generally similar to those of another survey of outpatient medication prescribing,[19,30,35–38] they do not provide direct estimates of person-year exposure to medications and may overestimate or underestimate the use of psychiatric medications. Underestimation may result from the exclusion of medications initiated in nursing homes, at hospital discharge, in the EDs and outpatient departments of federal and institutional hospitals, and through telephone or e-mail contact. Underestimation may also result from medication dispensing not tied to the outpatient visit prescriptions captured by the NAMCS and NHAMCS and from individual prescription visits corresponding to numerous refills and many days of supply. Overestimation of exposure may result from nonadherence, which may be particularly common for psychiatric medications.[39] In addition, the periods covered by the data from the NEISS-CADES and the data from the NAMCS and NHAMCS overlap but are not identical. Therefore, the estimates of ADE ED visits per outpatient prescription visits for a given medication could be too high or too low if the 2011 NAMCS and NHAMCS estimates of outpatient prescription visits were markedly higher or lower than the estimates for 2009 through 2010.

Conclusions

Attempts to reduce the use of psychiatric medications when risks outweigh benefits have had mixed success,[40,41] but the current burden of ADEs from therapeutic use of psychiatric medications, which conservatively includes almost 90 000 ED visits a year, suggests that such efforts should continue. Continued public health surveillance of psychiatric medication ADEs will be important for monitoring the results of developments such as the recent American Psychiatric Association cautions regarding antipsychotics,[24] new psychiatric diagnostic criteria in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*),[42,43] and future changes in the *DSM-5* implemented as part of its planned continual review and revision.[44] Efforts to reduce ADEs from therapeutic use of psychiatric medications should include adults of all ages but might first focus on medications causing high numbers and rates of ED visits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Numbers of Cases and National Estimates of Annual ED Visits for Psychiatric Medication Adverse Drug Events, by Patient and Case Characteristics in the United States, 2009 Through 2011

	ED Visits for Adverse Drug Events[a]		
		Estimated Annual	
Characteristic	**No. of Cases (n = 4048)**	**No. of Visits (n = 89 094)**	**Visits, % (95% CI)**
Age, y			
19–44	2013	44 039	49.4 (46.5–52.4)
45–64	1342	29 678	33.3 (30.7–35.9)
≥65	693	15 377	17.3 (14.7–19.8)
Sex			
Female	2435	55 174	61.9 (59.4–64.5)
Male	1613	33 920	38.1 (35.5–40.6)
Mechanism of adverse event			
Adverse reaction	2188	47 079	52.8 (48.6–57.0)
Unintentional therapeutic overdose	1358	30 094	33.8 (30.1–37.5)
Allergic reaction	479	11 493	12.9 (10.7–15.1)
Secondary effect	23	428	0.5 (0.2–0.8)
Disposition			
Admitted, observed, or transferred	830	17 188	19.3 (16.3–22.2)
Treated and released or left against medical advice	3218	71 906	80.7 (77.8–83.7)
No. of implicated medications			
1	2973	65 235	73.2 (71.0–75.4)
2	1075	23 859	26.8 (24.6–29.0)
No. of concurrent medications			
None	1297	30 645	34.4 (25.5–43.3)
1–3	1435	30 755	34.5 (29.6–39.4)
4–5	787	15 741	17.7 (14.4–21.0)
≥6	529	11 953	13.4 (10.8–16.0)

Abbreviation: ED, emergency department.

[a] Number of cases and national estimates are from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project.

Table 2

Numbers of Cases and National Estimates of Annual ED Visits for Psychiatric Medication Adverse Drug Events Among Adults 19 Years or Older, by Medication Category and Class in the United States, 2009 Through 2011

	ED Visits for Adverse Drug Events[b]				
			%		
Medication Category and Class[a]	No. of Cases	Estimated Annual No. of Visits	Proportion of Category Visits	Hospitalization Rate	Estimated Annual ED Visits per 10 000 Outpatient Prescription Visits, No. (95% CI)[c]
Sedatives and anxiolytics	1371	30 707	NA	23.5	3.6 (3.2–4.1)
Short-acting benzodiazepine	614	14 387	46.9	24.4	2.5 (2.2–2.9)
Nonbenzodiazepine	465	10 360	33.7	22.1	4.2 (3.6–4.9)
Long-acting benzodiazepine	128	2633	8.6	21.8	2.8 (2.3–3.3)
Miscellaneous[d]	164	3327	10.8	25.5	NA
Antidepressants	1076	25 377	NA	12.4	2.4 (2.1–2.7)
SSRIs	512	12 019	47.4	11.2	1.9 (1.6–2.2)
SNRIs	153	3887	15.3	*e*	1.8 (1.5–2.1)
Triazolopyridines	145	3443	13.6	18.5	3.7 (3.0–4.4)
Aminoketones	112	2573	10.1	*e*	2.1 (1.8–2.5)
Tricyclics	81	1835	7.2	*e*	1.8 (1.5–2.2)
Tetracyclics	25	655	2.6	*e*	2.3 (1.6–3.0)
MAOIs	6	*e*	*e*	*e*	*e*
Miscellaneous[d]	42	838	3.3	*e*	NA
Antipsychotics	1055	21 578	NA	15.3	11.7 (10.1–13.2)
Atypical	723	15 272	70.8	16.9	9.1 (7.8–10.4)
Typical	312	5804	26.9	10.6	26.1 (21.6–30.5)
Miscellaneous[d]	20	*e*	*e*	*e*	NA
Lithium salts	197	3620	NA	53.6	16.4 (13.0–19.9)
Stimulants	124	2779	NA	*e*	2.9 (2.3–3.5)
Amphetamines	108	2331	83.9	*e*	3.0 (2.4–3.7)
Miscellaneous[d]	16	*e*	*e*	*e*	NA

Medication Category and Class[a]	ED Visits for Adverse Drug Events[b]				Estimated Annual ED Visits per 10 000 Outpatient Prescription Visits, No. (95% CI)[c]
	No. of Cases	Estimated Annual No. of Visits	%		
			Proportion of Category Visits	Hospitalization Rate	
Two drugs from different psychiatric medication categories	225	5033	NA	24.2	NA

Abbreviations: ED, emergency department; MAOs, monoamine oxidase inhibitors; NA, not applicable; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

[a] Triazolopyridine class includes trazodone hydrochloride, aminoketone class includes bupropion hydrochloride, and tetracyclic class includes maprotiline and mirtazapine.

[b] Number of cases and national estimates of ED visits are from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project. The hospitalization rate is the ratio of ED visits resulting in admission, observation, or transfer to total ED visits for adverse drug events involving the specified medication category and class.

[c] Estimated annual numbers of outpatient prescription visits for each medication category and class are from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey for 2009 and 2010 and include outpatient prescription visits in which multiple psychiatric medications were prescribed at a single visit.

[d] Includes ED visits in which 2 medications from different classes in the same category were implicated, ED visits in which only the category of drug was specified, and ED visits involving medications from the specified category that do not fall under one of the other classes.

[e] Statistically unreliable estimate.

Table 3

Numbers of Cases and National Estimates of Annual ED Visits for Psychiatric Medication Adverse Drug Events, by Patient Age and Medication Category in the United States, 2009 Through 2011

Age Group and Psychiatric Medication	ED Visits for Adverse Drug Events[a]				Estimated Annual ED Visits per 10 000 Outpatient Prescription Visits, No. (95% CI)[b]
	No. of Cases	Estimated Annual No. of Visits	Proportion of Age Group Visits, % (95% CI)	Hospitalization Rate, %	
19–44 y					
Sedatives and anxiolytics	496	10 902	24.8 (22.1–27.4)	13.1	4.9 (4.2–5.6)
Antidepressants	561	13 432	30.5 (27.8–33.2)	7.2	4.3 (3.7–4.9)
Antipsychotics	682	13 778	31.3 (27.6–35.0)	9.9	19.4 (16.6–22.2)
Lithium salts	61	1047	2.4 (1.4–3.3)	34.8	10.7 (7.8–13.5)
Stimulants	107	2476	5.6 (4.4–6.8)	*c*	4.4 (3.5–5.3)
Two drugs from different psychiatric medication categories	106	2405	5.5 (4.1–6.9)	*c*	NA
45–64 y					
Sedatives and anxiolytics	495	11 312	38.1 (34.9–41.3)	27.2	3.1 (2.7–3.5)
Antidepressants	337	7881	26.6 (23.3–29.8)	14.9	1.7 (1.4–2.0)
Antipsychotics	284	5860	26.6 (23.3–29.8)	21.4	7.3 (6.0–8.5)
Lithium salts	109	2106	7.1 (4.9–9.3)	61.6	23.3 (17.6–28.9)
Stimulants	16	*c*	*c*	*c*	*c*
Two drugs from different psychiatric medication categories	101	2224	7.5 (6.0–9.0)	33.4	NA
≥65 y					
Sedatives and anxiolytics	380	8493	55.2 (50.9–59.5)	32.0	3.3 (2.8–3.8)
Antidepressants	178	4064	26.4 (22.9–30.0)	24.9	1.4 (1.2–1.7)
Antipsychotics	89	1940	12.6 (10.2–15.0)	35.0	5.8 (4.7–6.9)
Lithium salts	27	*c*	*c*	59.7	*c*
Stimulants	1	*c*	*c*	*c*	*c*
Two drugs from different psychiatric medication categories	18	*c*	*c*	*c*	NA

Abbreviations: ED, emergency department; NA, not applicable.

[a] Number of cases and national estimates of ED visits are from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project. The hospitalization rate is the ratio of ED visits resulting in admission, observation, or transfer to total ED visits for adverse drug events involving the specified medication category.

[b] Estimated annual numbers of outpatient prescription visits for each medication category are from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey for 2009 and 2010 and include outpatient prescription visits in which multiple psychiatric medications were prescribed at a single visit.

[c] Statistically unreliable estimate.

Table 4

Numbers of Cases and National Estimates of Annual ED Visits for Psychiatric Medication Adverse Drug Events Among Adults 19 Years or Older, by Most Commonly Implicated Medications in the United States, 2009 Through 2011

Medication	ED Visits for Adverse Drug Events[a]				Estimated Annual ED Visits per 10 000 Outpatient Prescription Visits, No. (95% CI)[b]
	No. of Cases	Estimated Annual No. of Visits	Proportion of Visits Due to All Psychiatric Medications, % (95% CI)	Hospitalization Rate, %	
Zolpidem tartrate	445	10 212	11.5 (9.5–13.4)	23.1	5.5 (4.6–6.3)
Quetiapine fumarate	320	6900	7.7 (6.5–9.0)	24.9	10.8 (9.2–12.4)
Alprazolam	241	5616	6.3 (5.0–7.6)	27.9	2.7 (2.3–3.1)
Lorazepam	233	5517	6.2 (4.8–7.5)	21.5	3.1 (2.6–3.6)
Haloperidol	250	4879	5.5 (4.3–6.7)	11.6	43.3 (34.5–52.2)
Clonazepam	215	4571	5.1 (4.3–6.0)	24.2	3.3 (2.7–3.9)
Trazodone	182	4249	4.8 (3.9–5.7)	22.2	4.6 (3.8–5.4)
Citalopram hydrobromide	175	4143	4.6 (3.9–5.4)	9.8	3.0 (2.5–3.5)
Lithium	217	4034	4.5 (3.4–5.7)	50.6	18.3 (14.5–22.1)
Risperidone	166	3662	4.1 (3.2–5.0)	*c*	11.3 (9.0–13.7)

Abbreviation: ED, emergency department.

[a] Number of cases and national estimates of ED visits are from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project. Emergency department visits for adverse drug events include visits in which the specified medication was either the only psychiatric medication implicated or was implicated along with other psychiatric medications. The hospitalization rate is the ratio of ED visits resulting in admission, observation, or transfer to total ED visits for adverse drug events involving the specified medication.

[b] Estimated annual numbers of outpatient prescription visits for each medication are from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey for 2009 and 2010 and include outpatient prescription visits in which multiple psychiatric medications were prescribed at a single visit.

[c] Statistically unreliable estimate.

Table 5

Adverse Effects of Psychiatric Medication Adverse Drug Events Leading to ED Visits Among Adults 19 Years or Older in the United States, 2009 Through 2011

	No. (95% CI)				
	Estimated Annual ED Visits per 10 000 Outpatient Prescription Visits by Therapeutic Category[b]				
Adverse Effect[a]	Sedatives and Anxiolytics	Antidepressants	Antipsychotics	Lithium Salts	Stimulants
Abnormal behavior or mood	0.2 (0.2–0.3)	0.3 (0.3–0.4)	1.6 (1.3–1.9)	*c*	0.6 (0.4–0.7)
Abnormal drug level	*c*	*c*	*c*	8.1 (6.0–10.1)	*c*
Altered mental status	1.0 (0.8–1.1)	0.2 (0.2–0.3)	1.4 (1.1–1.7)	5.0 (3.8–6.3)	*c*
Cardiovascular	0.3 (0.3–0.4)	0.3 (0.2–0.3)	0.8 (0.7–1.0)	*c*	0.8 (0.6–1.0)
Disturbance in consciousness	1.0 (0.8–1.1)	0.2 (0.2–0.2)	1.3 (1.1–1.5)	*c*	*c*
Fall or head injury	0.5 (0.4–0.6)	0.1 (0.1–0.1)	0.4 (0.3–0.5)	*c*	*c*
Gastrointestinal	0.2 (0.2–0.2)	0.4 (0.4–0.5)	0.7 (0.6–0.9)	2.8 (2.0–3.5)	*c*
Hypersensitivity reaction	0.3 (0.2–0.3)	0.5 (0.4–0.6)	2.1 (1.8–2.4)	*c*	*c*
Movement disorder or spasticity	0.2 (0.2–0.2)	0.3 (0.3–0.3)	3.7 (3.1–4.2)	5.1 (3.9–6.3)	*c*
Miscellaneous	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.4 (0.3–0.5)	*c*	*c*
Muscular	0.3 (0.3–0.4)	0.2 (0.1–0.2)	0.9 (0.7–1.1)	2.9 (2.1–3.7)	*c*
Pain	0.2 (0.2–0.3)	0.4 (0.3–0.5)	1.2 (0.9–1.4)	*c*	*c*
Respiration	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.6 (0.5–0.7)	*c*	*c*
Sensory	0.5 (0.4–0.6)	0.5 (0.5–0.6)	1.5 (1.2–1.8)	2.8 (2.0–3.6)	0.8 (0.6–1.0)

Abbreviations: ED, emergency department; NA, not applicable.

[a] Adverse effect categories are not mutually exclusive. A single ED visit for an adverse drug event may be counted under multiple adverse effect categories.

[b] National estimates of ED visits are from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project. Emergency department visits for adverse drug events include visits in which the specified medication was either the only psychiatric medication implicated or was implicated along with other psychiatric medications. Estimated annual numbers of outpatient prescription visits for each medication type are from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey for 2009 and 2010 and include outpatient prescription visits in which multiple psychiatric medications were prescribed at a single visit.

[c] Statistically unreliable estimate.