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Adverse Childhood Experiences and Prescribed Psychotropic Medications in Adults

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Abstract

Background—Prescription drugs are one of the fastest growing healthcare costs in the United States. However, the long-term influence of child abuse and related traumatic stressors on prescriptions for psychotropic medications in adults has not been described. This study assessed the relationship of eight adverse childhood experiences (ACEs) to rates of prescriptions for psychotropic medications throughout adulthood. These ACEs included: abuse (emotional, physical, or sexual), witnessing domestic violence, growing up with substance abusing, mentally ill, or criminal household members, and parental separation/ divorce.

Methods—Data about ACEs were collected between 1995 and 1997 from adult health maintenance organization patients; prescription data were available from 1997 to 2004. The number of ACEs (ACE Score: maximum 8) was used as a measure of cumulative traumatic stress during childhood. The relationship of the score to rates of prescribed psychotropic drugs was prospectively assessed among 15,033 adult patients eligible for the follow-up phase of the study (mean follow-up: 6.1 years). Data were analyzed in 2006. Multivariate models were adjusted for age, race, gender, and education.

Results—Prescription rates increased yearly during the follow-up and in a graded fashion as the ACE Score increased (p for trend <0.001). After adjusting compared with persons with an ACE Score of 0, persons with a score of equal to or more than 5 had a nearly threefold increase in rates of psychotropic prescriptions. Graded relationships were observed between the score and prescription rates for antidepressant, anxiolytic, antipsychotic, and mood-stabilizing/bipolar medications; rates for persons with a score of equal to or more than 5 for these classes of drugs increased 3-, 2-, 10-, and 17-fold, respectively.

Conclusions—The strong relationship of the ACE Score to increased utilization of psychotropic medications underscores the contribution of childhood experience to the burden of adult mental illness. Moreover, the huge economic costs associated with the use of psychotropic medications provide additional incentive to address the high prevalence and consequences of childhood traumatic stressors.

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Introduction

Prescription drugs are one of the fastest growing healthcare costs in the United States, with total spending for these drugs in 2003 estimated to be $180 billion, or 11% of national health expenditures. This amount was more than four times greater than the amount spent in 1990.[1] Antidepressants, anxiolytics, and antipsychotics are among the top-selling prescription drugs, with retail sales of these medications during 2000 totaling $10.4, $3.1, and $2.4 billion, respectively.[2] Similarly, the impact of mental illness on disability and quality of life is also being increasingly recognized and quantified as a national public health priority.[3]

Increased spending on psychotropic medications and the disability and morbidity associated with mental illness highlight: (1) the cost of mental illness to affected individuals, the healthcare system, and society; and (2) the increasing importance of identifying preventable contributors to these disorders.

Childhood abuse and related traumatic stressors are well-established risk factors for developing acute and chronic mental illness. Numerous studies have documented these relationships and have been reviewed elsewhere.[4,5] Data from the Adverse Childhood Experiences (ACE) study,[6–8] have demonstrated that an integer count of the number of categories of abuse, exposure to domestic violence, and other forms of serious household dysfunction (ACE Score)[9] experienced during childhood has a strong, graded relationship to a wide variety of health and social problems from adolescence to adulthood[6–8,10–25] including depressive disorders,[6,8,11,19] suicide attempts,[11] anxiety,[6] hallucinations,[6,20] panic reactions,[6] sleep disturbances,[6] and memory disturbances.[6,21]

The relationship of child abuse and related traumatic stressors to prescriptions for psychotropic drugs in adulthood has not been described. This analysis used data from the ACE study to prospectively assess the relationship of the ACE Score to prescription rates for four classes of psychotropic medications.

Methods

Study Population

The ACE study methods have been described in detail elsewhere.[6–8] Briefly, >50,000 adult members of the Kaiser Health Plan in San Diego, California, are evaluated annually at Kaiser Permanente's San Diego Health Appraisal Clinic, which includes a standardized health history, psychosocial evaluations, and physical examination. The ACE study was approved by the institutional review boards of Kaiser Permanente and the Office for Protection from Research Risks at the National Institutes of Health.

The ACE study included both retrospective and prospective data-collection components. Retrospective data were collected as follows: members who completed the standardized Health Appraisal Clinic evaluation during the baseline survey period from August 1995 to October 1997 were mailed an ACE study questionnaire that contained questions about childhood exposure to abuse, neglect, domestic violence, and other forms of serious and interrelated household dysfunction.[9] A total of 17,421 (68%) responded; 84 people had incomplete information on race and educational attainment, leaving an analytic sample of 17,337 people.[11]

Prospective (Follow-up) Data Collection

Follow-up data on prescriptions filled were available from Kaiser Permanente from January 1, 1997 through December 31, 2004. This analysis included people 18 to 90 years old to facilitate direct age standardization to the 2000 U.S. population. A total of 1053 (6.1%)

people were excluded because their membership had expired prior to their evaluation at the Health Appraisal Clinic or January 1, 1997 (because pharmacy claims data before that date are not available), or because their member record number was not considered valid.

For those who disenrolled and re-enrolled at least once (median/mean: one time; range: one to six times) during the follow-up period, 1233 (7.1%) were excluded because their ratio of time disenrolled/total possible time enrolled during follow-up exceeded 20%; such persons were considered to have inadequate continuity of follow-up to merit consideration for inclusion in the prospective analysis. Thus, the final sample size was 15,033/17,337 (86.7% of the analytic sample).

To assess any influence of including persons with discontinuous follow-up, the analyses included herein were repeated after excluding any persons whose follow-up was discontinuous.

Relationship of the ACE Score to Exclusion from Follow-up

The potential contribution of ACEs to the exclusion from follow-up as a source of bias was assessed using logistic regression. In this analysis, the risks (ORs) of exclusion from follow-up for persons with one, two, three, or equal to or more than four ACEs were 1.0 (95% CI, 0.9–1.1), 1.0 (0.9–1.2), 1.2 (1.0–1.4), and 1.1 (0.9–1.3), respectively. Thus, ACE Scores had no meaningful relationship to exclusion from follow-up.

Definitions of ACEs

All questions used to define ACEs pertained to the respondents' first 18 years of life (Table 1). Questions adapted from the Conflict Tactics Scale[26] had five response categories: "never," "once or twice," "sometimes," "often," or "very often." Three categories of childhood abuse were used: emotional abuse (two questions), physical abuse (two questions), or contact sexual abuse (four questions) by Wyatt.[27] Five categories of exposure of household dysfunction during childhood were used: exposure to substance abuse (defined by two questions),[28] mental illness (two questions), violent treatment of mother or stepmother (four questions),[26] criminal behavior in the household (one question), and parental separation or divorce (one question). Respondents were defined as exposed to a category if they responded "yes" to one or more of the questions in that category; the number of categories of ACEs reported were summed to produce the ACE Score (Table 1), as noted. The statistical validity of the ACE Score has been published elsewhere.[9]

Rates of Prescription Drug Use

The Kaiser pharmacy database includes 15 classes of drugs. For this analysis, data for pharmacy claims where the therapeutic class was listed as "central nervous system" were used, and included the following medications: antidepressants, anxiolytics, antipsychotics, and lithium-based products (mood stabilizers/bipolar medication). This therapeutic class also included attention-deficit/hyperactivity disorder medications, alcohol abuse medications, sleep medications–hypnotics, and stimulants; because there were relatively few prescriptions for these other drugs, they are not assessed as separate groups of drugs in this analysis.

To calculate rates of psychotropic prescription drug use, the numerator was a count of the total prescription drug claims and the denominator was cumulative person-time at risk during follow-up. Person-time at risk was calculated using electronic enrollment data files provided by Kaiser Permanente. Because pharmacy claims data were not available prior to January 1, 1997, this date was assigned as the beginning of follow-up for persons enrolled

before January 1, 1997. Prescription medications were available through December 31, 2004 (latest available data).

The maximum possible person-time at risk was calculated as the difference between December 31, 2004 and the later of either January 1, 1997 or the baseline appointment date for persons who were continuously enrolled. For persons with periods of disenrollment, the time spent out of the plan was subtracted from time at risk.

Statistical Analysis

Analyses were conducted in the summer of 2006 using SAS v 9.1 (SAS Institute, Cary NC, 2004).[29] The 2000 U.S. Standard Population was used for direct age-standardization of prevalences and risks.

To assess the independent relationship between the ACE Score and the rate of prescription drug use, prescription drug rates using rate ratios derived from multivariable-adjusted negative binomial regression models using PROC GENMOD[29] were compared. To allow for differing lengths of follow-up, the log of person-time was incorporated as the offset in the model. Rate ratios were obtained by exponentiating estimated regression coefficients. Age, race/ethnicity, and gender were forced into all models. All statistical inferences were based on a significance level of α (two-sided) = 0.05.

Results

Characteristics of Study Population

The study population included 8134 women (54%) and 6899 men (46%). The mean age (standard deviation) was 57 (15) years. Seventy-six percent of participants were white, 11% Hispanic, 4% black, 7% Asian, less than 1% Native American, and 2% other; 40% were college graduates, 36% had some college education, and 17% were high school graduates. Only 7% had not graduated from high school. The mean follow-up was 6.1 (SD, 2.4) years.

Prevalence of ACEs and the ACE Score

The prevalence of each of the eight individual ACEs and the ACE Score are presented in Table 1. Nearly two thirds (64%) of the cohort reported at least one ACE, and more than one third had two or more.

Prescription Rates by Year and ACE Score

A total of 88,475 prescriptions for psychotropic medications were written during 95,883 person-years of follow-up. The age-standardized prescription rate was 82.3 per 100 person-years.

Between 1997 and 2004, annual rates of prescriptions for psychotropic medications increased substantially in the study cohort (Table 2). In addition, the prescription rates increased substantially as the ACE Score increased within each year of follow-up (Table 2).

Prescription Rates by ACE Score

As the ACE Score increased, rates of prescribed psychotropic medication increased in a graded fashion (Model A, Table 3; p for trend <0.001). When a history of mental illness in the home was excluded from the ACE Score, the strength of the ACE-prescription rate relationship was not changed substantially (Model B, Table 3; p for trend <0.001).

ACE Score and Classes of Psychotropic Medications

The ACE Score also had a strong, graded relationship to prescription rates for antidepressant, anxiolytic, antipsychotic, and mood stabilizing medications (*p* for trend <0.001 for each class) (Table 4). After adjusting for demographic factors, rates for persons with a score ≥ 5 for these classes of drugs increased 3-, 2-, 10-, and 17-fold, respectively.

ACE Score and Prescription Rates by Age Group

A consistent graded relationship between the ACE Score and rates of antidepressant prescriptions was observed for younger (18–44 years), middle aged (45–64 years), and older (65–89 years) adults; *p* for trend <0.001 for each group. A similar and consistent pattern between the ACE Score and rates of anxiolytic prescriptions was also seen; *p* for trend <0.05 for each group. A graded relationship between the score and rates of antipsychotic prescription rates was observed for younger and middle aged adults (*p* for trend <0.001 for each group), but was not seen for older adults. Similarly, a graded relationship between the ACE Score and rates of lithium-based (bipolar/mood stabilizers) prescription rates was observed for younger (*p* for trend=0.07) and middle-aged adults (*p* for trend <0.01), but the number of prescriptions among older adults was inadequate for meaningful analysis.

When we repeated these analyses, after excluding persons with discontinuous follow-up, the results were not changed significantly or meaningfully.

Discussion

Prescription rates for antidepressant and anxiolytic drugs increased in a dose–response fashion as the ACE Score increased for young, middle-aged, and older adults. This finding suggests that the cost of prescription psychotropics extends throughout adulthood. Such relationships were also found among younger and middle-aged adults for antipsychotic and lithium-based drugs. The lack of a relationship between the score and antipsychotics in older adults is likely explained by the use of these medications to treat agitation and other severe symptoms in older persons with dementia.[30] These rates reinforce the notion that ACEs frequently have a lifetime effect on the emotional and mental health of millions of Americans.[3,6,11,19]

Despite intensive and increasingly sophisticated research using animal models, genetic studies, neuro-imaging, neurotransmitter, and other biologic assessments, the causes of anxiety and mood disorders remain unclear.[31] Family history is a predictor of depression,[32] and heritability of affective disorders is estimated to be approximately 40%.[33] Regardless, the biology of psychiatric disorders likely involves the interaction of polygenic factors, epigenetics, and early-life experiences.[34] Notably, the exclusion of a history of mental illness in the home from the ACE Score as a way of controlling for potential genetic influences had little effect on the strength of the ACE Score–prescription rate relationship. A recent discovery that a polymorphism in the serotonin transporter allele is associated with increased risk of depression in persons exposed to ACEs such as physical or sexual abuse[34] is consistent with this view of the multiple factors contributing to the occurrence of these disorders.[35] However, advances in genomic technology have not similarly advanced understanding of the etiology of psychiatric disorders.[31] The data presented herein and elsewhere[6,11,19] provide evidence for a role of early-life adversity in the manifestation and treatment of common psychiatric symptoms and disorders.

The strengths of this study are its prospective design and the use of prescription data, which reflect physician practices rather than patient self-reports. Use of prospectively collected data reduces the risk that the results were influenced by reporting or recall bias. Between 1997 and 2004, rates of psychotropic medication use increased in the study cohort. This

finding is consistent with recent increases in prescriptions for drugs treating mental illness among older adults in a population-based study in Ontario.[36] In addition, the relationship between the ACE Score and individual types of psychotropic drugs is strong and graded.

The relevance of ACEs to the treatment of mental illness is emerging. Childhood adversity may lead to psychiatric disorders that are neurobiologically distinct, require unique treatment approaches, have different treatment responses, or necessitate clinical trials that incorporate childhood adversity and understanding of the neurobiologic changes that accompany them into their design.[33] A 1992 survey of primary care providers indicated their reluctance to inquire about issues such as domestic violence for fear of opening a "Pandora's Box" of their own issues including lack of comfort, fear of offending, powerlessness, loss of control, and time constraints.[37] More than a decade later, discussion of barriers to screening and need for training for clinicians in the areas of child maltreatment, intimate partner violence, and related issues continues.[38,39] These issues are "… a significant health problem in the United States requiring support for the education and training of medical professionals."[39,40]

Research is needed to help clinicians in understanding how to prevent ACEs and intervene early with persons exposed to them (primary and secondary intervention) to impact the need for psychotropics later in life. In addition, many clinicians may not yet be aware that high levels of childhood adversity are associated with high risk of a wide variety of comorbid health and social problems[37] that may affect treatment outcomes when prescribing psychotropic medication.

The strong, graded relationship of ACEs to prescription rates for psychotropic medications in adults has implications for understanding the early life origins of the mental illness and human suffering for which they are prescribed. Moreover, the huge economic costs[1,2,36] and potential risks[41–47] associated with the use of psychotropic medications provide additional incentive to reduce the high prevalence and consequences of exposure to childhood traumatic stressors.

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Table 1

Definition and prevalence of each category of adverse childhood experience

Childhood abuse	**%**
Emotional	10.3
(Did a parent or other adult in the household …)	
1 Often or very often swear at you, insult you, or put you down?	
2 Sometimes, often, or very often act in a way that made you afraid you might be physically hurt?	
Physical	28.0
(Did a parent or other adult in the household …)	
1 Often or very often push, grab, slap, or throw something at you?	
2 Often or very often hit you so hard that you had marks or were injured?	
Sexual	20.4
(Did an adult or person at least 5 years older ever …)	
1 Touch or fondle you in a sexual way?	
2 Have you touch their body in a sexual way?	
3 Attempt oral, anal, or vaginal intercourse with you?	
4 Actually have oral, anal, or vaginal intercourse with you?	
Household dysfunction	
Substance abuse	26.6
1 Live with anyone who was a problem drinker or alcoholic?	
2 Live with anyone who used street drugs?	
Mental illness	19.0
1 Was a household member depressed or mentally ill?	
2 Did a household member attempt suicide?	
Mother treated violently	12.6
(Was your mother [or stepmother]):	
1 Sometimes, often, or very often pushed, grabbed, slapped, or had something thrown at her?	
2 Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard?	
3 Ever repeatedly hit over at least a few minutes?	
4 Ever threatened with or hurt by a knife or gun?	
Incarcerated household member	4.5
1 Did a household member go to prison?	
Parental separation or divorce	22.8
1 Were your parents ever separated or divorced?	
Number categories of adverse childhood experiences (ACE Score)	
0	36.4
1	26.2
2	15.9

Childhood abuse	**%**
3	9.3
4	6.1
5 or more	6.1

Percentages based on a total of 15,033 adults included in the analysis sample. The ACE Score is the sum of the number of categories adverse childhood experiences reported.

Table 2

Rates of prescriptions for psychotropic medications by year and ACE Score, ACE Study Cohort, 1997–2004[a]

		Prescription rates by year							
ACE score	**Sample size (*n*)**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**
0	5480	39.5	43.0	46.9	50.1	57.6	60.6	60.2	60.4
1	3938	56.4	60.9	71.2	81.6	81.6	87.3	81.7	87.5
2	2392	76.2	84.1	84.8	99.3	100.0	99.1	100.6	104.0
3	1394	93.5	101.7	89.6	95.6	105.5	109.8	119.9	110.2
4	915	106.2	126.1	136.1	153.9	165.1	152.7	140.4	122.8
5 or more	914	149.1	130.1	126.2	144.0	159.5	172.9	175.5	172.9
Overall	15,033	66.7	70.1	75.9	88.0	94.0	97.3	96.3	95.7

[a] Rates (per 100 person-years) are age-standardized to the 2000 U.S. population.

Table 3

Relationship between ACE Score and prescriptions for psychotropic medications, 1997–2004

ACE Score	*n*	Person-years	Rate[a]	Model A[b] RR (95% CI)	Model B[c] RR (95% CI)
0	5,480	35,594	51.7	1.0 (referent)	1.0 (referent)
1	3,938	25,293	73.5	1.3 (1.1–1.4)	1.2 (1.1–1.3)
2	2,392	15,205	89.6	1.6 (1.4–1.8)	1.4 (1.3–1.6)
3	1,394	8,620	108.1	1.6 (1.4–1.9)	1.8 (1.5–2.1)
4	915	5,644	139.1	2.3 (1.9–2.7)	2.1 (1.7–2.6)
≥5	914	5,527	146.4	2.9 (2.4–3.5)	2.4 (1.9–3.0)
Total	15,033	95,883	82.3	—	—

[a] The prescription rate (per 100 person-years) is age standardized to the 2000 U.S. population.

[b] Model A, association between the relative rate of prescribed medications for central nervous system disorders and ACEs adjusted for age, gender, race/ethnicity, education.

[c] Model B, association between the relative rate of prescribed medications for central nervous system disorders and ACEs adjusted for age, gender, race/ethnicity, education after removing household mental illness from the ACE Score.

RR, relative rate; CI, confidence interval.

Table 4

Relationship between ACE Score and prescriptions for antidepressants, anxiolytics, antipsychotics, and lithium-based (bipolar/mood stabilizers) drugs, 1997–2004

	Antidepressant		Anxiolytic		Antipsychotic		Lithium based (bipolar/mood stabilizer)	
ACE Score	**Rate[a]**	**RR (95% CI)[a]**	**Rate[a]**	**RR (95% CI)[b]**	**Rate[a]**	**RR (95% CI)[b]**	**Rate[a]**	**RR (95% CI)[b]**
0	32.8	1.0 (referent)	16.1	1.0 (referent)	1.9	1.0 (referent)	0.2	1.0 (referent)
1	50.1	1.3 (1.1–1.4)	16.7	1.1 (0.9–1.3)	3.6	1.3 (0.8–2.24)	1.3	4.1 (1.4–12.1)
2	65.0	1.7 (1.5–2.0)	19.2	1.2 (0.9–1.4)	2.3	1.6 (0.9–2.83)	1.6	4.6 (1.3–16.5)
3	73.2	1.8 (1.5–2.1)	28.2	1.3 (1.0–1.6)	4.9	2.4 (1.29–4.99)	0.2	1.4 (0.3–6.31)
4	97.0	2.4 (2.0–3.0)	28.4	1.6 (1.2–2.1)	10.1	4.8 (2.0–11.4)	0.8	8.4 (1.0–72.3)
≥5	99.5	2.9 (2.4–3.6)	32.8	2.1 (1.6–2.8)	10.2	10.3 (4.4–24.2)	2.7	17.3 (2.9–107.9)
Total	56.4	—	19.6	—	3.8	—	1.0	—

[a]The prescription rate (per 100 person-years) is age standardized to the 2000 U.S. population.

[b]Model adjusted for age, gender, race/ethnicity, education.

RR, relative rate; CI, confidence interval.