Sudden Deaths in Psychiatric Patients

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Background: Studies using death certificates have indicated an excess of sudden cardiac deaths among users of antipsychotic drugs compared to the general population, but they may have underestimated the presence of other known causes of sudden and unexpected death.

Objective: To assess the causes and risk factors for sudden death discovered by contemporaneous investigation of all deaths occurring over a 26-year period (1984–2009) in adults (119,500 patient-years) receiving care in one large psychiatric hospital in New York.

Method: Circumstances of death, psychiatric diagnoses, psychotropic drugs, and past medical history were extracted from the root cause analyses of sudden, unexpected deaths. After cases involving suicide, homicide, and drug overdoses were excluded, the remaining explained and unexplained cases of sudden death were compared regarding clinical variables and the utilization of antipsychotics.

Results: One hundred cases of sudden death were identified. The death remained unexplained in 52 cases. The incidence of unexplained sudden death per 100,000 patient-years increased from 7 (95% CI, 3.7–19.4) in 1984–1998 to 125 (95% CI, 88.9–175.1) in 2005–2009. Explained and unexplained cases were similar regarding psychiatric diagnoses and use of all psychotropic classes, including first- and second-generation antipsychotics. Dyslipidemia ($P = .012$), diabetes ($P = .054$), and comorbid dyslipidemia and diabetes ($P = .006$) were more common in the unexplained group.

Conclusions: In a consecutive cohort of psychiatric patients, the unexplained sudden deaths were not associated with higher utilization of first- or second-generation antipsychotics. The role of diabetes and dyslipidemia as risk factors for sudden death in psychiatric patients requires careful longitudinal studies.

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In January 2009, the *New England Journal of Medicine* published data from a retrospective cohort study demonstrating an increased risk of sudden cardiac death in patients 30–74 years of age treated with antipsychotic drugs.[1] The study compared the incidence of sudden cardiac death in a large cohort of users of typical antipsychotics, users of atypical antipsychotics, and propensity score–matched nonusers of antipsychotics, all Medicaid enrollees in Tennessee. According to death certificates, during the 1,042,159 person-years of cohort follow-up, there were 1,870 (1.79/1,000 person-years) sudden deaths that occurred in the absence of a known, noncardiac condition as the proximate cause of death. After adjustments for demographic variables and the presence of comorbid somatic conditions were applied, the incidence-rate ratios of sudden cardiac death were 1.99 for users of typical antipsychotics and 2.26 for individuals treated with atypical antipsychotics.[1] The study confirmed and expanded previous work by the same group using the death certificates matched to the Tennessee Medicaid database, in which current users of moderate dose antipsychotics (> 100 mg thioridazine equivalents) were shown to have a sudden cardiac death ratio of 2.39 compared to nonusers. Among cohort members with detectable cardiovascular disease, the rate ratio was 3.53.[2] In a methodologically similar assessment of 3 state-wide Medicaid programs, patients treated with antipsychotics had 1.7 to 3.2 incidence-rate ratios of cardiac arrest and ventricular arrhythmias compared with nonusers, depending on the antipsychotic used.[3]

The authors of these epidemiologic studies suggested that the excess of sudden cardiac death in patients treated with antipsychotics is due to the effect that these drugs have on myocardial repolarization, an outcome that is evident in the drugs' well-established potential for inducing the prolongation of the rate-corrected QT interval on electrocardiogram.[4] A prolonged QT is a risk factor for torsades de pointes, a ventricular arrhythmia that may degenerate into ventricular fibrillation and lead to sudden death.[4,5] However, torsades de pointes has not been identified in the epidemiologic surveys on sudden death in users of antipsychotic drugs.

The findings indicating that typical and atypical antipsychotic use is associated with a similar excess of sudden cardiac deaths[1] have been disputed by the American Psychiatric Association (APA) Council on Research in its online report "APA Guidance on the Use of Antipsychotic Drugs and Cardiac Sudden Death."[6] The APA Council stated that the use of death certificates may have led to overestimation of the sudden cardiac death incidence, underestimation of the cardiovascular morbidity of users of antipsychotic drugs, and inadequate control for important confounding variables.

Sudden and otherwise unexplained deaths are commonly due to ventricular fibrillation arising as a consequence of coronary artery disease.[7] Nonetheless, the determination of the cause of sudden and unexpected death is seldom easy or straightforward. The individual who develops chest pain and who is found to have ischemic changes on the electrocardiogram just before dying en route to the emergency room of the nearest hospital can be safely assumed to have had an acute coronary event. In many other cases, particularly in patients dying alone or in unclear circumstances, the death may remain unexplained even after careful postmortem

assessments. This reality, which is more likely to occur in patients with severe mental disorders, is indeed poorly captured in the death certificate.[8,9] A root cause analysis performed by a multidisciplinary team with access to all relevant information is clearly superior for the investigation of unexpected deaths. In fact, compared with a physician-based procedure that used clinical records, autopsy reports, and an informant (next-of-kin) interview, the death certificates had a sensitivity of only 24% and a specificity of 85% for the correct classification of cardiovascular and noncardiovascular deaths.[9]

In this study, we reviewed the root cause analyses of 100 consecutive cases of sudden death that occurred among the patients receiving care in a single behavioral health institution in New York City and compared the groups with explained and unexplained deaths. We hypothesized that unexplained sudden deaths reflect a high prevalence of major risk factors for coronary artery disease, rather than a greater utilization of antipsychotic drugs.

METHOD

Setting and Patient Population

The study was based on information contained in the Special Review Committee reports sent from 1984 to 2009 to the Chairman of the Department of Psychiatry, Zucker Hillside Hospital, a behavioral health component of the North Shore-Long Island Jewish Health System. The hospital is located in the borough of Queens in New York City and comprises a 230-bed acute inpatient facility, outpatient clinics, and day and partial hospital program. The inpatient facility had an average of 3,000 adult admissions/y throughout the period studied, with an average length of stay of approximately 30 days. There were 3,500 patient "slots" in the adult outpatient programs from 1984 through 1993 and 4,800 registrants from 1994 to 2009. The study was approved by the Institutional Review Board, North Shore-Long Island Jewish Health System, Manhasset, New York.

Data Collection

Beginning in 1977, the Special Review Committee has been investigating all deaths occurring in the inpatient and outpatient programs, including the 30-day period following discharge from these programs. The Committee is chaired by a physician and has as members 3 other physicians and 2 nurses managing the quality improvement activities of the department. All providers are obligated to report the death of any of their patients as soon as possible. The task of the committee is to establish the cause of death by reviewing all available medical records; interviewing the health care providers and family members; obtaining information, when appropriate, from the Emergency Medical Services and the Medical Examiner Office of the City of New York; and arranging for independent expert assessments. A structured report is generated within 120 days of each death. The report contains demographic information, psychiatric diagnoses, past medical history, medication regimen at the time of death, and a description of the terminal event and a statement with regard to the cause of death.

When the events were witnessed, the patients selected for this study had died suddenly and unexpectedly within 1 hour of symptom onset. If not witnessed, the subjects had been observed alive within 24 hours of their death.[10]

The structured root cause analysis of cases of sudden death occurring in patients treated with psychotropic drugs included a careful review of the available electrocardiograms to establish compliance with hospital policy mandating electrocardiograms for all patients prior to treatment with psychotropic drugs known to prolong the QT interval.

Selection of Cases

Included in this study were all cases of sudden and unexpected deaths in individuals 19–74 years of age that occurred from 1984 through 2009. Excluded were deaths due to trauma, suicide, homicide, or intentional or accidental drug overdoses. The contribution of nonprescribed substance use as the cause of death was excluded on the basis of postmortem toxicologic assessments. The cases were entered in the study cohort in reverse chronological order starting with patients who died in 2009. The 100-case mark was reached in 1984. The total cohort follow-up was estimated to be 119,500 patient-years, representing the total number of registrants in outpatient programs and one-sixth of inpatient admissions (ie, accounting for the average length of stay plus 30 days of mandatory follow-up). This estimate assumes that all outpatient slots were filled without any interruption. Therefore, the incidence ratios calculated using these estimate are conservative.

Statistical Analyses

Each death was classified as "explained" or "unexplained" based on the conclusion stated in the root cause analysis. We compared the explained and unexplained groups with regard to demographic characteristics, psychiatric diagnoses, psychotropic medications, and past medical history. The significance of the differences in proportions was assessed with χ^2 or Fisher exact tests, according to the lowest number of cases in the 2×2 contingency tables. Logistic regression analyses were also performed with all variables. Because the year of death could be a systematic confounder, we repeated the logistic regression analyses after including the year of death into the model.

RESULTS

Causes of Death

The cause of death was identified in 48 of the 100 cases (Table 1 and Figure 1). The most common explanations of sudden and unexpected death were acute coronary syndromes (15% of the cohort), followed by upper airway obstruction (due to choking on food in 3 cases and to obstructive sleep apnea in 2 patients), pulmonary emboli (4%), and thrombotic strokes (3%). Among the unusual causes were 2 cases of myocarditis (1 related to treatment

Table 1. Causes of Sudden Death (N = 100)

Cause	n
Cardiovascular diseases, total	22
Acute coronary syndrome	15
Heart failure	2
Aortic dissection	2
Myocarditis	2
Commotio cordis	1
Gas exchange failure, total	17
Upper airway obstruction	5
Pulmonary embolus	4
Bronchial asthma	2
Pneumonia	2
Respiratory failure NOS	4
Intracranial event, total	5
Thrombotic stroke	3
Brain hemorrhage	2
Diabetic ketoacidosis	1
Septic shock	1
Seizure	1
Gastrointestinal bleeding	1
Unknown	52

Abbreviation: NOS = not otherwise specified.

Table 2. Demographic and Psychiatric Characteristics

Characteristic	Total (N = 100)	Explained (n = 48)	Unexplained (n = 52)	*P* Value
Age, mean ± SD, y	49.4 ± 12.1	49.0 ± 12.7	49.7 ± 13.0	NS
Sex, n (%)				
Male	62 (62.0)	31 (64.6)	31 (59.6)	NS
Female	38 (38.0)	17 (35.4)	21 (40.4)	NS
Primary psychiatric diagnoses, n (%)[a]				
Psychotic disorders	33 (34.0)	17 (37.8)	16 (30.8)	NS
Schizophrenia	27 (27.8)	14 (31.1)	13 (25.0)	NS
Psychosis NOS	6 (6.2)	3 (6.3)	3 (5.8)	NS
Mood disorders	46 (47.4)	21 (43.8)	25 (48.1)	NS
Bipolar disorder	18 (18.6)	10 (22.2)	8 (15.4)	NS
Major depression	19 (19.6)	5 (11.1)	14 (26.9)	NS
Depression NOS	9 (9.3)	6 (13.3)	3 (5.8)	NS
Anxiety disorders	5 (5.2)	3 (6.3)	2 (3.8)	NS
Substance use disorders	9 (9.3)	2 (4.4)	7 (13.5)	NS
Other	4 (4.1)	2 (4.4)	2 (3.8)	NS
Psychotropic treatment, n (%)				
First-generation antipsychotics	9 (9.0)	5 (10.4)	4 (7.7)	NS
Second-generation antipsychotics	40 (40.0)	17 (35.4)	23 (44.2)	NS
Clozapine	9 (9.0)	4 (8.3)	5 (9.6)	NS
Olanzapine	8 (8.0)	6 (12.5)	2 (3.8)	NS
Quetiapine	11 (11.0)	0 (0.0)	11 (21.2)	.002
Risperidone	9 (9.0)	5 (10.4)	4 (7.7)	NS
Aripiprazole	2 (2.0)	2 (4.2)	0 (0.0)	NS
Ziprasidone	1 (1.0)	0 (0.0)	1 (1.9)	NS
Antidepressants	33 (33.0)	13 (27.1)	20 (38.5)	NS
SSRI	19 (19.0)	8 (16.7)	11 (21.2)	NS
SNRI	11 (11.0)	1 (3.1)	10 (19.2)	.012
Tricyclic	5 (5.0)	2 (4.2)	3 (5.8)	NS
Mirtazapine	5 (5.0)	1 (3.1)	4 (7.7)	NS
Mood stabilizers	16 (16.0)	7 (14.6)	9 (17.3)	NS
Lithium	6 (6.0)	4 (8.3)	2 (3.8)	NS
Valproate	6 (6.0)	3 (6.3)	3 (5.8)	NS
Gabapentin	4 (4.0)	0 (0.0)	4 (7.7)	NS
Lamotrigine	3 (3.0)	0 (0.0)	3 (5.8)	NS
Benzodiazepines	9 (9.0)	3 (6.3)	6 (11.6)	NS
Methadone	2 (2.0)	0 (0.0)	2 (3.8)	NS
Psychostimulants	3 (3.0)	1 (3.1)	2 (3.8)	NS

[a]Diagnostic data missing for 3 patients from the explained group.
Abbreviations: NOS = not otherwise specified, NS = nonsignificant, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitors.

Table 3. Past Medical History

Characteristic, n (%)	Total (N = 100)	Explained (n = 48)	Unexplained (n = 52)	*P* Value
Cardiovascular disease				
Coronary artery disease	13 (13.0)	5 (10.4)	8 (15.4)	NS
Arterial hypertension	35 (35.0)	15 (31.3)	20 (38.5)	NS
Congestive heart failure	4 (4.0)	3 (6.3)	1 (1.9)	NS
Other	5 (5.0)	1 (2.1)	4 (7.7)	NS
Metabolic disorder				
Dyslipidemia	26 (26.0)	7 (14.6)	19 (36.5)	.012
Diabetes	23 (23.0)	7 (14.6)	16 (30.8)	.054
Diabetes and dyslipidemia	11 (11.0)	1 (2.1)	10 (19.2)	.006
Hypertension and dyslipidemia	17 (17.0)	5 (10.4)	12 (23.1)	NS
Cerebrovascular disease	2 (2.0)	0 (0.0)	2 (3.8)	NS
Bronchial asthma or COPD	7 (7.0)	3 (6.3)	4 (7.7)	NS
Obstructive sleep apnea	2 (2.0)	0 (0.0)	2 (3.8)	NS

Abbreviations: COPD = chronic obstructive pulmonary disease, NS = nonsignificant.

with clozapine), 1 case of diabetic ketoacidosis in a patient receiving risperidone, a case of septic shock as the presenting symptom of perforated appendicitis, and a case of *commotio cordis* in a 22-year-old patient who was punched with moderate force in the chest. The cause of death remained unknown in 52% of the cohort.

Psychiatric Characteristics

The explained and unexplained groups were similar with respect to age, sex, primary psychiatric diagnoses and all medication classes, including first- and second-generation antipsychotics (Table 2). Prescriptions for quetiapine ($P = .002$) and serotonin-norepinephrine reuptake inhibitors (SNRIs) ($P = .012$) were more prevalent in the group with unexplained sudden death. The most commonly used SNRI in this group was venlafaxine (9 of 10 cases).

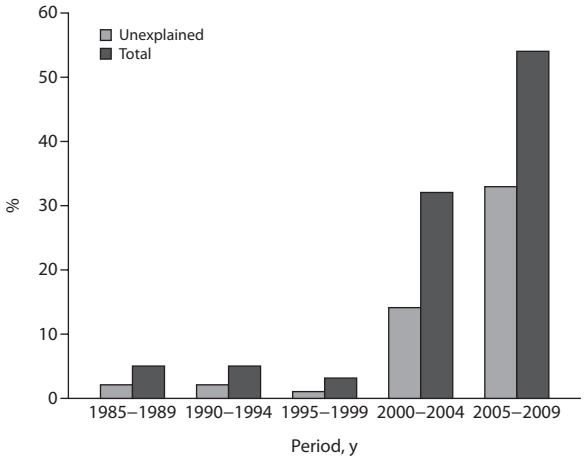
Past Medical History

Compared with the group of explained sudden death cases, significantly more subjects from the unexplained sudden death group had a history of dyslipidemia (36.5% vs 14.6%, $P = .012$) (Table 3). The comorbid associations of dyslipidemia with diabetes (19.2% vs 2.1%, $P = .006$) was also significantly more common in the unexplained sudden death group. In addition, diabetes was more than twice as common in the group with explained sudden death (30.8% vs 14.6%, $P = .054$).

Chronological Distribution of Sudden and Unexpected Deaths

The 5-year interval 2005–2009 had 54 cases of sudden death, of which 33 (61.1%) were unexplained (mean ± SD age = 50.9 ± 11.8 years) (Figure 1). In the preceding 5-year interval (1999–2004), there were 32 sudden deaths, of which 14 (43.8%) were unexplained (mean ± SD age = 50.7 ± 13.4 years). In contrast, there were only 13 cases of sudden death, of which 5 (38.5%) were unexplained (mean ± SD age = 41.2 ± 19.3 years), in the entire preceding 15-year period from 1984 through 1998 (Figure 1). The incidence of unexplained sudden death per 100,000 patient-years

Figure 1. Chronological Distribution of Sudden Deaths (percentages of 100-case cohort/5-year interval)



was 125 (95% CI, 88.9–175.1) in 2005–2009, 53 (95% CI, 31.7–88.5) in 1999–2004, and 7 (95% CI, 3.7–19.4) in 1984–1998.

Logistic Regression

In the logistic regression analysis, only the comorbid presence of dyslipidemia and diabetes (OR = 11.19; 95% CI, 1.37–91.14; $P = .024$) remained independently associated with unexplained cause of sudden death.

DISCUSSION

Sudden death may occur as the outcome of many life events or pathological processes, including posttraumatic injury of vital organs, accidental or intentional poisoning, and upper airway obstruction with foreign bodies or laryngeal spasm or edema. Most nontraumatic and otherwise unexplained sudden deaths are due to ventricular fibrillation. These arrhythmogenic sudden cardiac deaths are produced by structural or functional abnormalities of the heart (Table 4). Ample autopsy data indicate that active coronary lesions are observed in up to 80% of sudden cardiac death victims.[7] Other structural cardiac disorders that may end in sudden cardiac death are distinctly less common. Dilated cardiomyopathies, a chronic heart muscle disease characterized by left ventricular dilatation and impairment of systolic function, accounts, at most, for 7% of sudden cardiac deaths.[7,11] Hypertrophic cardiomyopathy (an inherited disorder of genes encoding sarcomeric proteins) and the right ventricular cardiomyopathy (due to fibrofatty replacement of the right ventricular myocardium) explain 4% of arrhythmogenic sudden deaths in the general population.[7,12] In a small minority of adults, the arrhythmogenic sudden cardiac deaths may occur in persons whose hearts have no detectable lesions on routine autopsies. The root cause of these deaths can be traced to abnormal myocardial repolarization (congenital or acquired

Table 4. Causes of Arrhythmogenic Sudden Cardiac Death

Structural abnormalities
Coronary artery disease
Hypertrophic cardiomyopathy
Right ventricular cardiomyopathy
Dilated cardiomyopathy
Aortic stenosis
Mitral valve prolapse
Myocarditis
Anomalous origin of coronary arteries
Myocardial bridging
Functional abnormalities
Long QT syndrome
Brugada syndrome
Preexcitation syndromes
Catecholaminergic polymorphic ventricular tachycardia
Atrioventricular conduction abnormalities

QT prolongation and Brugada syndrome), atrioventricular preexcitation (Wolff-Parkinson-White syndrome), abnormal response to stress (catecholaminergic polymorphic ventricular tachycardia), or to idiopathic ventricular tachycardia.[7]

Our study used structured root cause analysis of death and indicated that the incidence of sudden and unexpected deaths among psychiatric patients has increased greatly in the first decade of the 21st century. Slightly less than half of these cases (48%) had a defined cause of death, with acute coronary syndromes being by far the most common. The unexplained cases demonstrated a significantly higher prevalence of dyslipidemia and its comorbid associations with diabetes. This correlation must be confirmed by large longitudinal studies, but the signal registered by our study should strengthen efforts to understand the relationship between these metabolic abnormalities and genetic predispositions specific to persons suffering from severe mental illnesses in the global context of rapidly increased prevalence of obesity and diabetes. Dyslipidemia is the primary risk factor for coronary events, ie, myocardial infarction and sudden death.[13] Diabetes is associated with increased risk of sudden death, a complication related mostly to its role in determining the severity of coronary atherosclerosis (macrovascular effect). Microvascular complications of diabetes, such as microalbuminuria and retinopathy, are also strong independent correlates of sudden death.[14] The presence of patchy areas of myocardial fibrosis in patients with evidence of microvascular complications of diabetes may explain their increased risk for lethal ventricular arrhythmias.[14] In the Atherosclerosis Risk in Community study,[15] the proportional hazard ratio of the association of baseline diabetes with sudden death over an average follow-up period of 12.4 years was 3.77, independent of blood pressure, lipids, inflammation, hemostasis, and renal function. Finally, the comorbid associations between dyslipidemia, diabetes, and arterial hypertension most likely reflect the presence of metabolic syndrome, a plurifactorial risk factor that is known to double the 10-year probability of coronary events in patients treated with atypical antipsychotics.[16]

In univariate analyses, our study identified a higher use of quetiapine and venlafaxine in the group of patients with unexplained sudden death. We could not find published

clinical reports of sudden deaths in patients receiving quetiapine in approved dosages. In postmarketing surveillance, cardiovascular disorders have been identified as the most common cause of death (31.2% of all deaths) in patients treated with quetiapine,[17] but there is no indication that quetiapine is more dangerous than other second-generation antipsychotics, as shown in the study comparing users and nonusers of antipsychotic drugs in which the incidence-rate ratio of sudden cardiac death was 1.88 for quetiapine, 2.04 for olanzapine, 2.91 for risperidone, and 3.67 for clozapine.[1] With regard to venlafaxine, the adjusted odds ratio of sudden cardiac death or near death associated with this antidepressant was 0.66 relative to fluoxetine and 0.89 compared to citalopram use.[18] As most cases of unexplained sudden death occurred in the past 10 years, it is possible that the frequent use of venlafaxine and quetiapine in this group reflects the increased utilization of these drugs among patients with severe psychiatric disorders.[18,19]

Similar to other studies of sudden death in psychiatric patients,[1–3] the interpretation of our findings is limited by lack of data with regard to changes in body mass index and QT intervals prior to sudden death and the quality of medical care received by these psychiatric patients. Other limitations include a relatively small sample size and the fact that, although all deaths had been referred to the Office of the Medical Examiner, a complete autopsy was performed in only 18 of the 100 cases.

The findings provide preliminary evidence that unexplained sudden deaths of psychiatric patients are most likely due to coronary events. We found no evidence to support the antipsychotic-induced QT prolongation, leading to torsades de pointes and ventricular fibrillation, as a cause of death. Although larger studies are clearly required to confirm and expand our findings, we feel confident that our results suggest that psychiatric providers must intensify the identification and adequate treatment of dyslipidemia, diabetes, and arterial hypertension for all of their patients. From this standpoint, a number of recent studies have shown disconcertingly low adherence rates to generally accepted cardiometabolic monitoring guidelines of patients treated with antipsychotics.[20–23] We think that the field is in urgent need to develop education programs and campaigns that increase the monitoring to the desired and required levels. In addition, system-level and individual provider–level interventions are needed to improve the medical care in mentally ill patients with identified medical problems.[24–27] Importantly, our study results suggest that adequate monitoring and management of cardiometabolic risk factors will most likely not only reduce morbidity and mortality directly related to cardiovascular disorders but also decrease sudden cardiac death risk.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), methadone (Methadose and others), quetiapine (Seroquel), risperidone (Risperdal and others), olanzapine (Zyprexa), venlafaxine (Effexor and others), ziprasidone (Geodon).

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Potential conflicts of interest: **Dr Manu** has served on the speaker/advisory boards of Eli Lilly, Pfizer, Bristol-Myers Squibb, and Forest. **Dr Kane** has been a consultant to AstraZeneca, Janssen, Eli Lilly, Bristol-Myers Squibb, Otsuka, Takeda, Targacept, and Johnson & Johnson and has received honoraria for lectures from Boehringer-Ingelheim. **Dr Correll** has been a consultant to Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Hoffman-LaRoche, Medicure, Otsuka, Pfizer, and Vanda; has received honoraria from Cephalon, GlaxoSmithKline, Lundbeck, Ortho-McNeil-Janssen, Pfizer, and Supernus; and has served on advisory boards for Bristol-Myers Squibb, Actelion, Otsuka, Pfizer, Schering-Plough, Takeda, and AstraZeneca.

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