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The incidence and associated risk factors for sudden unexplained death in psychiatric in-patients in England and Wales

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Abstract

Clinical characteristics and risk factors associated with sudden unexplained death (SUD) in the psychiatric population are unclear. Psychiatric in-patients (England, Wales) who met criteria for SUD were identified (1 March 1999–31 December 2005). Cases were matched with controls (in-patients alive on the day a SUD occurred). Data were collected via questionnaires. Some 283 cases of SUD were identified (41 annually), with a rate of 2.33/10,000 mental health admissions (in England). Electrocardiograms were not routine, cardiopulmonary resuscitation equipment was sometimes unavailable, attempts to resuscitate patients were carried out on one-half of all patients and post mortems/inquiries were not routine. Restraint and seclusion were uncommon. Risk factors included: benzodiazepines (odds ratio (OR): 1.83); ≥2 antipsychotics (OR: 2.35); promazine (OR: 4.02); diazepam (OR: 1.71); clozapine (OR: 2.10); cardiovascular disease (OR: 2.00); respiratory disease (OR: 1.98); diagnosis of dementia (OR: 2.08). Venlafaxine and a diagnosis of affective disorder were associated with reduced ORs (OR: 0.42; OR: 0.65). SUD is relatively rare, although it is more common in older patients and males. Prevention measures may include safer prescribing of antipsychotics and improved physical health care. The contribution of restraint or seclusion to SUD in individual cases is unclear. A uniform definition of SUD may help to identify contributing factors.

Keywords

Drug treatment, psychiatric in-patients, sudden death

Introduction

Over the past four decades there has been growing concern over the incidence of sudden unexplained death (SUD) in psychiatric patients (Royal College of Psychiatrists, 1997), particularly in the context of pharmacological treatment. However, a lack of systematic, national studies has led to a gap in the literature regarding the number and rate of SUD. Differences in study populations, data sources and definition have led to substantial variations in the reported rate of SUD (6.6/100,000 persons per year to 190/100,000 persons per year) (Anderson et al., 1994; Bowker et al., 2003; Glassman and Bigger, 2001; Ray et al., 2001; Shen et al., 1995; Straus et al., 2004; Tungsanga and Sriboonlue, 1993; Wannamethee et al., 1995).

There are relatively few controlled epidemiological studies addressing the issue of SUD in patients taking antipsychotic drugs. Straus et al. (2004) reported a three-fold increase in the risk of SUD among those using antipsychotics in a community sample, while the risk of SUD in people with a history of treatment for mental illness was increased five-fold (Ruschena et al., 1998). Elevated risk of SUD has been associated with a number of antipsychotic drugs (Morentin et al., 2003; Ray et al., 2001; Straus et al., 2004), particularly typical antipsychotics such as thioridazine (Glassman and Bigger, 2001; Hennessy et al., 2002; Mehtonen et al., 1991;

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Reilly et al., 2002) and droperidol (Reilly et al., 2002). More recently, Ray et al. showed that the risk of SUD is also increased following exposure to atypical antipsychotics in a community sample of current users of antipsychotics (Ray et al., 2009).

One mechanism by which some antipsychotics are thought to contribute to an increased risk of SUD is through the lengthening of the QT interval (an electrocardiogram (ECG) measure of cardiac repolarization), leading to fatal ventricular arrhythmia (e.g. torsade de pointes) (Glassman and Bigger, 2001; Hennessy et al., 2002; Reilly et al., 2002). However, not all antipsychotic drugs carry a high risk of QT prolongation and it may be that the mechanism by which individual or classes of drugs are associated with an increased risk of SUD differs. Non-drug factors may also contribute to SUD in psychiatric patients, including poor physical health (Ray et al., 2001; Reilly et al., 2002) and restraint (Banerjee et al., 1995), although these factors have not been studied in detail.

We sought to overcome some of the limitations of previous research by carrying out a national study of sudden and unexplained death in a psychiatric in-patient population. The specific objectives of the study were to: (1) determine the number and rate of SUD in mental health in-patients; (2) describe the socio-demographic and clinical antecedents of SUD; and (3) carry out a national case-control study identifying independent risk factors for SUD. Specifically, we examined the hypotheses that SUD cases would be associated with:

polypharmacy, higher doses of antipsychotic drugs, and drugs known to be associated with QT prolongation (e.g. thioridazine, droperidol)
pre-existing cardiac disease
restraint and seclusion.

Method

Cases

People aged 15–75 years (inclusive) who died on a psychiatric in-patient ward in England and Wales between 1 March 1999 and 31 December 2005 (6 years and 10 months) were identified from national datasets of all in-patients provided by Hospital Episode Statistics (HES) for England, and Health Solutions for Wales (HSW). These datasets record anonymized patient details, medical specialty, admission dates, type of discharge (including death), and hospital and consultant codes. Cases were also notified to us from additional sources (i.e. psychiatrists registered with the Royal College of Psychiatrists, independent hospitals, secure units, the Mental Health Act Commission, and the voluntary organizations Rethink and Inquest).

Cases of SUD were those in-patients who were confirmed by the treating clinician to have died from an unknown cause or a cardiac cause unrelated to myocardial infarction (confirmed by ECG, cardiac enzymes or post-mortem) within 1 h of the patient being observed in their usual state of health. Death occurring within 60 min of the onset of symptoms is an internationally recognized criterion for SUD (World Health Organization, 1993) and has been used in previous studies (Reilly et al., 2002). All potential SUD cases notified to us by the respondent were cross-checked against our national suicide database (Appleby et al., 2006) and any cases of suicide removed from the current study.

Patients over the age of 75 years were excluded because the study was primarily designed to examine care and drug factors contributing to SUD. The rate of sudden death from natural causes in the elderly is high, complicating a detailed examination of specific treatment-related factors (Reilly et al., 2002).

Case validation

Case notes for every SUD case were requested for review. The decision on whether a death met the SUD criteria was confirmed by a clinical member of the research team.

Controls

For the case-control study, up to four individually matched controls per case were selected from HES and HSW datasets. There were four matching criteria: a) alive on a mental health ward on the same day that the death of the case occurred; b) date of admission the same as the case; c) gender; and d) age. If fewer than four suitable controls were identified, the analysis was carried out using the available controls. If more than four controls of equal suitability were available, the control subject with the closest date of birth to the case was selected. Matching closely for age was difficult for a small number of subjects, e.g. long-term in-patients, recently admitted patients, but cases and controls were matched to within 3 years on average. We did not match on the in-patient unit of death, as overmatching could have obscured the effects of important differences in clinical care.

Data collection

For each in-patient death identified through HES, HSW, or other sources, the treating consultant was sent a study questionnaire. Consultants were identified through TRUD (Terminology Reference-date Up Distribution service, formerly the National Administrative Code Service (NACS)), which provided trust and consultant codes for identification purposes. The first section of the questionnaire determined whether the person died by SUD according to the above criteria. Where cases met the criteria the consultant was asked to complete the remaining nine sections, covering demographic information, psychiatric history, diagnoses, physical health, substances taken prior to death including psychotropic medication, details of final admission, circumstances of death, additional information, and respondent details.

Statistical analyses

We aimed to investigate the rate of SUD overall, and by calendar year. Due to the availability of admissions denominator data (i.e. number of NHS mental health and learning disability admissions) this was only possible for SUD cases in England aged 15–74. Cases aged 75 years ($N = 12$) and cases occurring in Wales ($N = 20$) were excluded from the analysis of rates. An incidence rate ratio (IRR) was calculated to

investigate longitudinal trends in the rate of suicide across the time period of the study. An IRR of less than 1 indicates a decrease in the trend across the study period.

All SUD cases are included in the descriptive analysis ($N = 283$). Descriptive analyses are presented as the number and proportion of valid cases for each variable. For the case-control analyses, only data from cases and controls notified to us via HES and HSW data sources ($N = 242$) were used, to ensure consistent ascertainment for cases and controls. Conditional logistic regression was used to calculate odds ratios (OR) for the association between the key variables of interest and SUD. The reported p-values relate to the z-values, which are calculated by dividing the predictor coefficient by its standard error. Analyses of drug exposures refer to the 24 h before death or index date. Initially, an unadjusted univariate analysis was carried out. This was repeated after adjusting for the following likely confounding variables: smoking, history of cardiovascular (CV) disease, and history of respiratory disease. We also included age as a covariate because the controls were found to be younger than the cases, despite matching.

Polypharmacy was defined as the concurrent exposure to two or more drugs. Dosage for antipsychotic drugs was calculated in two ways. First, the median chlorpromazine equivalent doses for antipsychotic drug exposures were calculated for typical and atypical antipsychotic drugs (Atkins et al., 1997; Yorston and Pinney, 2000; Woods, 2003). Second, drugs were grouped into low dose (<100 mg), moderate dose (100–299 mg) and high dose (≥300 mg) exposures of chlorpromazine equivalent doses for typical and atypical antipsychotics (Ray et al., 2009).

We present both unadjusted and adjusted analyses in the results section but we discuss only the adjusted analyses in detail. The level of statistical significance for an association between SUD and individual variables was set at $p \leq 0.05$. Significance levels were two-tailed.

In order to investigate which treatment-related variables were independently associated with SUD, psychiatric drug and care variables (found to be associated with SUD in the unadjusted analysis) were entered into a multivariate predictor model. The model was then adjusted for age, smoking, history of CV disease and history of respiratory disease. When both an individual drug and the drug class to which it belonged were independently associated with SUD we included the drug class. Psychiatric diagnosis was not included in the multivariate predictor model because of collinearity with the pharmaceutical variables. To allow for risk factors that might be important, particularly in combination with other risk factors, variables with a p-value of <0.10 from the univariate analysis were included in the multivariate predictor modelling procedure (see Dupont, 2002).

Intercooled STATA 10.0 for Windows 98/95/NT (Stata Corporation, 2003) was used to carry out all analyses.

Results

Case ascertainment

Figure 1 summarizes recruitment to the study. During the study period, 4495 in-patient deaths in mental health units were recorded (a rate of 342 per 100,000 mental health admissions). In 229 (5%) cases, a questionnaire could not be sent or completed because the patient, consultant or case notes could not be identified or located. Questionnaires were sent out for 4266 (95%) individuals and were returned for 4026 individuals (a response rate of 94%). Of these, 324 (8%) respondents identified a case of SUD.

Of the 324 cases identified by the respondent, 294 (91%) cases were validated by the SUD research team. Of these, there was agreement between the respondent and the SUD team on 253 (86%) cases. Forty-one (14%) cases were removed following validation as the cases did not meet SUD criteria. In total, 283 SUD cases were included in the descriptive study.

Of all SUD cases included in the study ($N = 283$), 252 (89%) were notified to the research team from our primary sources (i.e. HSW, HES). Thirty-one (11%) were notified to us via other reporting routes (e.g. individual clinicians, Rethink).

Number and rate of SUD

The annual number and rate of SUD in England is shown in Table 1. There were on average 41 SUD cases notified to the research team per year (range: 30–47). On average, SUD cases accounted for 7% of all psychiatric in-patient deaths (range: 5–8%). Of the 283 SUD cases, rates of SUD per 10,000 NHS mental health and learning disability admissions were calculated for the 251 SUD cases occurring in England who were under 75 years of age. The overall rate was 2.33 per 10,000 NHS admissions (95% CI: 2.05–2.64) with no significant increase in SUD across the time period of the study (IRR: 1.05, 95% CI: 0.99–1.12, $p = 0.13$). Overall, rates of SUD per 10,000 admissions were higher in males (2.67 per 10,000 admissions) than females (1.97 per 10,000 admissions) and increased with increasing age (15–44 years: 1.00 per 10,000 admissions; 65–74 years: 7.95 per 10,000 admissions).

Characteristics of all SUD cases

The median age of the sample was 61 years, of whom 50 (18%) were under 40 years of age. Overall, SUD cases were predominately white ($N = 251$, 90%) and male ($N = 168$, 59%). Patients were in poor mental and physical health characterized by: a primary diagnosis of schizophrenia ($N = 102$, 36%), affective disorders ($N = 78$, 28%) or dementia ($N = 55$, 20%) and multiple admissions (>5 previous admissions: $N = 94$, 34%). Just under half of all patients had a history of CV disease ($N = 128$, 46%), and had experienced symptoms of CV disease in the month prior to death ($N = 119$, 45%).

It is possible that some patients may not have been optimally managed. For example, although a full physical exam had been carried out during the final admission in nearly all cases ($N = 257$, 92%), an ECG had been carried out in less than half of all patients ($N = 105$, 42%) in the year prior to death. Cardiopulmonary resuscitation (CPR) was attempted in only 148 (55%) cases, although in 136 (87%) cases staff had been trained in CPR and CPR equipment was available on 161 (70%) of all wards. Following a death, the majority of cases were discussed with the team who had been caring for the patient ($N = 231$, 90%) and relatives of the patient

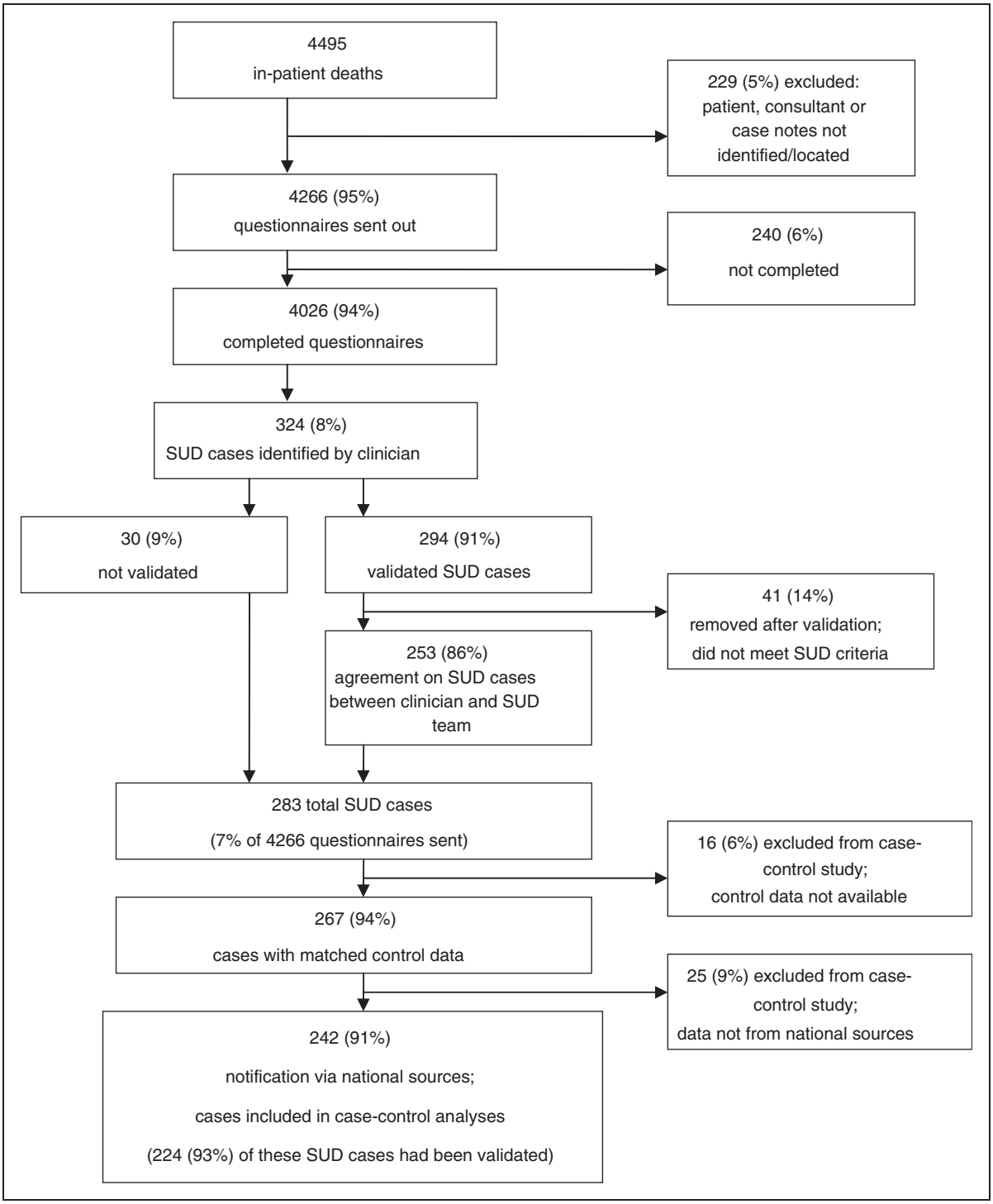

Figure 1. Case ascertainment for sudden unexplained death (SUD).

($N = 216$, 88%). However, a post-mortem took place in 161 (69%) of all cases while an inquiry (either internal or external) was carried out in 56 (22%) cases.

In total, there were nine cases who had been restrained and/or secluded in the 24 h prior to death. Seven cases had been restrained in the 24 h prior to death (of whom five were from an ethnic minority background and five were under 40 years of age). Seven cases had been secluded in the 24 h prior to death. Of these seven cases, five were from an ethnic minority background and four were under 40 years of age. Of all nine cases who had been restrained and/or secluded in the 24 h prior to death, five had been both restrained and secluded.

In total, there were seven patients who had been restrained and/or secluded in the 1 h prior to death. Five patients had been

Table 1. Annual rates of sudden unexplained death in England per 10,000 NHS mental health and learning disability admissions, by gender

	Males		Females		All	
Calendar Year	*N*	Rate (95% CI)	*N*	Rate (95% CI)	*N*	Rate (95% CI)
*1999	16	2.08 (1.19–3.39)	15	2.12 (1.19–3.50)	31	2.10 (1.43–2.99)
2000	26	2.99 (1.96–4.39)	9	1.11 (0.51–2.10)	35	2.08 (1.45–2.90)
2001	14	1.61 (0.88–2.70)	9	1.11 (0.51–2.10)	23	1.37 (0.87–2.05)
2002	21	2.47 (1.53–3.77)	18	2.30 (1.37–3.64)	39	2.39 (1.70–3.27)
2003	23	2.87 (1.82–4.31)	23	3.17 (2.01–4.76)	46	3.01 (2.21–4.02)
2004	27	3.54 (2.33–5.15)	16	2.35 (1.34–3.81)	43	2.98 (2.16–4.01)
2005	23	3.30 (2.09–4.95)	11	1.78 (0.89–3.19)	34	2.58 (1.79–3.61)
Total	**150**	**2.67 (2.26–3.13)**	**101**	**1.97 (1.60–2.39)**	**251**	**2.33 (2.05–2.64)**

*1 March 1999–31 December 1999.

restrained in the 1 h prior to death (of whom three were from an ethnic minority). Six patients had been secluded in the hour prior to death (of whom four were from an ethnic minority). Of all seven patients who had been restrained and/or secluded only, four were under 40 years of age. Out of the seven cases that had been restrained and/or secluded in the hour prior to death, four patients had been both restrained and secluded.

SUD cases from national sources versus other sources

Thirty-one cases were *not* notified to the SUD team from national sources (e.g. HES). These cases were different from nationally notified cases on some variables. These cases were more likely to have longstanding and severe mental illness (duration of final admission 1–5 years: $N=21$ (8%) vs. $N=7$ (23%), $p=0.02$; primary diagnosis of schizophrenia: $N=85$ (34%) vs. $N=17$ (55%), $p=0.02$). They were more likely to have been detained for treatment ($N=46$ (18%) vs. $N=13$ (43%), $p<0.01$), and to have been physically restrained ($N=3$ (1%) vs. $N=4$ (14%), $p<0.01$) or been in seclusion ($N=3$ (1%) vs. $N=4$ (13%), $p<0.01$) in the time period prior to death; an inquiry into the death of these individuals was more common ($N=43$ (19%) vs. $N=13$ (46%), $p<0.01$).

Case–control study

Of the 283 SUD cases identified during the study period, we were able to obtain valid controls for 267 (94%). Of these, 242 (91%) were notified to us via national sources (i.e. HES, HSW), and 25 (9%) were notified to us from other sources (i.e. psychiatrists registered with the Royal College of Psychiatrists, independent hospitals, secure units, the Mental Health Act Commission, and the voluntary organizations Rethink and Inquest). Of the 242 cases included in the case-control study, 224 (93%) cases had been validated by the SUD research team.

Only data relating to the 242 cases and matched controls from national sources are presented in the remainder of the paper. Descriptive analyses indicated some differences between cases notified from national (e.g. HES) and non-national sources. Further, omission of SUD cases notified from other sources ensured consistent ascertainment of cases and controls.

The 242 cases were matched with 823 controls. Of these, 138 cases were matched with four controls, 70 cases were matched with three controls, 27 cases were matched with two controls and seven cases were matched with one control.

Types and classes of drugs

The association between SUD and types and classes of drugs is shown in Table 2. Exposure to benzodiazepines was significantly associated with an increased OR which remained after controlling for confounding variables (age, smoking, CV disease, respiratory disease). Chlorpromazine equivalent dosages of typical and atypical antipsychotic drugs were not significantly associated with SUD when examined as median chlorpromazine equivalent doses, or low, moderate or high dose exposures, in either unadjusted or adjusted analyses.

Individual psychotropic drugs

There was a low exposure rate to most individual drugs, resulting in wide confidence intervals. However, some individual drugs were significantly associated with SUD. Promazine (typical antipsychotic) was associated with an increased OR (cases: 8 (3%), controls: 6 (1%); OR: 4.79; 95% CI: 1.65–13.87, $p<0.01$) as was diazepam (benzodiazepine) (cases: 32 (13%), controls: 67 (8%); OR: 1.69; 95% CI: 1.07–2.68, $p=0.02$). Venlafaxine (serotonin-norepinephrine reuptake inhibitor, SNRI) was associated with a reduced OR (cases: 9 (4%), controls: 62 (8%); OR: 0.47; 95% CI: 0.23–0.97, $p=0.04$). After adjusting for potential confounding variables (age, history of CV disease, history of respiratory disease, smoking) promazine (OR: 4.02; 95% CI: 1.33–12.14, $p<0.01$), diazepam (OR: 1.71; 95% CI: 1.05–2.79, $p=0.03$) and venlafaxine (OR: 0.42; 95% CI: 0.19–0.92, $p=0.03$) all remained significantly associated with SUD. In addition, clozapine (atypical antipsychotic) (cases: 16 (7%), controls: 35 (4%); OR: 2.10; 95% CI: 1.03–4.31, $p=0.04$) was significantly associated with an increased risk of SUD in the adjusted analyses. Further, exposure to two or more antipsychotics (i.e. polypharmacy) was associated with an increased OR (cases: 21 (9%), controls: 36 (4%); OR: 2.40; 95% CI: 1.34–4.31, $p<0.01$). This association remained significant after adjusting for confounding variables (i.e. age, smoking, CV disease, respiratory disease) (OR: 2.35; 95% CI: 1.28–4.32, $p=0.01$).

Table 2. The number, percentage and unadjusted and adjusted odds ratios (OR) (95% CI) for types and classes of psychotropic drugs

Variable	Cases ($N = 242$) N (%)	Controls ($N = 823$) N (%)	Unadjusted OR OR* (95% CI)	p-value	Adjusted OR** OR* (95% CI)	p-value
Drug types and classes						
Atypical antipsychotics	91 (38%)	279 (34%)	1.29 (0.95–1.77)	0.11	1.28 (0.92–1.80)	0.15
Typical antipsychotics	51 (21%)	149 (18%)	1.18 (0.82–1.71)	0.38	1.30 (0.88–1.92)	0.18
Tricyclic antidepressant	24 (10%)	70 (9%)	1.13 (0.69–1.86)	0.62	1.03 (0.60–1.77)	0.92
Depot antipsychotics	33 (14%)	104 (13%)	1.11 (0.72–1.71)	0.64	1.19 (0.74–1.90)	0.48
QT-prolonging antipsychotics[1]	10 (4%)	22 (3%)	1.55 (0.67–3.58)	0.31	1.92 (0.79–4.67)	0.15
SSRIs	34 (14%)	143 (17%)	0.78 (0.52–1.19)	0.25	0.70 (0.45–1.08)	0.11
SNRI/other	10 (4%)	62 (8%)	0.52 (0.26–1.04)	0.07	0.46 (0.22–0.97)	0.04
Mood stabilizers	58 (24%)	206 (25%)	0.97 (0.69–1.36)	0.85	0.97 (0.68–1.39)	0.87
Benzodiazepines	73 (31%)	168 (20%)	1.74 (1.25–2.42)	<0.01	1.83 (1.29–2.58)	<0.01
Non-benzodiazepine hypnotic	41 (17%)	116 (14%)	1.29 (0.87–1.91)	0.20	1.31 (0.87–1.98)	0.20
Anti-parkinsonian	36 (15%)	102 (12%)	1.27 (0.84–1.93)	0.26	1.48 (0.95–2.30)	0.09
Median chlorpromazine equivalent doses[†]						
Typical antipsychotics	300 (range: 10–2500)	200 (range: 20–4000)	1.00 (0.99–1.00)	0.19	1.00 (0.99–1.00)	0.22
Atypical antipsychotics	250 (range: 12.5–1450)	200 (range: 13–1750)	1.00 (0.99–1.00)	0.25	1.00 (0.99–1.00)	0.08
Chlorpromazine equivalent doses[†]						
Typical antipsychotics						
Low dose	13 (26%)	40 (29%)	1.00	–	1.00	–
Moderate dose	11 (22%)	56 (41%)	0.12 (0.01–1.59)	0.11	0.09 (0.01–3.30)	0.19
High dose	26 (52%)	40 (29%)	1.40 (0.17–11.67)	0.75	0.51 (0.04–7.09)	0.62
Atypical antipsychotics						
Low dose	10 (13%)	38 (14%)	1.00	–	1.00	–
Moderate dose	31 (39%)	114 (43%)	1.25 (0.43–3.66)	0.69	0.73 (0.20–2.66)	0.63
High dose	38 (48%)	112 (42%)	1.29 (0.43–3.85)	0.64	0.78 (0.20–2.94)	0.71

[1]Droperidol, IM Droperidol, Pimozide, Thioridazine.
*Non-exposure was used as the index category unless otherwise stated (e.g. schizophrenia).
**Adjusted for age, history of cardiovascular disease, history of respiratory disease and smoking history.
[†]Excluded all individuals with no exposure to atypical or typical antipsychotic drugs.
SNRI: serotonin-norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor.

Social and clinical factors

The association between SUD and social and clinical variables is shown in Table 3. A history of CV disease was associated with a significantly increased risk of SUD, as was a history of respiratory disease in both unadjusted and adjusted analyses. There were no associations with smoking, drug and alcohol misuse (separately or combined). A primary diagnosis of dementia was significantly associated with an increased risk of SUD, even after adjusting for confounding variables. Affective disorder was associated with a reduced risk of SUD, which remained after adjustment for confounding variables.

Restraint and seclusion were not significantly associated with an increased risk of SUD. There was no association with ethnicity.

Multivariate predictor model

The multivariate predictor model is shown in Table 4. Variables that remained significantly associated with an increased risk of SUD were: promazine, clozapine, and benzodiazepines, as a class of drug. SNRIs and paroxetine were associated with a significantly reduced risk of SUD. Further, although trazodone remained in the multivariate predictor model the association with SUD did not reach significance.

Discussion

During the study period, 283 cases of SUD were identified (7% of all deaths on psychiatric in-patient wards), equating to approximately 41 cases per year. The incidence rate of SUD (in England) was 2.33 per 10,000 mental health admissions with no significant increase in the rate of SUD across the time period of the study; rates were higher in older people and males. Patients were predominately male and 10% were from an ethnic minority. Patients were characterized by severe mental illness and poor physical health (i.e. CV and respiratory problems). It may be that some patients did not receive optimal care (i.e. ECGs were not routinely carried out, CPR equipment was not readily available on all wards, attempts to resuscitate patients were carried out on only half of all patients). Post-mortem examinations were carried out in two-thirds of all cases, and an inquiry in only one-fifth of cases. Restraint and seclusion were used in very few cases, although their contribution to SUD is unclear. In the case-control analysis an increased risk of SUD was associated with drugs (i.e. benzodiazepines, promazine,

Table 3. Associations between social and clinical factors and sudden unexplained death

Variable	Cases ($N = 242$) N (%)	Controls ($N = 823$) N (%)	Unadjusted OR OR* (95% CI)	p-value	Adjusted OR** OR* (95% CI)	p-value
Age in years (median and range)	63 (17–75)	60 (15–75)				
Male	140 (58%)	458 (56%)				
Ethnicity						–
White	216 (91%)	728 (90%)	1.00	–	1.00	
Non–white	22 (9%)	77 (10%)	1.12 (0.66–1.88)	0.68	1.31 (0.75–2.27)	0.35
Civil status						
Married	77 (32%)	228 (28%)	1.00	–	1.00	–
Single	90 (38%)	314 (38%)	0.79 (0.53–1.18)	0.24	0.90 (0.58–1.39)	0.63
Divorced/widowed	72 (30%)	274 (34%)	0.79 (0.54–1.15)	0.22	0.74 (0.49–1.12)	0.15
Smoking[1]						
Never smoked	71 (29%)	250 (30%)	1.00	–	1.00	–
Ex–smoker	36 (15%)	110 (13%)	1.14 (0.72–1.82)	0.58	0.93 (0.57–1.52)	0.77
Current smoker	99 (41%)	348 (42%)	1.00 (0.70–1.42)	1.00	0.84 (0.57–1.24)	0.38
Missing data	36 (15%)	115 (14%)	1.12 (0.71–1.78)	0.62	1.04 (0.62–1.73)	0.89
History of cardiovascular disease (CV)	111 (47%)	251 (31%)	2.27 (1.63–3.15)	<0.01	2.00 (1.42–2.82)	<0.01
History of respiratory disease	65 (28%)	127 (16%)	2.07 (1.45–2.94)	<0.01	1.98 (1.36–2.90)	<0.01
History of alcohol misuse in lifetime	57 (24%)	219 (27%)	0.81 (0.57–1.15)	0.24	0.94 (0.64–1.37)	0.73
History of drug misuse in lifetime	34 (15%)	121 (15%)	1.01 (0.62–1.66)	0.95	1.32 (0.77–2.26)	0.32
Psychiatric diagnosis						
Schizophrenia	83 (34%)	280 (34%)	1.02 (0.73–1.42)	0.91	1.06 (0.74–1.51)	0.76
Affective disorder	68 (28%)	298 (36%)	0.67 (0.48–0.93)	0.02	0.65 (0.45–0.92)	0.02
Dementia	49 (20%)	95 (12%)	2.27 (1.48–3.48)	<0.01	2.08 (1.29–3.34)	<0.01
Learning disabilities	10 (4%)	38 (5%)	0.79 (0.36–1.76)	0.57	0.90 (0.38–2.15)	0.82
Other diagnosis	31 (13%)	109 (13%)	0.95 (0.62–1.47)	0.83	1.02 (0.65–1.61)	0.93
Patient physically restrained 24 hours prior to index date	3 (1%)	3 (0.5%)	3.09 (0.62–15.46)	0.17	3.50 (0.68–18.15)	0.14
Patient in seclusion 24 hours prior to index date	3 (1%)	3 (0.5%)	3.30 (0.66–16.42)	0.14	4.71 (0.90–24.70)	0.07

*Non-exposure was used as the index category unless otherwise stated (e.g. schizophrenia).
**Adjusted for age, history of cardiovascular disease, history of respiratory disease and smoking history.
[1]The group of patients with missing data on history of smoking had a higher OR compared with the other categories and were therefore included in the analysis as a separate category.

Table 4. Multivariate predictor models including drug and care variables within 24 h of death

Variable	OR	95% CI	p-value
Promazine	5.46	(1.68–17.79)	0.01
Clozapine	2.16	(1.03–4.55)	0.04
Paroxetine	0.35	(0.13–0.97)	0.04
Trazodone	2.17	(0.94–4.98)	0.07
Benzodiazepines	1.87	(1.32–2.67)	<0.01
SNRIs	0.42	(0.19–0.89)	0.03

Note. Adjusted for age, history of cardiovascular disease, history of respiratory disease and smoking history.
SNRI: serotonin-norepinephrine reuptake inhibitor.

clozapine, diazepam) and clinical variables (i.e. primary diagnosis of dementia, CV and respiratory disease). There was no dose-related increased risk of SUD following exposure to antipsychotics. SNRIs (venlafaxine) and a primary diagnosis of affective disorder were associated with a decreased risk of SUD.

Methodological issues

The findings of this paper should be viewed within the methodological limitations of the study. Although we aimed to validate all cases of SUD this was not possible for practical and resource reasons. A clinician on the SUD team reviewed the case notes for 294 of 324 (91%) consultant-identified SUD cases. Psychiatric case notes sent by the treating clinician were used to validate cases of consultant-identified SUD. The SUD team did not have access to other sources of patient information (i.e. primary care records). Of the 294 case notes reviewed, there was agreement on the status of the cases as a SUD between the treating consultant and the SUD clinician in 253 of 294 (86%) SUD cases reviewed. If the overall level of agreement is applied to the 30 cases that were not validated we estimate that 26 cases would have been confirmed and four cases would have been excluded. Therefore, the total number of cases included in the study would have fallen to 279 (283), or 40 per year. Of course, it is also possible that our methodology missed some cases. A preliminary validation of a selected sample of non-cases by the research team suggested an error rate (that is, proportion of non-cases that were

judged by the research team to be cases) of only 2%. Further, the clinicians who completed questionnaires used case notes as their main source of information, thereby reducing recall bias. However, patient records were often incomplete on important variables (i.e. smoking, weight, family history of premature death, post-mortem information).

There are three additional methodological limitations specific to the case-control study. First, the association between drug factors and SUD may have been confounded by psychiatric diagnosis. Future research should focus on elucidating the independent associations between psychiatric diagnoses and treatment variables, particularly drug treatment. Second, cases identified to us from other sources (e.g. independent hospitals) were excluded from the current study. Although this had the effect of reducing the power of the study, it ensured consistent ascertainment of cases and controls and eliminated potential bias. Third, there were significant differences between the validated ($N=253$) and non-validated ($N=30$) samples on two variables: duration of admission 1–5 years ($N=21$; 8% vs. $N=7$; 23%, $p>0.01$) and physical restraint in the 24 h prior to SUD ($N=4$; 2% vs. $N=3$; 11%, $p<0.03$). However, numbers of non-validated cases were small and interpretation of these data are unclear.

Interpretation of results

Despite the limitations, this study is the first national study to report the number, rates and characteristics of SUD in the psychiatric in-patient population, and the findings of this study have several implications for clinical practice and future research.

First, although SUD is relatively uncommon, services should be aware that SUD is more likely to occur in those who are male, older and physically ill. Monitoring physical health factors includes the appropriate management of modifiable risk factors for heart disease such as lifestyle factors (e.g. smoking, obesity), particularly for older patients and those with pre-existing physical health problems (Cormac et al., 2004). Although our study does not provide direct evidence for the utility of ECG measurement in psychiatric in-patients, it would seem clinically prudent that an ECG should be carried out when physical health is being evaluated. In this study under half of cases had an ECG in the year prior to death, and this proportion was 57% in those with a history of CV disease.

Second, services might improve the response to and treatment of cardiac arrest. In the current study, we found CPR equipment was not available on nearly one-third of wards, and CPR was attempted in just over half of all cases, although nearly 90% of staff had been trained in CPR. The management of cardiac arrest or other collapse requires appropriate equipment to be available and adequate numbers of staff with the necessary training to provide CPR. Response times for cardiac arrest teams trained in advanced life support should be as short as possible and local arrangements should be justifiable, taking into account the numbers and types of patients in a unit, and the possible dispersal of in-patients within a multi-site trust.

Third, the use of restraint and seclusion were uncommon in the current study and we cannot say whether these factors contributed to SUD in these cases. Further monitoring of patients who die in the context of restraint or seclusion is required. Fourth, there is currently no uniform definition of SUD (Bowker et al., 2003) and SUD is not systematically identified by coroners. The development of a uniform practice of identifying SUD would help identify factors contributing to SUD. Post-mortem examinations and clinical reviews of all SUD occurring on psychiatric in-patient wards are encouraged.

Further, the findings from the case-control study make an important contribution to our understanding of risk factors for SUD in a psychiatric in-patient population. Clozapine, an atypical antipsychotic, was associated with an increased risk of SUD. Some studies have shown that atypical antipsychotics may be associated with an increased risk of QT prolongation as with typical antipsychotics (Ray et al., 2009). However, it may be that the mechanism underlying the association with SUD is not always related to the QT interval (Coulter et al., 2001; Glassman, 2005; Hägg et al., 2001; Kang et al., 2000; Killian et al., 1999; Titier et al., 2005; Wetterling, 2001). Although treatment with antipsychotic drugs – particularly atypical antipsychotics – is an important therapeutic option, clinicians should carefully weigh up the benefits of drug treatments with the risks to the individual patient.

Promazine, a typical antipsychotic, was also associated with an increased risk of SUD. QT prolongation resulting in torsade de pointes has been proposed as the mechanism underpinning sudden death in patients prescribed some typical antipsychotics. Generally, there was careful prescribing of drugs known to carry a high risk of QT prolongation, with few exposures to these drugs. However, there have been changes in prescription practices during the time period of the study (e.g. removal of droperidol; black box warning for thioridazine). The small number of exposures to drugs with a high risk of QT prolongation may reflect careful prescribing of these drugs specifically, and drugs known to increase the risk of QT prolongation more generally. However, the known association between some typical antipsychotics and SUD suggests continued cautious prescribing of psychotropic drugs, particularly in patients with pre-existing CV problems.

The risk of SUD increased after exposure to benzodiazepines. Benzodiazepines are used to manage acute agitation or behavioural disturbances. Although these are an important therapeutic option, one side effect of benzodiazepines is respiratory depression and cautious prescribing of these drugs to patients with respiratory disease is indicated (British National Formulary, 2007).

Concurrent exposure to two or more antipsychotic drugs was significantly associated with an increased risk of SUD. Polypharmacy is not uncommon in people with mental illness, particularly in older patients and those with co-morbid physical health problems. There may be a higher risk of SUD in users of multiple medications because of drug interactions or the additive risks of drugs. Further, it may be that patients with current exposure to two or more drugs were more severely ill than other patients.

Venlafaxine (and SNRIs more broadly) was associated with a reduced risk of SUD. This finding is interesting given the known association between cardiac toxicity and exposure

to venlafaxine (Howell et al., 2007), (although Isbister (2009) showed that cardiotoxicity was not a common feature of venlafaxine overdose except where exposure exceeded 8 g). It may be that guidance suggesting the careful prescription of SNRIs for depressed patients, particularly patients with pre-existing cardiac disease, may have affected its use during the study period (National Institute for Clinical Excellence, 2004). Alternatively, it may be that the association is due to unidentified confounding (e.g. more recently diagnosed psychiatric illness). Further, the weak association between selective serotonin reuptake inhibitors (SSRIs) and SUD is interesting. Although paroxetine (an SSRI) was associated with a reduced OR in the multivariate predictor model, SSRIs were not associated with SUD in any other analyses. Similarly, trazodone (a tricyclic-related drug) was associated with an increased risk of SUD in the multivariate predictor model, although the association did not reach significance in the unadjusted or adjusted analyses. Further investigation of the association between SUD and antidepressants is warranted.

Physical health problems, specifically a history of CV disease and respiratory disease, resulted in approximately a two-fold increase in the risk of SUD. To help reduce the occurrence of SUD on psychiatric in-patient wards, mental health services should seek to improve the physical health care of mental health patients, with a particular emphasis on patients with pre-existing CV and respiratory problems. The association between primary diagnosis and SUD merits discussion. The increased risk of SUD in patients with a primary diagnosis of dementia may be the result of poorer physical health of older patients.

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Declaration of interest

Louis Appleby was the National Director of Mental Health for England and is now the National Director for Health and Criminal Justice.

Contributors

The study was principally designed by L Appleby, J Shaw, T Amos, G Lewis, S Thomas and N Ferrier, but all authors had input into aspects of study design. Procurement of data from the NWCS and HES and collection of questionnaire data was carried out by P Turnbull, K Hadfield, K Windfuhr, U Hiroeh, C Dixon, S Flynn, and H Watkinson, supported by T Amos. Initial data manipulation was carried out by P Turnbull, D While, K Windfuhr, U Hiroeh, C Dixon, and S Flynn. Case validation was carried out by N Swinson, H Mehta and H Watkinson, with supervision from N Kapur, S Thomas, and N Ferrier. Data analysis was carried out by P Turnbull, D While, U Hiroeh, and P Skapinakis with supervision from N Kapur, G Lewis, and L Appleby. The manuscript was prepared by K Windfuhr, P Turnbull, D While, and U Hiroeh with supervision from N Kapur. All authors commented on drafts of the paper and contributed to the final version.

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