Mortality in schizophrenia: a measurable clinical endpoint

Chris J Bushe[1], Mark Taylor[2,3] and Jari Haukka[4]

Abstract

Over the last five years, large data sets on mortality in schizophrenia have been published which have established mortality as a measurable clinical endpoint. Four issues need clarification: whether mortality rates are declining, what the causes of death are, the effects antipsychotic treatments have on mortality and whether these data inform as to how mortality may be reduced in the future. A PubMed search was carried out to identify relevant publications. The search strategy was conducted as a review focusing predominantly on data since 2006. A large number of retrospective epidemiological and prospective studies have been published on mortality rates and causation in schizophrenia, predominantly from 2006–2009. Data suggest that the mortality gap with the general population increased from the 1970s but may have peaked in the mid-1990s. The main causes of mortality are suicide, cancer and cardiovascular disease, with evidence that cancer mortality rates are similar to cardiovascular mortality rates. Mortality causation is dependent upon age of the cohort, length of follow up and type of study. Antipsychotic treatments reduce mortality when compared with no treatment and atypical antipsychotics do not appear to increase cardiovascular mortality and morbidity compared with conventionals; further research is required for any definitive conclusion.

Keywords

Antipsychotics, cancer, cardiovascular disease, database, mortality, schizophrenia, suicide

Introduction

In general medicine, mortality endpoints for treatments such as thrombolysis in acute myocardial infarction and evaluation of longer-term hypertension treatment have been commonplace since the mid-1980s (ISIS-2 Collaborative Group, 1988). By comparison, although the first cited mention of mortality in 'lunacy' dates from the 17th century (Graunt, 1662), psychiatry has been somewhat slow to accept this clearly defined endpoint. Over the previous 50 years, psychiatry has moved through many clinical endpoints, beginning with the degree of noise reduction in long-stay hospital wards through various rating scales, often too complex for clinical usage, to more pragmatic endpoints including treatment discontinuation and hospital discharge and, most recently, remission and recovery. Mortality has been regarded as a potential clinical outcome measure in schizophrenia since 2005 (Drew, 2005) and represents a crucial variable with which to compare the impact of various forms of treatment, recently being described as the gold standard of clinical outcome (Brown et al., 2010). Indeed, mortality can be viewed as a good proxy for measurement of overall standard of care, but it is additive and cannot replace other well-established endpoints. For example, when evaluating cardiac-related outcomes after treatment, it is a more robust endpoint than cardiovascular morbidity (Kelly et al., 2010).

During the time period up to 2006, there have been a number of excellent systematic reviews, meta-analyses and clinical reviews detailing mortality rates and, to some extent, the causation of mortality in schizophrenia compared with the general population. The Brown meta-analysis included 18 mortality studies of which only three derived from Scandinavia with many studies coming from the USA and the UK. However, many of these studies were relatively small (Brown, 1997). The more recent advent of national databases and registers primarily pioneered in Finland, Sweden and Denmark has provided for the routine collection of clinical information which has allowed mortality evaluations in populations of significant size. For example, the Laursen et al. study included 3942 schizophrenia deaths (Laursen et al., 2007).

In 2007, a systematic review (Saha et al., 2007) concluded from data published up to that time that mortality rates in schizophrenia were significantly greater than in the general population, median standardized mortality ratio (SMR) 2.58 (10–90% quantile, 1.18–5.76) and the mortality gap between schizophrenia patients and the general population had continued to increase during the 1970s and 1980s. There seems little doubt that these data are correct. Excess mortality in

[1]Eli Lilly and Company Ltd, Basingstoke, UK.
[2]NHS Lothian and University of Glasgow, UK.
[3]University of Glasgow, UK.
[4]Department of Public Health, University of Helsinki, Finland.

Corresponding author:
Dr Chris J Bushe, Eli Lilly and Company, Lilly House, Priestley Road, Basingstoke, Hampshire RG24 9NL, UK
Email: bushe_chris@lilly.com and beesbeesbees@blueyonder.co.uk

schizophrenia patients compared with the general population in various studies covering the time period from 1926 to 2000 ranges from SMR 1.51 to SMR 3.34 (Fors et al., 2007) with length of follow up ranging from 4 to 40 years and cohort size (not deaths) from 200 to 66,000. Furthermore, SMR for mortality remains elevated until 80 years of age (Mortensen and Juel, 1993). Some of these data have allowed mortality comparisons between schizophrenia and other forms of severe mental illness (SMI). Laursen et al. reported a register-based linkage study from Denmark comparing mortality rates and causes among more than 250,000 psychiatric patients with various types of SMI with over 20 years follow up (Laursen et al., 2007). When schizophrenia was compared with unipolar depressive disorder, bipolar affective disorder and schizoaffective disorder, schizophrenia had a lower mortality from unnatural causes of death but a higher mortality from natural causes than the other forms of SMI.

The next question to address is what exactly do schizophrenia patients die from? Data are fairly consistent, indicating that for almost all natural and unnatural causes of death, the SMR is elevated (Saha et al., 2007; Laursen et al., 2009). The commonly cited meta-analysis from Brown (1997) provided the statistic that the relative contributions to excess mortality were suicide (28%), accidents (12%) and natural causes (60%). This was an important data set that further clarified earlier findings from a 40-year follow up study of male schizophrenia patients that concluded decreased survival was caused by suicide, accidents and infectious diseases (Tsuang et al., 1980). By 2001, there was an acceptance that natural causes have a significant role to play in elevating schizophrenia mortality (Brown et al., 2000). The actual contribution of each illness to mortality remains widely discussed although until recently the primary focus was on cardiovascular disease (CVD) rather than cancer, accidents or respiratory disorders.

Over the last 5 years, many more data have emerged that were not available at the time of these earlier reviews and 2008–2009 in particular saw a plethora of mortality data (Capasso et al., 2008; Dean and Thuras, 2009; Peuskens et al., 2009; Tiihonen et al., 2009; Tran et al., 2009). The purpose of this review is to evaluate mortality data that have emerged since 2006 to determine whether any definitive clinical answers can be derived and to propose clinical questions that may need to be addressed in future research. One aspect of this is the realization that traditional, randomized controlled trials alone are unlikely to provide definitive, long-term mortality outcomes due to the need for large cohorts; in contrast, country-specific databases allow for longer-term follow up. There has been much debate over the use of clinical data derived retrospectively from epidemiological databases for illness such as diabetes in schizophrenia patients and the appropriateness and quality of these databases needs to be confirmed (Bushe and Leonard, 2004, 2007; De Hert et al., 2010). Thus, our review also considers the relevance of databases when examining the mortality issue.

The main clinical questions to be addressed are as follows:

1. What is the current trend with respect to both mortality rates in schizophrenia and the mortality gap with the general population?

2. What are the current causes of mortality in schizophrenia and is there evidence of any change in aetiology?
3. What effects do antipsychotic treatments have on mortality?
4. How well suited are databases to measuring mortality rates?
5. Are there recommendations for future research?

Methods

A PubMed search was conducted using the Medical Subject Heading (MeSH) terms 'mortality' and 'schizophrenia'. The search was conducted on data published in the English language in the time period from January 2006 to January 2010. The search was not defined as a systematic review although most of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) criteria were met. An initial search found 101 references: 16 relevant publications, 5 letters in reply, 10 case reports or series, 3 non-English language publications and 67 publications that were not considered relevant. Reference lists of review papers were searched for further publications and authors were contacted for further data when relevant.

Results and clinical discussion

Current trends in mortality rates in schizophrenia and the mortality gap with the general population

In 2007, a meta-analysis of mortality (Saha et al., 2007) found that not only were mortality rates greater in schizophrenia (median SMR 2.58) than in the general population, but that there had been a linear increase in SMR over the previous three decades leading to an increase in the mortality gap (median SMRs for the 1970s, 1980s and 1990s were 1.84, 2.98 and 3.2, respectively). This incremental SMR was also reported from Sweden during 1980–1995 (Osby et al., 2000), but in this instance was attributed to deinstitutionalization. The Saha meta-analysis was a seminal publication given that 37 studies were included detailing SMRs for different causes of deaths from 25 countries using data published in the period 1980–2006. Two previous meta-analyses using published data from 1969–1996 reported all-cause SMRs of 1.51 and 1.57 (Brown, 1997; Harris and Barraclough, 1998). The Saha et al. meta-analysis was also in agreement with other data (Harris and Barraclough, 1998) that the increased risk of mortality relates to men and women equally. This was postulated to be due to a failure of schizophrenia patients to receive the improving healthcare given to the general population and this theory has been supported by many data sets including the Western Australian CVD mortality and treatment data from 1980–1998 (Lawrence et al., 2003; Kisely et al., 2009). The hospital admission rates for CVD in schizophrenia patients in the Australian study were 60% of those for the general population despite mortality rate ratios (MRRs) for males being 1.78. Furthermore, schizophrenia patients underwent significantly fewer revascularization procedures, around only 30–35% of those received by the general population. In the Saha analysis of studies published between 1980 and 2006,

only three of the 37 studies were from Scandinavia (Saha et al., 2007). Suicide was associated with the highest median SMR (12.86) and cardiovascular mortality had a SMR of 1.79. A 2005 report from the National Association of State Mental Health Program Directors found a mortality gap of 25 years between schizophrenia patients and the general population and concluded that 40% of the excess mortality was related to suicide and other unnatural causes, with 60% related to natural causes (Parks et al., 2006). Cardiovascular mortality rose from 1976 to 1995, with the greatest increase from 1991 to 1995. A small Swedish cohort ($n = 255$) followed for 10 years up to 2000 found higher mortality rates in schizophrenia patients (23%) than in the national population (11.2%), relative risk (RR) 2.5 ($p = 0.0001$) (Fors et al., 2007).

There are, however, data that suggest that mortality rates at worst peaked around 1995 or, at best, are in decline, although data are not definitive. A confounder that is complex to address is that in the USA even different states have been shown to have widely differing SMRs in their respective schizophrenia populations. For example, data from 1997 show SMRs varying from 2.0 to 4.9 (Colton and Manderscheid, 2006) and it is reported that while in some states, such as Texas, the SMR decreased over the period 1997 to 1999, no change was measured in other states (Colton and Manderscheid, 2006). A meta-analysis found the highest SMR from studies published in the 1980s (1.91) rather than either the 1970s (1.52) or the 1990s (1.4) (Brown, 1997). Not all data however are in agreement. In a cohort ($n = 319$) followed for a median of 23.5 years (1950–2005), Capasso et al. (2008) in many ways replicated an earlier published study (Tsuang et al., 1980) and reported an almost identical survival curve over a 30-year period following diagnosis. Mortality was significantly increased ($p < 0.001$) compared with a Caucasian Mid-Western USA population. Ethnicity of comparative groups is often limited and may represent an important confounder. Their conclusion was that the mortality gap continued to increase versus the general population. An 11-year follow up of the complete schizophrenia population in Finland ($n = 66,881$) compared mortality rates with the total Finnish population (5.2 million) during 1996–2006 (Tiihonen et al., 2009). The mortality gap versus the general population did not widen further and showed a numerical decline from 25 years in 1996 to 22.5 years in 2006. Although the majority of mortality data come from epidemiological-based studies, there are two recent mortality studies with an open randomized design, the ziprasidone observational study of cardiac outcomes (ZODIAC) and the sertindole prospective cohort study (SCOP) (ZODIAC, 2010; Peuskens et al., 2009). ZODIAC randomized 18,154 patients to ziprasidone or olanzapine with 1-year follow up between 2002 and 2007. The mortality rate was identical in both cohorts (1.13%). SCOP randomized 9809 patients to sertindole or risperidone with 2-year follow up over a similar time period to ZODIAC (2002–2007) and, at the International Congress of Schizophrenia Research in 2009, a mortality rate of 0.8/100 person years was reported (Peuskens et al., 2009). Hence, not only were both studies randomized, recent and powered with a primary endpoint of mortality, but both reported far lower mortality rates in all cohorts than had been expected. SCOP was powered on an anticipated mortality rate of 2/100 person years. The mortality rate per person-years of follow up in ZODIAC has not been reported but can be estimated as between 1.2 and 1.7/100 person-years (based on either 18,000 or 12,000 person-years follow up). In contrast, the Dean and Thuras mortality study undertaken over the time period 1991–2001 reports a mortality rate of 5.07/100 person-years (Dean and Thuras, 2009). These data support a hypothesis that mortality rates in schizophrenia are currently declining; it is unclear whether the mortality gap with the general population is also narrowing although evidence supports a plateau since the mid-1990s. The Tran et al. prospective mortality study suggests that in France the mortality gap may not be decreasing with overall SMR for males and females 3.6 and 4.3, respectively (Tran et al., 2009).

Current causes of mortality in schizophrenia and evidence of any change in aetiology

The predominant causes of mortality in schizophrenia are now well recognised to be cardiovascular, unnatural deaths (including suicide), respiratory and cancer related. It is salient to note, however, that it is only in the last 10 years that the contribution of natural causes to this excess mortality has been fully recognized. The Brown meta-analysis concluded that there was a larger increase in SMR from suicide and only a moderate increased SMR from natural causes (Brown, 1997). Many studies and commentaries have, however, focused on CVD and not evaluated the role of other natural causes particularly cancer and respiratory disease in this elevated mortality (Barnett et al., 2007).

The actual contributions of CVD, cancer and suicide to mortality rates are dependent on both the type of study, length of follow up and cohort age. Studies that recruit first-episode patients will measure suicide mortality with greater accuracy whereas studies that include populations aged over 40–50 years are more likely to detect cancer cases. In contrast, studies that follow patients outside these age parameters may underestimate these causes of mortality. These critical factors thus may be relevant when comparing mortality causation across studies (Table 1). In addition, prospective studies designed specifically to measure mortality will provide greater accuracy of both mortality rates and causation (Tran et al., 2009; Peuskens et al., 2009). Comparison across studies is further complicated by the fact that cause of death is not reported uniformly with some studies combining a number of causes. Furthermore, there are many other relevant confounders which means that any form of adjustment is impractical, including the availability of medications and types of care provided during the study period.

Data from Australia (Lawrence et al., 2000) and Denmark (Dalton et al., 2008) concur that mortality rates for most major cancer types are elevated in schizophrenia when related to their incidence. The debate over whether cancer incidence is decreased in schizophrenia has been complex and is only now being addressed systematically (Catts et al., 2008; Bushe et al., 2009; Lichtermann et al., 2001). Cancer is probably the wrong metric as it consists of many different types with often varying aetiologies and may be best explored individually.

Table 1. Causes of mortality in recent major schizophrenia studies

	Mortensen and Juel (1993)	Brown (1997)	Brown et al. (2000)	Fors et al. (2007)	Capasso et al. (2008)	Dean and Thuras (2009)	Tran et al. (2009)[a]	Chong et al. (2009)
Characteristics								
Cohort age (mean)	n/a	n/a	39 (male) 43 (female)	n/a		49	39	60
Study period	1970–1987	n/a	1981–1994	1991–2000	1950–2005	1991–2001	1993–2003	2000–2006
Follow up (years)	9	n/a	13	10	55	10	11	6
Cohort size	9156	66,161	370	255	319	1208	3434	608
Number of deaths	1100	10,260	79	59	140	205	476	72
Cause of death[b] (%)								
Cardiovascular	12	n/a	18	49[c]	29	24	15	17
Cancer	7	n/a	18	19	19	21	16	17
Suicide	46	12	18	14		7	30	0
Cerebrovascular accident	3	n/a	n/a	n/a		8	n/a	n/a
Accidental	11	n/a	4			5	10	n/a
Respiratory					17			
Other natural causes	n/a	n/a	20	n/a			18	66

[a]Accidental deaths were defined as 'accidental or non-suicide poisoning'.
[b]Actual percentage of deaths based on total number of deaths.
[c]Includes cerebrovascular accident.
n/a: Not available.

The question of confounders is also relevant as smoking remains the single largest risk factor for a number of cancers. Pragmatically, the clinically relevant question may be to address the incidence of cancer without adjustment for postulated confounders. The two main cancers in schizophrenia (lung and breast) have a higher incidence than the general population (Bushe et al., 2009; Catts et al., 2008, Hippisley-Cox et al., 2007). The study from Capasso et al. was the first to fully address the role of cancer in mortality elevation and to discuss the implications (Capasso et al., 2008). Cancer is also an illness of more elderly patients, with no evidence to date that it is diagnosed at an earlier age in schizophrenia. Many cohorts may not include substantial numbers of patients over 50 years who are the cohort predominantly at risk of incident cancer and subsequent mortality. One of the findings from our previous work in breast cancer is that certain 'quality factors' need to be accounted for when analysing cancer incidence rates, most critically, having a cohort where there is significant follow up after 50 years of age (Bushe et al., 2009). In breast cancer, 80% of incident cases arise in patients over 50 years (Bushe et al., 2009). Even in the Capasso et al. cohort, the median age at study onset was 34 years with a median follow up of 23.5 years, yet the average age of death of patients with cancer was 64 years. The Saha et al. meta-analysis finds the median SMR for neoplastic diseases elevated at 1.37 in contrast with CVD (1.79) and suicide (12.86) (Saha et al., 2007). Neither age of the cohort, nor person-years follow up is stated and this may have implications for cancer mortality. One of the largest mortality studies in schizophrenia following a cohort of 17,600 schizophrenia patients over a prolonged period that extended to 28 years in some cases from 1973–2001 found MRR for CVD 2.07 and 1.72, suicide 25.38 and 45.59 and malignant neoplasms 1.24 and 1.32, for males and females,

respectively (Laursen et al., 2007). As with other data, the cohort was relatively young with maximal cohort age of 48 years at the end of follow up and this may have led to lower cancer mortality than expected. Recent data, both prospective mortality studies and epidemiological cohort-based analyses, have provided further information regarding the actual contributions of these causes (Table 1). Data collected from before 2000 in general finds CVD or circulatory disease to be the most common cause of death. Fors et al. reported 46% deaths due to circulatory causes (CVD and cerebrovascular accident [CVA]) during 1991–2000 follow up (Fors et al., 2007).

A 55-year follow up study of 319 patients (median follow up 23.5 years) published in 2008 (Capasso et al., 2008) found cancer to be the second most common cause of death (19%), with cardiovascular (CVD, arrhythmias and other cardiac causes) the most common (29%). Suicide deaths were low (3%), however, some suicides may have been misclassified as 'accidental' deaths which accounted for 6% of the total mortality. Difficulties in these analyses are emphasized by the death certificate not being available in 9% of cases and a further 9% of deaths being due to 'unspecified causes'. The strength of long-term follow up studies is that they allow for the development of cancers from factors such as smoking (Capasso et al., 2008; Lawrence et al., 2009). Recently, an 11-year prospective mortality study from France in 3470 schizophrenia patients reported a 14% mortality rate: suicide 4.2%, cancer 2.2%, CVD 2.0% and 1.4% attributed to 'accidental or non-suicide poisoning'. The mortality rate was almost four-fold greater than in the general population (SMR all cause death 3.6, 95% CI 3.3–3.9 for males and SMR all cause death 4.3, 95% CI 3.7–5.1 for females). Cancer was the second most frequent cause of mortality (SMR 1.5, 95% CI 1.2–1.9) with 50% of cancer in males

being lung and 39% of cancer in females being breast. Suicide rates would potentially be even greater if this category was combined with the accidental or non-suicide poisoning cohort, rising to 5.6%. A 10-year follow up study in the USA in 1621 patients with a mean age of 49 years at first observation found 24% of deaths attributable to cardiovascular causes compared with cancer (21%) and suicide (7%) (Dean and Thuras, 2009).

Suicide. Suicide mortality rates may be best defined using first episode studies and birth cohort studies as many suicides happen in the early years of illness. The Northern Finland 1966 prospective population birth cohort followed 100 schizophrenia patients from 16 years of age up until their 39th birthday and found that 14% of the cohort had died. Half of these deaths ($n = 7$) were the result of suicide, 2.9% females and 9.2% males (Alaräisänen et al., 2009). In terms of comparison with other data sets, it is crucial that 71% of these suicides occurred within the first 3 years after onset of illness and that suicide risk continues throughout the illness. This is supported by Palmer et al.'s meta-analysis where suicide mortality was significantly greater in first-episode cohorts than those followed up later in their illness (5.6% and 1.8%, respectively) (Palmer et al., 2005). Similar data come from a first-admitted 8-year follow up study in Denmark in 9156 schizophrenia patients where suicide accounted for 46% of the 1100 deaths and accidents an additional 11% (Mortensen and Juel, 1993). Suicide mortality is probably higher than measured as around 25% of accidental and undetermined deaths are suicide (Allebeck et al., 1996). There is little clarity as to any change in suicide rates as factors such as deinstitutionalization of patients may be a confounder (Osby et al., 2000).

Data from Wales showed that suicide rates were as much as 20-fold higher in the 1990s than in the period 1875–1924, although it is salient to note that the increase was from 0.5% to 4.7% (Healy et al., 2006) and a review in 2005 found a lifetime risk of 4.9% (Palmer et al., 2005), seemingly lower than the 10–13% figure from Caldwell and Gottesman (1990).

The contribution of suicide to mortality thus varies widely dependent on the age of the study cohort, length of follow up and type of study and may be underestimated. The percentage of all deaths attributed to suicide ranges from 0% to 46% (Table 1).

Cardiovascular disease. There is little doubt that schizophrenia patients have greater mortality from cardiovascular disease than the general population. The UKGPRD study found CVD mortality in schizophrenia to be elevated almost four-fold (hazard ratio [HR] 3.61) in patients aged 18–49 years with a doubling of risk in the 50–75-year-old cohort (HR 1.96) (Osborn et al., 2007). Mortensen and Juel reported a SMR in men for CVD of 1.69 in a large first-admission cohort study of essentially young patients, with a modal age at start of 25–29 years, and follow up of around 8 years. These data suggest that this enhanced CVD risk in schizophrenia has an early onset (Mortensen and Juel, 1993) and a recent Finnish first episode study concluded that the greatest SMR for CVD mortality was measured in the cohort aged 20–24 years (Kiviniemi et al., 2010). However, the number of deaths attributable to CVD is hugely variable dependent on factors similar to those that affect suicide mortality rates and range from 12–46%.

Cancer. Cancer is recorded as the reason for death in 7–21% of deaths (Table 1). The lowest figure of 7% comes from a first-admitted cohort followed for only 8 years and is thus surprisingly high (Mortensen and Juel, 1993). There is a consistency of cancer mortality rates in the other studies (16–21%) which is not dissimilar to CVD mortality rates. Only two studies with cohort ages at entry of 49 years and 60 years and follow up of 10 years and 6 years, respectively, follow patients beyond the age at which cancer might be expected to be diagnosed and relate to mortality (Chong et al., 2009; Dean and Thuras, 2009).

Other natural causes. Specific causes of other natural deaths are not recorded consistently across studies and are seen to account for between 18% and 66% of all deaths (Table 1) (Tran et al., 2009; Chong et al., 2009). Respiratory causes and infections are common significant contributors to these findings, but, as for other causes, are partly dependent on study type. This can be seen in an in-patient study in elderly Asian patients where 66% of deaths were ascribed to infections (Chong et al., 2009).

Overview of causes of death in schizophrenia patients. Although numerically CVD is the most common mortality cause in most studies, cancer is reported almost as frequently. The type of study, cohort entry age and length of follow up are all critical factors when reviewing mortality data. Long-term follow up of first episode patients prospectively would be the optimum tool to answer this important question. Studies that include younger cohorts and first episode patients predominately measure suicide rates whereas those that include older cohorts may be more accurate for cancer mortality rates; studies that essentially miss these age groups may under-report cancer and suicide deaths, and inadvertently report higher CVD mortality rates. These limitations are relevant for future clinical research in mortality in schizophrenia.

Antipsychotics and mortality

The premise has often been stated that second-generation antipsychotics (SGAs) may increase cardiovascular risk as many are associated with weight gain and worsening of metabolic parameters, often to a significantly greater degree than first-generation antipsychotics (FGAs) (Lieberman et al., 2005; Kahn et al., 2008). Clozapine, olanzapine and quetiapine are often cited as the antipsychotics with the most adverse metabolic profile (Hennekens et al., 2005). At present, somewhat surprisingly, we could find no evidence to support this hypothesis of increased cardiovascular risk. In contrast, many current data sets that compare FGAs and SGAs find

either increased (Dean and Thuras, 2009; Enger et al., 2004; Osborn et al., 2007) or unchanged (Tiihonen et al., 2009) cardiovascular morbidity and mortality with FGAs.

A 10-year follow up study in the USA in 1621 patients with a mean age of 49 years at first observation found FGAs were associated with a doubling of mortality compared with SGA (RR 2.00, 95% CI 1.13–3.53) and had numerically greater association with cardiovascular mortality than SGA (rates per 100,000/year; 519 and 1178, significance not stated) (Dean and Thuras, 2009). The UK GPRD study reported significantly lower CVD mortality in SMI patients taking SGAs than FGAs (Osborn et al., 2007) and Enger et al. reported a five-fold increased risk of myocardial infarction in patients taking FGAs (Enger et al., 2004). During a 10-year follow up, recent data have also shown that the risk of CVD mortality does not differ between risperidone and clozapine despite known differences in their metabolic risk profiles (Kelly et al., 2010).

Where previously commentators have associated increased CVD mortality rates to antipsychotics (De Hert et al., 2010; Weinmann et al., 2009), it is salient to note that often these studies evaluated essentially only FGA (Joukamaa et al., 2006). The FIN 11 study concluded that mortality rates were heterogeneous amongst antipsychotics and were able to show dissonance in mortality rates between the individual FGAs haloperidol and perphenazine (Tiihonen et al., 2009). Overall mortality rates in the haloperidol cohort were significantly greater than the perphenazine cohort and some SGAs (Tiihonen et al., 2009). This review cannot address the potential reasons for these findings but it may be salient to focus on the recent finding that in a first-episode cohort in Finland, the greatest SMR for circulatory disease mortality was measured in the cohort aged 20–24 years (Kiviniemi et al., 2010).

In 2010 there seems little doubt that antipsychotic treatments reduce mortality with significant mortality elevations reported in the first admitted Finnish cohort (2006) and the complete Finnish cohort (2009), in patients who did not take antipsychotic treatments, with worsening of outcomes according to length of non-adherence to medications (Tiihonen et al., 2006, 2009). Even in short-term clinical trials there are similar findings (Khan et al., 2007; Issac and Koch, 2010) where the US Food and Drug Administration and European Medicines Agency have published mortality rates for antipsychotics in comparison to placebo cohorts. Schizophrenia patients in the placebo cohorts have elevated mortality rates compared with antipsychotic cohorts. Poor adherence to medication has been shown to be predictive of suicide in both small case–control studies (Pompili et al., 2009) and a large cohort study from Finland (Tiihonen et al., 2006). Mortality rates in the large Finland study in first admission schizophrenia patients with a mean follow up of 3 years were increased at least five-fold in the cohort not receiving any medication (adjusted RR 37.4; 95% CI 5.1–276) for suicide (Tiihonen et al., 2006) and by at least six-fold (adjusted RR 12.3: 95% CI 6.0–24.1) for overall mortality. In the 11-year follow up study of all schizophrenia patients in Finland, long-term exposure (7–11 years) to antipsychotic treatment was associated with around a 20% lower mortality than no drug use (Tiihonen et al., 2009) with an inverse relation between length of treatment and mortality rate.

Polypharmacy has often been associated with increased mortality (Joukamaa et al., 2006) though only with conventionals. A recent Danish case–control study in over 27,000 schizophrenia patients over a 10-year follow up (1996–2005) reported an unchanged mortality rate for the risk of natural death when utilising antipsychotic polypharmacy with up to three antipsychotics (conventionals were prescribed in 64% of patients) (Baandrup et al., 2010). An association was, however, reported for increased mortality when using benzodiazepines with a long elimination half-life (OR 1.78) that may require further clarification. The current findings that SGA have as a minimum similar associations with CVD mortality with FGA do require further study and importantly may require far longer follow up than currently reported.

The role of databases in measuring mortality rates

Population-based studies on mortality are possible in those Nordic countries that have similar sets of administrative registers of relevance to healthcare although their availability and commencement dates vary somewhat between the countries. 'Cause of death' registers are among the oldest registers in all of the Nordic Countries, for example, the Finnish Causes of Death Register maintained by Statistics Finland, provides date and cause of death and also stores death certificates. The register includes the personal identification number of each deceased person, sex, age, place of residence and principal, underlying and contributory causes of death. The routine validation of death certificates ensures that the accuracy of Nordic cause of death registers is good by international standards (Johansson and Westerling, 2000; Haukka et al., 2008; Lahti and Penttilä, 2001).

Cause of death registers have been used in psychiatric research for studying such topics as on mortality due to various somatic disorders, and especially suicides (Heilä et al., 2005).

In all Nordic countries it is, in principle, possible to link information about psychiatric disorders such as schizophrenia to mortality data and to carry out large-scale, historical cohort studies that allow research into the differences in mortality (all-cause and cause-specific) between subpopulations defined by psychiatric disorders. However, databases may not be operational in all Nordic countries and country-specific confidentiality issues may need to be addressed. Thus, to interpret some of these data further, additional data on prescribing and adherence will be required.

Conclusions

Mortality can now be regarded as an additional measurable endpoint in schizophrenia that can supplement but not necessarily replace other types of measured outcome. Data suggest that mortality rates in schizophrenia have plateaued and may even be in decline following a peak around 1995 although further confirmation is needed. The heterogeneity of many of the cohorts combined with the relative short-term follow up of the most recent data deriving from randomized controlled trials make any definitive conclusions impossible. At a minimum, however, there is no evidence that mortality rates are further increasing although the degree to which this relative improvement is related to the advent of SGAs is

speculative at this time. Evidence from three large studies is supportive that mortality rates associated with the SGAs in relation to CVD are lower than those of the FGAs (Enger et al., 2004; Dean and Thuras, 2009; Osborn et al., 2007) although this was not confirmed in a recent 11-year mortality follow up (Tiihonen et al., 2009). Any concerns over these agents increasing cardiovascular mortality may have been allayed in the short term, however it may be prudent to await longer-term data before forming definitive views.

The utilization of SGAs increased in Finland from 13% to 64% during the period 1996 to 2006 with a similar pattern worldwide. There remains a substantial mortality gap with the general population however which needs to be addressed. In contrast, each of the main causes of mortality can be further addressed. Cardiovascular mortality rates could be expected to decline with effective health screening programmes and utilization of procedures and medications such as statins, anti-hypertensives and hypoglycaemic drugs which are currently grossly underused in schizophrenia patients. Effective medication regimes combined with psycho-social treatments may reduce the suicide mortality. Cancer mortality can be reduced by engagement of schizophrenia patients in general population screening programmes. There is increasing evidence that the two most common cancers, breast and lung, have increased incidence rates in schizophrenia, however, the impact of confounders such as smoking and prolactin is unclear and adjusted cancer rates in their absence are unknown. There is also a challenge to the belief that suicide and CVD are the main causes of mortality as cancer deaths may be of similar magnitude.

Future research into mortality needs to ascertain the success of long-term treatments designed to reduce mortality rates and to quantify important fiscal outcome measures that should include quality-adjusted life-years (QALYS). The optimum design for these studies may entail long-term, prospective follow up of a large first-episode cohort and, as a minimum, researchers should be encouraged to standardize their methodology for reporting mortality causes to allow easier cross-study comparisons. The interpretation of SMRs across varied cohorts is complex and any further research which reports age- and stage-specific mortality from various causes may be instructive. In particular, contemporaneous research utilizing doses of FGAs lower than in the past and evaluating different potency FGAs needs to establish whether any mortality differential may continue to be established with SGAs. Mortality is a robust endpoint and it is to be expected that many of our remaining questions will be addressed over the coming decades.

Conflict of interest statement
CB is an employee of Eli Lilly and Company, the manufacturer of olanzapine. MT is an NHS employee and has accepted fees and/or hospitality from Astra Zeneca, Bristol Myers Squibb, Eli-Lilly and Company and Janssen-Cilag in the past 5 years. JH has participated in research collaborations with Janssen-Cilag and Eli Lilly and Company, and has been a member of an expert advisory group for Astellas.

References

Alaräisänen A, Miettunen J, Räsänen P, Fenton W, Koivumaa-Honkanen HT and Isohanni M (2009) Suicide rate in schizophrenia in the Northern Finland 1966 Birth Cohort. *Soc Psychiatr Psychiatr Epidemiol* 44: 1107–1110.

Allebeck P, Brandt L, Nordstrom P and Asgard U (1996) Are suicide trends among the young reversing? Age, period and cohort analyses of suicide rates in Sweden. *Acta Psychiatr Scand* 93: 43–48.

Baandrup L, Gasse C, Jensen VD, Glenthoj BY, Nordentoft M, Lublin H, et al. (2010) Antipsychotic polypharmacy and risk of death from natural causes in patients with schizophrenia: a population-based nested case–control study. *J Clin Psychiatry* 71: 103–108.

Barnett AH, Mackin P, Chaudhry I, Farooqi A, Gadsby R, Heald A, et al. (2007) Minimising metabolic and cardiovascular risk in schizophrenia: diabetes, obesity and dyslipidaemia. *J Psychopharmacol* 21: 357–373.

Brown S (1997) Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry* 171: 502–508.

Brown S, Inskip H and Barraclough B (2000) Causes of the excess mortality of schizophrenia. *Br J Psychiatry* 177: 212–217.

Brown S, Kim M, Mitchell C and Inskip H (2010) Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry* 196: 116–121.

Bushe CJ, Bradley AJ, Wildgust HJ and Hodgson RE (2009) Schizophrenia and breast cancer incidence: a systematic review of clinical studies. *Schizophr Res* 114(1–3): 6–16.

Bushe C and Leonard B (2004) Association between atypical antipsychotic agents and type 2 diabetes: review of prospective clinical data. *Br J Psychiatry Suppl* 47: S87–S93.

Bushe CJ and Leonard BE (2007) Blood glucose and schizophrenia: a systematic review of prospective randomized clinical trials. *J Clin Psychiatry* 68: 1682–1690.

Caldwell CB and Gottesman II (1990) Schizophrenics kill themselves too: a review of risk factors for suicide. *Schizophr Bull* 16: 571–589.

Capasso RM, Lineberry TW, Bostwick JM, Decker PA and St Sauver J (2008) Mortality in schizophrenia and schizoaffective disorder: an Olmsted County, Minnesota cohort: 1950–2005. *Schizophr Res* 98: 287–289.

Catts VS, Catts SV, O'Toole BI and Frost ADJ (2008) Cancer incidence in patients with schizophrenia and their first-degree relatives—a meta-analysis. *Acta Psychiatr Scand* 117: 323–336.

Chong SA, Tay JA, Subramaniam M, Pek E and Machin D (2009) Mortality rates among patients with schizophrenia and tardive dyskinesia. *J Clin Psychopharmacol* 29: 5–8.

Colton CW and Manderscheid RW (2006) Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis* 3: A42.

Dalton SO, Steding-Jessen M, Engholm G, Schüz J and Olsen JH (2008) Social inequality and incidence of and survival from lung cancer in a population-based study in Denmark, 1994–2003. *Eur J Cancer* 44: 1989–1995.

De Hert M, Correll CU and Cohen D (2010) Do antipsychotic medications reduce or increase mortality in schizophrenia? A critical appraisal of the FIN-11 study. *Schizophr Res* 117: 68–74.

Dean CE and Thuras PD (2009) Mortality and tardive dyskinesia: long-term study using the US National Death Index. *Br J Psychiatry* 194: 360–364.

Drew LR (2005) Mortality and mental illness. *Aust N Z J Psychiatry* 39: 194–197.

Enger C, Weatherby L, Reynolds RF, Glasser DB and Walker AM (2004) Serious cardiovascular events and mortality among patients with schizophrenia. *J Nerv Ment Dis* 192: 19–27.

Fors BM, Isacson D, Bingefors K and Widerlöv B (2007) Mortality among persons with schizophrenia in Sweden: an epidemiological study. *Nord J Psychiatry* 61: 252–259.

Graunt J (1662) Natural and political observations mentioned in a following index, and made upon the bills of mortality. In: Hunter RA and Macalpine I (eds) (1963) *Three Hundred Years of Psychiatry*. London: Oxford University Press, 166.

Harris EC and Barraclough B (1998) Excess mortality of mental disorder. *Br J Psychiatry* 173: 11–53.

Haukka J, Tiihonen J, Härkänen T and Lönnqvist J (2008) Association between medication and risk of suicide, attempted suicide and death in nationwide cohort of suicidal patients with schizophrenia. *Pharmacoepidemiol Drug Saf* 17: 686–696.

Healy D, Harris M, Tranter R, Gutting P, Austin R, Jones-Edwards G, et al. (2006) Lifetime suicide rates in treated schizophrenia: 1875–1924 and 1994–1998 cohorts compared. *Br J Psychiatry* 188: 223–228.

Heilä H, Haukka J, Suvisaari J and Lönnqvist J (2005) Mortality among patients with schizophrenia and reduced psychiatric hospital care. *Psychol Med* 35: 725–732.

Hennekens CH, Hennekens AR, Hollar D and Casey DE (2005) Schizophrenia and increased risks of cardiovascular disease. *Am Heart J* 150: 1115–1121.

Hippisley-Cox J, Vinogradova Y, Coupland C and Parker C (2007) Risk of malignancy in patients with schizophrenia or bipolar disorder: nested case–control study. *Arch Gen Psychiatry* 64: 1368–1376.

Isaac M and Koch A (2010) The risk of death among adult participants in trials of antipsychotic drugs in schizophrenia. *Eur Neuropsychopharmacol* 20: 139–145.

ISIS-2 Collaborative Group (1988) Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 2: 349–360.

Johansson LA and Westerling R (2000) Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. *Int J Epidemiol* 29: 495–502.

Joukamaa M, Heliövaara M, Knekt P, Aromaa A, Raitasalo R and Lehtinen V (2006) Schizophrenia, neuroleptic medication and mortality. *Br J Psychiatry* 188: 122–127.

Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IPM, et al., for the EUFEST study group (2008) Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* 371: 1085–1097.

Kelly DL, McMahon RP, Liu F, Love RC, Wehring HJ, Shim JC, et al. (2010) Cardiovascular disease mortality in patients with chronic schizophrenia treated with clozapine: a retrospective cohort study. *J Clin Psychiatry* 71: 304–311.

Khan A, Schwartz K, Stern C, Redding N, Kolts RL, Brown WA, et al. (2007) Mortality risk in patients with schizophrenia participating in premarketing atypical antipsychotic clinical trials. *J Clin Psychiatry* 68: 1828–1833.

Kisely S, Campbell LA and Wang Y (2009) Treatment of ischaemic heart disease and stroke in individuals with psychosis under universal healthcare. *Br J Psychiatry* 195: 545–550.

Kiviniemi M, Suvisaari J, Pirkola S, Häkkinen U, Isohanni M and Hakko H (2010) Regional differences in five-year mortality after a first episode of schizophrenia in Finland. *Psychiatr Serv* 61: 272–279.

Lahti RA and Penttilä A (2001) The validity of death certificates: routine validation of death certification and its effects on mortality statistics. *Forensic Sci* 115: 15–32.

Laursen TM, Munk-Olsen T, Agerbo E, Gasse C and Mortensen PB (2009) Somatic hospital contacts, invasive cardiac procedures, and mortality from heart disease in patients with severe mental disorder. *Arch Gen Psychiatry* 66: 713–712.

Laursen TM, Munk-Olsen T, Nordentoft M and Mortensen PB (2007) Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. *J Clin Psychiatry* 68: 899–907.

Lawrence DM, Holman CD, Jablensky AV and Hobbs MS (2003) Death rate from ischaemic heart disease in Western Australian psychiatric patients 1980–1998. *Br J Psychiatry* 182: 31–36.

Lawrence D, Holman CD, Jablensky AV, Threlfall TJ and Fuller SA (2000) Excess cancer mortality in Western Australian psychiatric patients due to higher case fatality rates. *Acta Psychiatr Scand* 101: 382–388.

Lawrence D, Mitrou F and Zubrick SR (2009) Smoking and mental illness: results from population surveys in Australia and the United States. *BMC Public Health* 9: 285.

Lichtermann D, Ekelund J, Pukkala E, Tanskanen A and Lönnqvist J (2001) Incidence of cancer among persons with schizophrenia and their relatives. *Arch Gen Psychiatry* 58: 573–578.

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators (2005) Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 353: 1209–1223.

Mortensen PB and Juel K (1993) Mortality and causes of death in first admitted schizophrenic patients. *Br J Psychiatry* 163: 183–189.

Osborn DP, Levy G, Nazareth I, Petersen I, Islam A and King MB (2007) Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. *Arch Gen Psychiatry* 64: 242–249. Erratum in: *Arch Gen Psychiatry* 2007; 64: 736.

Osby U, Correia N, Brandt L, Ekbom A and Sparén P (2000) Time trends in schizophrenia mortality in Stockholm county, Sweden: cohort study. *BMJ* 2000; 321: 483–484.

Palmer BA, Pankratz VS and Bostwick JM (2005) The lifetime risk of suicide in schizophrenia: a reexamination. *Arch Gen Psychiatry* 2005; 62: 247–253.

Parks J, Svendsen D, Singer P and Foti M (2006) *Morbidity and Mortality in People with Serious Mental Illness*. National Association of State Mental Health Program Directors (NASMHPD) Medical Directors Council, Alexandria, VA 22314. Available at: www.nasmhpd.org/general_files/publications/med_directors_pubs/Technical%20Report%20on%20Morbidity%20and%20Mortaility%20-%20Final%2011-06.pdf (accessed 17 March 2010).

Peuskens J, Tanghøj P and Mittoux A (2009) Outcome of the prospective sertindole prospective (SCOP) study. All-cause mortality. *Schizophr Bull* 35: 347.

Pompili M, Lester D, Grispini A, Innamorati M, Calandro F, Iliceto P, et al. (2009) Completed suicide in schizophrenia: evidence from a case–control study. *Psychiatry Res* 167: 251–257.

Saha S, Chant D and McGrath J (2007) A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 64: 1123–1131.

Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, et al. (2009) 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 374: 620–627.

Tiihonen J, Wahlbeck K, Lönnqvist J, Klaukka T, Ioannidis JP, Volavka J, et al. (2006) Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ* 333: 224.

Tran E, Rouillon F, Loze JY, Casadebaig F, Philippe A, Vitry F, et al. (2009) Cancer mortality in patients with schizophrenia: an 11-year prospective cohort study. *Cancer* 115: 3555–3562.

Tsuang MT, Woolson RF and Fleming JA (1980) Causes of death in schizophrenia and manic-depression. *Br J Psychiatry* 136: 239–242.

Weinmann S, Read J and Aderhold V (2009) Influence of antipsychotics on mortality in schizophrenia: systematic review. *Schizophr Res* 113: 1–11.

ZODIAC (2010) PhRMA Web Synopsis. Zodiac Trial Results; Protocol A128062. www.clinicalstudyresults.org/drugdetails/?sort = d.study_names&page = 2&drug_id = 3913 (accessed 10 March 2010).