Morbidity and mortality in schizophrenia

Schizophrenia is known to increase morbidity and mortality. Physical illness in schizophrenia is influenced by a combination of genetic and environmental factors. This review highlights the multifactorial aetiology of morbidity and mortality in schizophrenia and considers the use of antipsychotics for patients with this disorder.

Schizophrenia is a relatively common disorder ranked among the top ten leading causes of disability worldwide (Lopez and Murray, 1998). There is a twelve-fold increased risk of suicide and all-cause mortality is two to three times greater in this patient group (Saha et al, 2007). Alarmingly two thirds of these deaths are attributable to 'natural' causes such as cardiovascular, respiratory disease, stroke, cancer and thromboembolism (Parks et al, 2006; Parker et al, 2010). The most common causes of mortality in this patient group are myocardial infarction, strokes and cancers (Dean and Thuras, 2009). This may result from genetic predisposition to physical illness and lifestyle intrinsic to this patient group. Another contributing factor under debate is the effect of antipsychotics on physical illness and subsequent morbidity and mortality.

Schizophrenia and genetic predisposition to physical illness

Having schizophrenia confers a genetic risk of medical health problems independent of lifestyle. Higher rates of insulin resistance, impaired glucose tolerance and autoantibodies associated with diabetes have been discovered in drug-naïve patients (Ryan et al, 2003), which may account for higher incidence of diabetes (Wright et al, 1996). This adverse metabolic profile in combination with social factors as discussed further confers an increased risk of cardiovascular disease.

Schizophrenia and the lifestyle of the patient group

The lifestyles of people with mental illnesses are often characterized by poor diets and low exercise levels, in addition to having higher levels of smoking and alcohol use than the general population (Regier et al, 1990; Kelly and McCreadie, 2000). These are recognized risk factors for increasing the rates of cardiopulmonary, metabolic, gastrointestinal diseases and cancers. Illicit drug use is increased by six-fold and engagement in high-risk sexual behaviour among individuals with schizophrenia is associated with higher risk of blood-borne and sexually transmitted infectious diseases, including hepatitis and human immunodeficiency virus (Regier et al, 1990). These behaviours do partially explain the higher rates of comorbid medical conditions.

Social issues need to be considered as stress is a risk factor for ill health. Social drift is a known phenomenon in schizophrenia (Goldberg and Morrison, 1963). There are high rates of unemployment, homeless and/or substandard living conditions in addition to low social support and increased psychosocial stresses compared to the general population (Eklund and Hansson, 2007).

Lifestyle factors have a major impact on health, and management should include lifestyle improvement strategies and screening for physical disorders, in combination with effective antipsychotic treatment at the earliest possible stage.

Schizophrenia and the effect of antipsychotics on physical health

The role of antipsychotics and their effects on physical health and subsequent mortality has been controversial. The first-generation 'conventional' antipsychotic are effective against psychotic symptoms but have high rates of neurological side effects, such as extrapyramidal side effects and tardive dyskinesia. The introduction of second-generation, or 'atypical', antipsychotic drugs promised enhanced efficacy and safety and appear more efficacious than conventional drugs in reducing negative symptoms (i.e. apathy, anhedonia and social withdrawal).

The advantages of the atypical drugs have been questioned owing to their propensity to induce weight gain and alter glucose and lipid metabolism. Studies in the 1990s suggested that atypical antipsychotics adversely affect mortality by increasing the incidence of cardiovascular events and strokes (Osborn et al, 2007). Outcomes of the ZODIAC observational study of cardiac outcomes in schizophrenia found that excess mortality existed after adjusting for possible confounders and concluded that this may result from antipsychotic use (Strom et al, 2008).

More recent research demonstrated that the mortality of individuals with schizophrenia was increased over ten-fold if they did not take medication compared with those who took at least one prescribed typical or atypical antipsychotic (Tiihonen et al, 2006). Other studies found that the use of atypical antipsychotics including clozapine, olanzapine, quetiapine and risperidone did not

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appear to lead to an excess of cardiovascular mortality in the elderly compared to typical antipsychotic use (Wang et al, 2005).

The most recent FIN-11 study looked at the all-cause mortality during treatment with six of the most commonly used atypical antipsychotics in Finland over 11 years, using perphenazine as a baseline typical antipsychotic (Tiihonen et al, 2009). The number of patients in this study equalled the total number of patients in all previous studies. They did not find atypical antipsychotics to adversely affect the life expectancy with the possible exceptions of risperidone and quetiapine.

An important finding is that clozapine use had the lowest risk of overall mortality compared to all other antipsychotics, despite it having the highest risk of weight gain and metabolic syndrome. Owing to the risk of neutropenia, National Institute for Health and Clinical Excellence (2009) guidelines state that clozapine should only be used if two antipsychotics have been tried unsuccessfully. Consequently this results in a selection bias of more severely ill patients. Clozapine is known to reduce mortality by suicide but surprisingly this study found that deaths from other causes including ischaemic heart disease are reduced (Tiihonen et al, 2009). A confounding factor considered is the regular blood monitoring required with clozapine. This enables regular contact between patients and mental health teams to provide better psychosocial and general health monitoring, and better management of the overall health. However, the InterSEptt study found improved mortality rates with clozapine despite identical intensity of monitoring with both olanzapine and clozapine (Meltzer et al, 2003). This demonstrates that monitoring by itself does not explain the improved mortality outcomes.

Despite protective effects of antipsychotics on mortality, they are associated with weight gain and adverse lipid profile which must be addressed through lifestyle advice and medical management. National Institute for Health and Clinical Excellence (2009) guidelines for schizophrenia seek to promote cardiovascular risk reduction through annual health checks to monitor smoking status and the metabolic profile. Dyslipidaemia in patients on antipsychotics has been successfully treated with statins (Hanssens et al, 2007). Programmes to encourage smoking cessation can be effective and have long-lasting effects (Lasser et al, 2000). Regular physical activity will lower the risk of developing cardiovascular disease, diabetes and some cancers (Warburton et al, 2006). These measures will be essential in counteracting some of the negative effects of the antipsychotics and improving quality of life.

Relevance to secondary care doctors

The vast majority of patients with schizophrenia have comorbid disease (estimates range from 50–74%) and have high levels of contact with clinicians in all medical and surgical specialties (Green et al, 2003; Jones et al, 2004). Patients with schizophrenia have unfavourable mortality rates from comorbid conditions such as cardiovascular diseases, cancers and strokes compared to the general population (Hennekens et al, 2005; Tran et al, 2009). An American study demonstrated a reduced proportion of people with schizophrenia having angiograms for ischaemic coronary disease, leading to higher mortality rates (Druss et al, 2000). This may be secondary to poor access to health services resulting from physician- and patient-led barriers. These barriers may vary as a result of the cultural influences, and the health-care arrangements present in different countries.

Physician-led barriers include social stigma, preconceptions of schizophrenia and the presumed effects of antipsychotics. These barriers can affect assessment of patients and identification of comorbid disease as physical symptoms may be attributed to patients' mental health.

Patient-led barriers can include the cognitive deficits, which in turn can affect symptom recognition, attendance at follow-up appointments, and adhering to complex drug regimens (Mohamed et al, 1999). Patients with schizophrenia have higher pain thresholds, are less likely to recognize illness symptoms and less likely to report physical symptoms spontaneously or only when they are of high severity (Jeste et al, 1996). Paranoia associated with cases of schizophrenia can prevent help-seeking behaviour. For example, these patients often fail to register with primary care (Goldberg and Jackson, 1992).

Increased awareness of these barriers amid physicians can lead to more proactive management and rigorous follow-up. A holistic wellbeing support programme involving screening and individualized lifestyle advice will be key in reducing morbidity and mortality. The re-evaluation of risk/benefit assessments of the various antipsychotics in collaboration with psychiatrists may provide opportunity to improve treatment patterns.

Conclusions

There is a complex interplay of intrinsic predisposition, patients' lifestyles and the role of medication affecting mortality in people with schizophrenia. Management of this patient group should encompass a holistic approach including effective antipsychotic treatment at the earliest stage, screening for cardiovascular risk factors and common cancers, and ensuring that all individuals with schizophrenia receive the most appropriate and effective treatments. What is interesting is how the thinking towards the side effects of antipsychotics is slowly beginning to change. Even though side effects of antipsychotics such as insulin resistance and dyslipidaemia should lead to higher risk of morbidity, there is significant evidence to the contrary. Doctors working in secondary care need to bear these factors in mind when they come into contact with patients taking antipsychotic medications. Close liaison with psychiatrists should be sought in order to provide the most effective management for this group of patients. BJHM

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KEY POINTS

- Patients with schizophrenia suffer from excess mortality attributable to suicide and natural causes.
- Patients must be screened for cardiovascular risk factors and symptoms of common cancers.
- Long-term typical or atypical antipsychotic use improves life expectancy despite possible derangement of the metabolic profile.
- Risk benefit analysis of antipsychotic drug choice is complex and should be undertaken in close liaison with psychiatrists.

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