Introduction

Symptoms of schizophrenia typically first appear in adolescence, a time of transition involving biological, social and emotional changes. Schizophrenia and related psychotic illnesses can significantly impair educational and social development; consequently, early identification and treatment is paramount and can affect long-term outcome. Singh (2010) states that early intervention is cost effective and does ameliorate the course of early psychosis, referring specifically to specialist early intervention teams, and their impact on long-term disease outcome and prognosis. Much research is now available in this area, and the papers selected for this supplement focus on intervention at this critical stage, related side effects as well as mortality risk factors associated with schizophrenia.

The stress–vulnerability model for schizophrenia suggests that the onset and course of schizophrenia may be determined by an underlying vulnerability, with clinical manifestation being modulated by environmental stressors. It has long been recognized, since the days of Kraepelin (1913), that people with schizophrenia are more likely to be obese and to suffer from metabolic problems such as diabetes mellitus. Leonard et al. review evidence concerning a disordered immune system in schizophrenia and postulate that the relationship between the therapeutic benefits of antipsychotics, the pathology of schizophrenia and these metabolic syndromes are linked to chronic, low-grade inflammation. As maternal infections have been implicated as a causative factor, the resulting inflammatory changes could contribute to neurodevelopmental difficulties, and a sensitized immune system that activates in adolescence. Leonard et al. review evidence concerning a disordered immune system in schizophrenia and postulate that the relationship between the therapeutic benefits of antipsychotics, the pathology of schizophrenia and these metabolic syndromes are linked to chronic, low-grade inflammation. As maternal infections have been implicated as a causative factor, the resulting inflammatory changes could contribute to neurodevelopmental difficulties, and a sensitized immune system that activates in adolescence. Leonard et al. also discuss the important role played by pro-inflammatory cytokines which modulate neuronal action, differentiation and survival during neurodevelopment, and more specifically influence activity and survival of neurons that utilize neurotransmitters such as serotonin, glutamate and dopamine. Interleukin-6 is particularly important in schizophrenia as it could augment dopaminergic function which, in turn, would affect psychotic symptoms. In addition to the dopaminergic system, some pro-inflammatory cytokines enhance the activity of the glutamatergic system, via the tryptophan–kynurenine pathway, and this might contribute to the cognitive decline sometimes seen in schizophrenia. The inflammation hypothesis of schizophrenia raises the possibility of using anti-inflammatory drugs, such as COX-2 inhibitors, as adjuncts to traditional antipsychotic medication.

Van Haren et al. find further evidence to suggest that schizophrenia is a progressive brain disease, and that the most significant decline in grey matter volume occurs in the critical first year of illness. Indeed, there appears to be a linear correlation of grey matter loss with age in schizophrenia, as opposed to the exponential decline seen in healthy individuals. Van Haren et al. also suggest there is a link between the extent of volume loss and severity of symptoms and social functioning, but do acknowledge other studies refute this theory. Although antipsychotic medication remains a confounding factor for grey matter loss, studies in first-degree relatives and at-risk individuals show that cumulative antipsychotic intake can only explain some of these brain volume changes. This review highlights the need for further large studies that follow patients over a long period of time, to further clarify the relationship between brain volume change, antipsychotic intake and outcome. Indeed, the potential to attenuate brain volume changes could potentially improve long-term outcome, which again highlights the need for early intervention and effective treatment in this morbid disease.

The advent of ‘atypical’, or second generation antipsychotics, engendered a therapeutic optimism in the treatment of first-episode patients (NICE, 2002). Taylor et al. reviewed the effectiveness of antipsychotic medications in first episode schizophrenia and found traditional randomized controlled trials (RCTs), whilst being necessary, lacked generalizability to real-world clinical scenarios. A need for long-term observational studies to complement the RCTs was recognized, and several high-profile studies have now been published, often using discontinuation rate of antipsychotic medication as the primary outcome. The rationale behind this is that a...
medication will be discontinued if it is ineffective or its adverse effects are intolerable. Taylor et al. review these studies, and conclude that there is some broad agreement between the main effectiveness studies, but the optimism that came with these newer agents has waned somewhat due to a lack of clear superiority over the older ‘typical’ antipsychotics, as well as increasing recognition of their own significant side effect profiles. However, it is also recognized that atypical antipsychotics do represent an incremental advance for patients with first-episode schizophrenia (Salimi et al., 2009), especially in the area of neurological side effects, despite metabolic concerns that are associated with many of the atypical agents, and with the limited benefits they have in ameliorating cognitive and negative symptoms.

The initial episode of psychosis can be confusing and traumatic to the patient and their family, and lack of understanding can lead to delays in treatment. In addition to this, increased sensitivity to side effects from antipsychotics can leave the patient with a sense of hopelessness when faced with a lifetime trade-off between disabling psychotic symptoms and distressing side effects. Hyperprolactinaemia is a common side effect associated with antipsychotic medication, and Cookson et al. expertly review existing evidence regarding drug-induced hyperprolactinaemia, specifically in first-episode patients. While raised prolactin levels occur in 40–50% of these patients, levels high enough to cause adverse effects are less common. It was found that markedly raised levels tend to occur after the chronic use of antipsychotics, in particular amisulpride, sulpiride and risperidone. Side effects associated with hyperprolactinaemia can be particularly distressing, and include galactorrhoea, gynaecomastia, menstrual abnormalities and sexual dysfunction. Despite being uncommon they are often cited as reasons for stopping medication. It is possible that these sexual side effects are a particular problem for young first-episode patients, influencing medication adherence and hence long-term outcome. Osteoporosis and pathological fracture are also associated with chronic hyperprolactinaemia, and bones do not reach maximum density until the mid-twenties, so it is possible that younger patients are more sensitive to these adverse effects.

Haddad et al. consider the problem of extrapyramidal symptoms (EPS) in early psychosis and their relationship to antipsychotic treatment. There are four specific EPS syndromes: Parkinsonism, which presents within weeks of treatment; acute dystonia and akathisia, which can present within days; and tardive dyskinesia, which can take years to develop and is potentially irreversible. Haddad et al. found that patients seem to be more susceptible to developing acute dystonia and Parkinsonism at the beginning of antipsychotic therapy, than after long-term medication. EPS have various negative impacts on patients including increased physical morbidity, stigma and reduced quality of life. It is therefore important to consider such effects when prescribing antipsychotic medication and to take into account the risk of adverse effects and a patient’s prior response to medication. The risk can be reduced if the antipsychotics are started at a low dose and increased slowly. If a patient develops EPS the dose should be decreased or, if possible, stopped completely. If this is not possible, the concurrent use of anticholinergics for acute dystonia and Parkinsonism, and benzodiazepines or propranolol for akathisia, should be considered. Haddad et al. recommend routinely screening for EPS for early detection and effective treatment.

It is worth noting that in addition to addressing the symptoms of the disease, attention must be paid to alleviating the personal, social and economic burden of psychosis on affected individuals, their families and the community. As such, treatment of the first episode requires a comprehensive biopsychosocial approach and a range of specialist treatments aimed at treating not only the person’s primary psychotic symptoms, but also assisting them in overcoming the secondary personal and social difficulties which accompany the disease. Beary et al. point out important risk factors for premature mortality in schizophrenia, and recommend evidence-based preventative measures to reduce mortality risk in schizophrenia. They reviewed medical risk factors for those with schizophrenia and the general population, and found the risk factors in the general population are the same for those with schizophrenia, namely: low fitness levels, smoking, hypertension, diabetes and poor diet. However, some risk factors, including suicide, low birth weight, damaged telomeres and abnormal platelet function, are not so prominent in the general population. Beary et al. also found that a lack of access to health services and prejudice contributed to increased mortality in schizophrenia. The authors propose simple lifestyle and health improvements, such as reducing alcohol intake, smoking cessation, and regular exercise, that can increase life expectancy by up to 14 years. Beary et al. do, however, note a complex relationship between body mass index (BMI) and suicide, as much, but not all, the evidence suggests an inverse relationship between BMI and risk of completing suicide. Beary et al. also recommend regular screening for diabetes, lipid abnormalities and hypertension in order that early intervention here can facilitate effective treatment.

Early intervention in first-episode schizophrenia not only aims to reduce the severity of the initial psychosis and minimize the consequences of untreated psychosis, but also endeavours to establish a therapeutic rapport between patient and health care professional to facilitate effective treatment and engender patient confidence in the health system. It is a strategy that can provide considerable long-term benefits, both in terms of treatment of the psychosis and also in reducing mortality caused by non-psychiatric risk factors. This supplement also highlights the need for the clinician to be acutely aware of the adverse effects of medication and the potentially important effect that they can have on patient adherence and consequently on outcome. Early intervention and its success at a stage when the disease is arguably at its most aggressive, and the patient at their most sensitive or vulnerable, can set the mould for the future care of schizophrenia.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest
The authors declare that they have no conflict of interest.
References


