Dangerous liaisons: The relationship between schizophrenia and diabetes

Danny D Meetoo

Citation: Meetoo DD (2013) Dangerous liaisons: The relationship between schizophrenia and diabetes. *Journal of Diabetes Nursing* **17**: 104–11

Article points

1. Studies suggest that prevalence of type 2 diabetes in people with schizophrenia is 2–4 times greater than that of the general population.
2. Various explanatory models exist to explain the comorbidity of schizophrenia and diabetes. These include environmental, genetic, neuro-endocrine and iatrogenic effects.
3. Healthcare professionals need to be aware of this association and interdisciplinary collaboration is required to ensure that people with serious mental illness are treated successfully.

Key words

- Antipsychotic medication
- Schizophrenia

Authors

Danny Meetoo, Lecturer in Multi-Professional Post-Graduate Studies, School of Nursing, Midwifery & Social Work, University of Salford.

The prevalence of type 2 diabetes is rising at an alarming rate and the principal driver for this is obesity, combined with comorbidities including schizophrenia (SZ) and other severe mental illness (SMI). While diabetes self-care is considered to be one of the most psychologically demanding of the chronic conditions, often it is compounded by its association with SMI. The relationship between diabetes and SMI, in particular SZ, is well recognised with epidemiological studies showing that type 2 diabetes in people with SZ is 2–4 times greater than in the general population. It is important for healthcare professionals to be aware of the complex relationship between the two conditions and adapt the system of care accordingly. Interdisciplinary collaboration is imperative if people with SMI are to be treated successfully.

There perhaps ought to be a universal law of nature whereby a person with one chronic condition cannot have another. Unfortunately, this is not always the case, as with the comorbidity of diabetes and schizophrenia (SZ). This dual diagnosis compounds an individual's quality of life and often leads to other conditions such as depression. The aim of this article is to discuss the co-existence of diabetes and SZ and other severe mental illness (SMI), and highlight the importance of interdisciplinary collaboration to ensure the care outcome is successful.

Diabetes: The magnitude of the problem

The prevalence of diabetes has reached epidemic levels, with a devastating human, social and economic impact. Recent figures from the International Diabetes Federation (International Diabetes Federation, 2009) project that the number of people with diabetes worldwide will rise from 366 million in 2011 to 380 million in 2025 and then 552 million in 2030. The overall worldwide estimate does not account for the 183 million people who are unaware that they have diabetes. The global prevalence of this condition has reached a 5% increase, with type 2 diabetes accounting for 90–95% of all cases (Diabetes UK, 2012). A recent UK study showed that the number of people with diabetes has risen from 1.8 million in 2004 to the current 2.9 million with a further 1 million people remaining undiagnosed with type 2 diabetes (Diabetes UK, 2012).

The condition has potential to lead to serious complications such as cardiovascular disease, blindness, renal failure and amputation (Massi-Bennedetti and CODE-2 Advisory Board, 2002). The life expectancy of people with type 2 diabetes may be shortened by as much as 15 years, with up to 75% of people dying of cardiovascular diseases (Davies et al, 2004).

Diabetes and severe mental illness

The observation that diabetes is more common among people with SMI than in the general

population is not new. As far back as 1879, the eminent Victorian psychiatrist Sir Henry Maudsley wrote in *The Pathology of Mind* that "diabetes is a disease which often shows itself in families in which insanity prevails" (Maudsley, 1879). Over a century later, after increasingly sophisticated research, these observations about the association between severe psychiatric disorders and diabetes still appear to hold true. More than 300 years ago, the association of depression with diabetes was also noted in the scientific literature when Thomas Willis, a British physician, observed that diabetes was the result of "sadness or long sorrow" (Willis, 1971).

Evidence of impaired glucose metabolism (Braceland et al, 1945; Kooy, 1919) and insulin resistance (Braceland et al, 1945) in psychiatric patients emerged in the first half of the 20th century, prior to the introduction of antipsychotic drugs, with reports of diabetes treatment beginning to emerge from the 1950s onwards (Thonnard-Newmann, 1968; Brambilla et al, 1976). Many of the early clinical and epidemiological studies are difficult to interpret today since their publications pre-date the time at which a distinction was established between type 1 and type 2 diabetes. The large variations in the criteria defining SZ in the general and hospitalised populations studied also make it difficult to draw any meaningful conclusions. Furthermore, in the last few decades, the treatment of SZ has evolved considerably and the biological criteria used to diagnose diabetes have been re-defined. Recent cross-sectional studies assessing the prevalence of SZ have established that this group of people are at increased risk of developing diabetes and that SZ should be considered to be an independent risk factor for the condition (Bushe and Holt, 2004).

Prevalence

Several studies assert that the prevalence of type 2 diabetes in individuals with SZ is 2–4 times greater than that in the general population (Mukherjee et al, 1996; Dixon et al, 2000; Lindenmayer et al, 2003; Subramaniam et al, 2003). The results of a French study of 3474 people diagnosed with SZ also indicate that the incidence of diabetes was 2–4-fold higher than in the general population (Casadebaig et al, 1997). Data gathered by the Schizophrenia Patient Outcome Research Team in the US demonstrated that the prevalence of diabetes was between 10.8% and 14.9% with increased prevalence in older people, females, African-Americans, and other non-White individuals (Dixon et al, 2000). In another study comprising 38 632 people with schizophrenia, Sernyak et al (2002) demonstrated a statistically significant association for diabetes in those receiving atypical neuroleptics (n=22 648) versus those receiving typical neuroleptics (n=15 984).

In a review study of 208 people with psychotic disorders receiving antipsychotic medications, Gupta et al (2003) reported a prevalence of 17% of diabetes while Subramaniam et al (2003) found that of 607 people with SZ who had never received antipsychotics, the prevalence of diabetes under the age of 60 was twice as high when compared with the general population. In a post-neuroleptic era study of 26 drug-naïve Caucasian subjects (15 men and 11 women) with SZ, 15.4% had impaired glucose tolerance as well as higher levels of plasma glucose, insulin, cortisol and less insulin sensitivity than the sex-matched healthy comparison subjects (Ryan et al, 2003).

In the UK, data from primary care records of people with SMI and learning disabilities (Disability Rights Commission, 2006) demonstrated that 41% of people diagnosed with diabetes and SZ are under the age of 55 compared with 30% of others, and that 19% of people with SZ and diabetes died prematurely compared with 9% of people with no SMI. These findings would suggest that as well as developing diabetes at a younger age than the general population, people with SMI also face a poor prognosis.

Diabetes self-care management

The complex daily management of diabetes depends on each individual's willingness to be an active and consistent participant (Connelly, 1993; Peterson and Hughes, 2002). Diabetes self-care involves lifestyle changes, which often means that adherence can be difficult (Glasgow et al, 2001). The lives of people with diabetes revolve around a temporal regularity in which insulin doses must be calculated and administered at precise times and daily oral anti-diabetes agents must be taken as recommended (Meetoo, 2004). Moreover, meals, exercise, rest and monitoring of blood glucose need to planned and

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1. The observation that there is an association between diabetes and severe mental illness dates back as far as 300 years ago.
2. Studies have shown that people with schizophrenia are far more likely to have diabetes than the general population, with one study showing a 2–4-fold increase in prevalence in people with schizophrenia.
3. Research also shows that people with severe mental illness are also more likely to develop diabetes at a younger age and are more likely to have a poor prognosis.

"The complexity of diabetes self-management can be more challenging for people with a comorbid severe mental illness."

performed to match those times when insulin levels tend to drop or peak. Often, there are instances when people with diabetes may experience many inter-personal (for example, poor communication with healthcare professionals), socio-cultural (for example, poor access to healthcare), and psycho-social (for example, depression, low self-efficacy and poor social support) challenges (Schultz et al, 2001; Telles-Zenteno and Cardiel, 2002).

The complexity of diabetes management can be more challenging for people with a comorbid SMI. For individuals with psychotic disorders, self-care requires the ability to understand the effects of diabetes and know when to seek medical support, to successfully perform self-care tasks, to modify treatment to manage adverse effects and to adopt healthy lifestyle practices (Getty et al, 1998). Diabetes self-care may be compromised in individuals with schizophrenia owing to poverty, poor access to healthcare and cognitive symptoms which prevent them from fully understanding the seriousness of the condition. People with SZ who do not participate in their diabetes self-care activities inevitably become vulnerable to numerous high-risk complications of poorly-controlled diabetes.

It is therefore suggested that the long-term prediction for diabetes outcome among people with SZ is poor. The relative risk of mortality associated with schizophrenia is 1.6–2.6 times higher than that of the general population (Newman and Bland, 1991; Brown et al, 2000), with cardiovascular disease being the leading cause of death (Osby et al, 2000). Furthermore, the average age of death is 61 years for individuals with SZ versus 76 years for the general population (Newman and Bland, 1991). Those diagnosed with SZ have a high prevalence rate of smoking which has been reported to be as high as 75% (McCredie and Scottish Schizophrenia Lifestyle Group, 2003). Finally, non-adherence to treatment regimen is common and estimated to be as high as 50% (Perkins, 2002).

Proposed explanatory models

The link between schizophrenia and diabetes is considered to be multi-factorial, including environmental, genetic, neuro-endocrine factors and iatrogenic effects.

Environmental model

Evidence suggests that poor lifestyle choices are an important factor in diabetes in individuals diagnosed with SZ. For example, it has been shown that leisure-based physical inactivity compounded by a diet high in fat and low in fibre results in obesity, which in turn increases the risk of diabetes (Dixon et al, 2000; Ryan and Thakore, 2002; Peet, 2004). Other evidence depicts that people with SZ have a higher waist-to-hip ratio than the general population, thus acting as an indicator of increased visceral fat deposition, obesity and risk of diabetes (Ryan and Thakore, 2002). Poverty and the low educational levels associated with SZ further adds to the risk of obesity and other medical sequelae (Dixon et al, 2000; Gary, 2007). Furthermore it has been estimated that 60–90% of people with schizophrenia are nicotine-dependent while 20–70% will abuse substances at some point (Ryan and Thakore, 2002).

Given the harsh conditions that people with SMI often face, one may wonder if stress, anxiety, safety issues, isolation, marginalisation and stigma of mental illness are omnipresent and help keep those with SMI in crises. Nonetheless, these established risk factors may explain the increased incidence of diabetes among people with SZ.

Genetic model

There is a consensus that genetic factors have a key role in the association between SZ and diabetes. Several studies have clearly demonstrated that 50% of people with SZ have a familial history of type 2 diabetes, compared with only 4.6% of healthy adult controls (Mukherjee et al, 1989; Cheta et al, 1990). The argument proposed by Mukherjee et al (1989) relates to the role of insulin in brain maturation, in that fetal alpha-melatonin stimulating hormone, thought to be a determinant of early fetal growth, has been found to be abnormally high in the infants of people with diabetes. They therefore hypothesise that a family history of diabetes could constitute an independent risk factor for SZ via, in the case of maternal diabetes, effects on brain development and its maturation. An alternative aetiological proposition for diabetes and SZ suggested by Andrews (1992) relates to the gestational zinc deficiency that might damage organs with high zinc requirements, such as the pancreas and hippocampus.

Neuro-endocrine model

Psychosocial stress has been included in most models of SZ, frequently as a precipitating factor for psychosis in vulnerable individuals (Ryan and Thakore, 2002; Corcoran et al, 2003). Several other studies have also reported dysregulation of the hypothalamic-pituitary-adrenal axis in individuals with SZ, with higher than normal levels of serum cortisol (Deroche et al, 1992; Walker and Diforio, 1997). Researchers have proposed a variety of pathways that may be involved in developing excess adiposity and diabetes and cortisol appears to be particularly essential. For example, elevated cortisol secretion decreases the circulating levels of leptin resulting in increased appetite, weight gain, excessive accumulation of visceral fat, insulin resistance and dyslipidaemia (Chrousos, 2000; Ryan and Thakore, 2002; Chiodini, 2007).

Iatrogenic factors

Although antipsychotics form the therapeutic foundation for psychotic disorders, primarily in the acute exacerbation of SZ and the prevention of its relapses, they nevertheless have also been known to contribute to a number of complications. For example, it has been estimated that antipsychotics, and in particular second-generation antipsychotics (see *Table 1*), contribute to the prevalence of obesity in an estimated 40–60% of people receiving medication (Dixon et al, 2000). The degree of weight gain reported has varied. During a 1-year period, 36% of patients treated on clozapine gained over 10% of their initial body weight and this continued for 30 weeks before a plateau effect was noticed (Hummer et al, 1995). Weight gain associated with risperidone and quetiapine appears to be related and is lower than with olanzapine and clozapine. Such an effect is negligible with ziprasidone (not licensed in the UK) and around 2 kg a year among those receiving aripiprazole. Among second-generation antipsychotic medication, weight gain is as follows: clozapine > olanzapine > risperidone = quetiapine > ziprasidone = aripiprazole (American Diabetes Association et al, 2004).

The mechanism of antipsychotic-induced weight gain has not been conclusively established. However, several neuro-transmitters have been implicated. For example, histamine receptor blockade has been proposed to be responsible for the conventional antipsychotic-induced weight gain (Wirshing et al, 1999). Olanzapine, which has the highest affinity for histamine receptors, has been found to be associated with high rates of weight gain. Conversely aripiprazole, associated with lower risks of weight gain, have lower affinities for histamine receptors.

Antipsychotics and metabolic syndrome

The metabolic syndrome (MetS) is a cluster of risk factors including hyperglycaemia, dyslipidaemia, hypertension, a pro-thrombotic state and central obesity predisposing to type 2 diabetes and cardiovascular disease and they are linked by insulin resistance (Reaven, 1988). Studies examining the development of metabolic syndrome in people receiving antipsychotic agents are limited. However, available evidence suggests that the prevalence of MetS is around 50%, or increased 2–3-fold among people with SMI (De Hert et al, 2006; Meyer, 2006). This rate of incidence could provide a possible explanation for the increased prevalence of diabetes and cardiovascular disease in SZ (Heiskanen et al, 2003). However, evidence suggests that not all features of MetS, such as hypertension, are necessarily increased in SZ (Lund et al, 2001).

The rationale for the increase in MetS is unclear and is likely to be multi-factorial (see *Figure 1*). Studies suggest that people with SZ are more likely to have a family history of diabetes than the general population (Mukherjee et al, 1989; Cheta

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1. Research has shown that people with schizophrenia have higher than normal levels of serum cortisol and this may be associated with weight gain.
2. Antipsychotics, particularly second-generation antipsychotics, have also been implicated as contributing to weight gain but a mechanism for this has not been established.

Table 1. First- and second-generation antipsychotics.

First-generation	Second-generation
Chlorpromazine	Clozapine
Promazine	Risperidone
Haloperidol	Olanzapine
Sulpiride	Quetiapine
Pimozide	Aripiprazole
Trifluoperazine	Amisulpride

"While a person with psychosis may not be able to change their lifestyle or adhere to complex drug regimens, this should not be used a basis to deny them effective therapy because of concerns of future metabolic side effects."

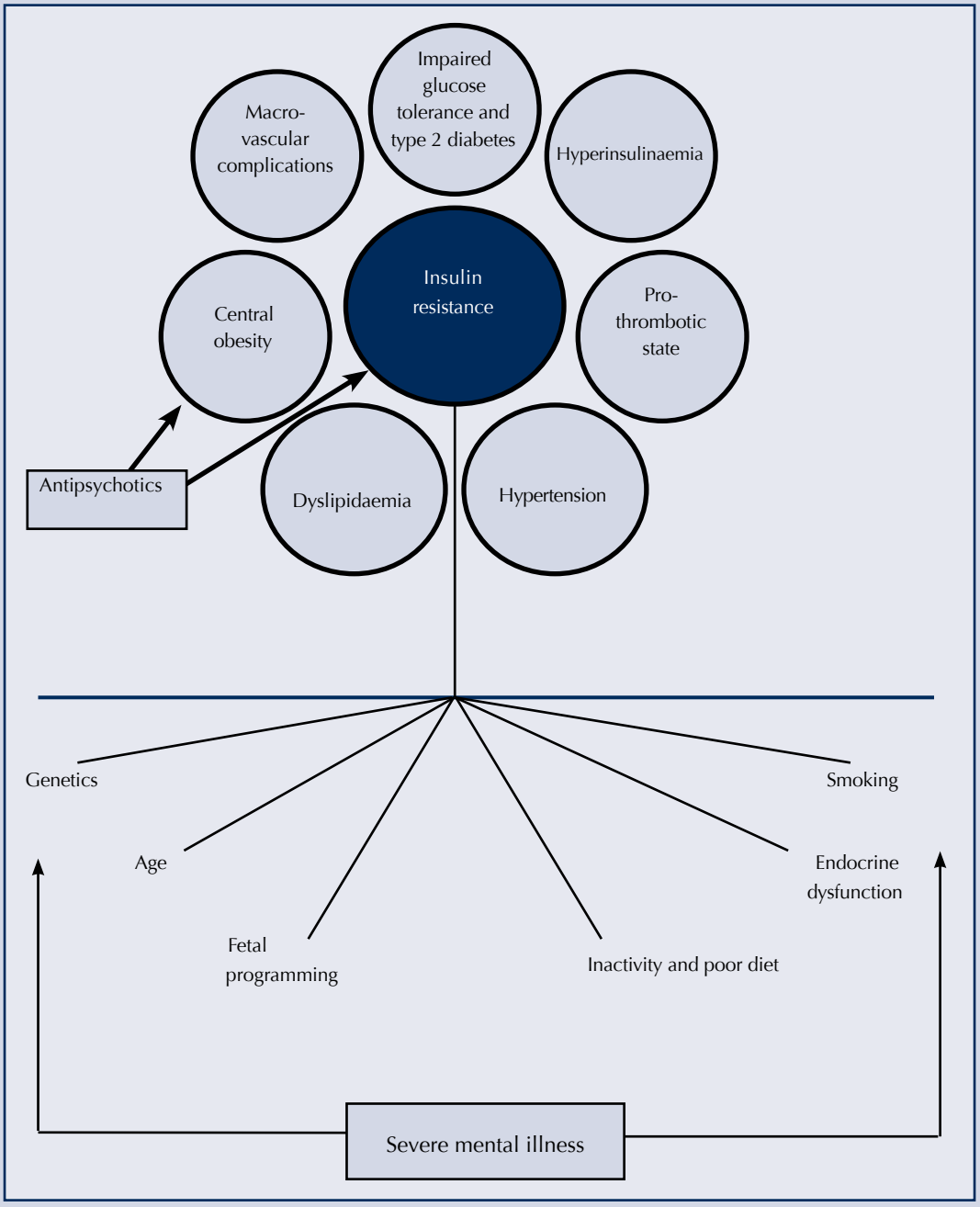

Figure 1. A diagram to show metabolic syndrome and its interaction with severe mental illness and antipsychotic drugs. Reproduced, with permission, from Holt (2006).

et al, 1990). Furthermore, it has been shown that low birth weight, which predisposes to the development of MetS, is more prevalent in those with SZ (Susser and Lin, 1992). People with SMI tend to be more physically inactive and they eat diets that are rich in saturated fats and refined sugars and, as such, their lifestyle may increase their risk of MetS (Brown et al, 1999). SZ may itself predispose to MetS as people with this diagnosis show signs of increased stress as manifested by hypercortisolaemia, which is a known risk factor for MetS (Ryan and Thakore, 2002). Therefore, the need to screen for diabetes among those individuals diagnosed with SMI irrespective of their treatment has been recommended (Citrome and Yeomans, 2005).

Clinical implications

Good management of diabetes and its related complications in people with SZ and other SMIs is vital in order to reduce the burden of physical illness. This entails the prompt identification of individuals at risk and appropriate management of risk factors (Sowell et al, 2003). Evidence suggests that there is little systematic physical health monitoring of people with SMI. For example, a survey by Rethink (2009) found that only 52% of 942 people with SMI were offered an annual medical check by their GPs.

In an audit by Taylor et al (2000), only 41% of people had received screening for diabetes while screening for dyslipidaemia occurred rarely. Consequently, assessment of cardiovascular risk has been recommended and it is suggested that high-risk individuals be treated as the rest of the population since SMI is not a contraindication to primary cardiovascular disease prevention. Similarly, there is a need to screen for diabetes as this is frequently undiagnosed in people with SMI (Schizophrenia and Diabetes 2003, 2004). Screening for diabetes with fasting blood glucose is likely to pose a clinical challenge as it is unlikely that people with SMI will fast prior to the test. However, a reasonable alternative could be a random blood glucose test (Holt et al, 2005) although the recent recommendation by the World Health Organization to use HbA_{1c} as a diagnostic criterion may improve the rate of diabetes screening.

The poor quality of care observed in this population probably relates to patient characteristics, clinician behaviour and the system in which this care occurs. People with SMI are less likely than those without mental illness to seek care and adhere to prescribed treatments (Brown et al, 2000). Primary care clinicians may be uncomfortable or lack necessary skills to treat patients with SMI (Lester al, 2005). Psychiatrists may not believe physical health is their responsibility or may not feel knowledgeable about physical medicine (Newcomer et al, 2004). Time constraints and competing demands perceived by physicians may limit willingness and ability to expand scope of practice (Grumbach and Bodenheimer, 2002). Those with SMI may be less able than others to communicate symptoms, and physicians may question the veracity of complaints (Goff, 2007).

Role of the nurse

Nurses have a key role to play in encouraging healthy lifestyles in people with SMI. In fact, recent studies (Alvarez-Jimenez et al, 2008; Holt et al, 2010) have challenged the belief that promoting healthy lifestyle choices is difficult, if not impossible, among individuals diagnosed with SMI. The Cromwell House Clinic, pioneered by Pendlebury in 2010, represents a unique example of how changes in lifestyle choices can be successfully achieved (Holt et al, 2010). There should also be an awareness that although some people with SMI may never have received basic health education, they can still be motivated by nurses to stop smoking, eat healthily and take part in leisure-based physical activities.

While antipsychotic drugs may have adverse effects on features of MetS, these side effects should be balanced against the benefits of treating the person's mental state. A person with psychosis may not be able to change their lifestyle or adhere to complex drug regimens but this should not be used a basis to deny them effective therapy because of concerns of future metabolic side effects. While nurses at the frontline of care can recognise, assess and screen many of the problems presented by individuals with SZ and other SMI, it is suggested that a unified effort at the clinical level through explicit recognition of the problem and interdisciplinary collaboration is imperative if the care outcome is to be successful. For example, in a survey of 168 mental health nurses working in the inpatient and community setting, 71% reported that physical care impacted on their weekly workload, while 30% reported that such an impact occurred on a daily basis (Nash, 2005), therefore indicating training needs in the realm of physical health to fulfil their role.

To this end, psychiatrists and primary care physicians as well as discipline-specific nurses need to function collaboratively to promote and evaluate effective interdisciplinary education, support and models of care for this population.

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1. Good management of diabetes and its related complications is vital in people with severe mental illness in order to reduce the burden of physical illness.
2. Nurses have a key role to play in this management, in particular by encouraging healthy lifestyle choices.
3. Interdisciplinary collaboration is imperative if the care outcome of people with severe mental illness is to be successful.

"The management of the physical consequences of schizophrenia and other severe mental illness is challenging and requires a multidisciplinary approach involving both physical and mental health services."

Conclusion

A Department of Health (DH) publication, *Making a Difference* (2001) states:

> *"Nurses, midwives and health visitors must play a full role in developing and implementing national service frameworks and clinical governance."*

For those working in the discipline of mental health, this would imply the need to extend the scope of practice in order to provide effective diabetes care.

The incorporation of such practices is evident in the National Service Framework for Diabetes (Department of Health, 2001) and in the NICE (2008) guidelines. Improving the physical well-being of people with SZ and other forms of SMI has also been echoed by the Chief Nursing Officer (DH, 2006) and further stressed in objective 3 of the recent document from HM Government (2011) which states that:

> *"More people with mental health problems will have good physical health [and] fewer people with mental health problems will die prematurely, and more people with physical ill health will have better mental health."*

The management of the physical consequences of SZ and other SMI is challenging and requires a multidisciplinary approach involving both physical and mental health services. Although this effort may not redress larger system failures and policy shortcomings, it is a starting point within reach of practitioners and it has the potential to benefit those that we are failing to serve with current care models. Only by working together will the burden of physical illness be reduced in those with SMI. ■

Acknowledgements

The author would like to acknowledge his heartfelt gratitude to Angie Chadwick, Lecturer in Mental Health, for her invaluable advice on the first draft of this article.

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"Only by working together, will the burden of physical illness be reduced in those with severe mental illness."