

Physical illness in patients with severe mental disorders.

I. Prevalence, impact of medications and disparities in health care

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The lifespan of people with severe mental illness (SMI) is shorter compared to the general population. This excess mortality is mainly due to physical illness. We report prevalence rates of different physical illnesses as well as important individual lifestyle choices, side effects of psychotropic treatment and disparities in health care access, utilization and provision that contribute to these poor physical health outcomes. We searched MEDLINE (1966 – August 2010) combining the MeSH terms of schizophrenia, bipolar disorder and major depressive disorder with the different MeSH terms of general physical disease categories to select pertinent reviews and additional relevant studies through cross-referencing to identify prevalence figures and factors contributing to the excess morbidity and mortality rates. Nutritional and metabolic diseases, cardiovascular diseases, viral diseases, respiratory tract diseases, musculoskeletal diseases, sexual dysfunction, pregnancy complications, stomatognathic diseases, and possibly obesity-related cancers are, compared to the general population, more prevalent among people with SMI. It seems that lifestyle as well as treatment specific factors account for much of the increased risk for most of these physical diseases. Moreover, there is sufficient evidence that people with SMI are less likely to receive standard levels of care for most of these diseases. Lifestyle factors, relatively easy to measure, are barely considered for screening; baseline testing of numerous important physical parameters is insufficiently performed. Besides modifiable lifestyle factors and side effects of psychotropic medications, access to and quality of health care remains to be improved for individuals with SMI.

Key words: Physical illness, severe mental illness, bipolar disorder, depression, schizophrenia, psychotropic medication, health disparities

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A number of reviews and studies have shown that people with severe mental illness (SMI), including schizophrenia, bipolar disorder, schizoaffective disorder and major depressive disorder, have an excess mortality, being two or three times as high as that in the general population (1-21). This mortality gap, which translates to a 13-30 year shortened life expectancy in SMI patients (4,5,22-27), has widened in recent decades (11,28-30), even in countries where the quality of the health care system is generally acknowledged to be good (11). About 60% of this excess mortality is due to physical illness (27,31).

Individuals with SMI are prone to many different physical health problems (Table 1). While these diseases are also prevalent in the general population, their impact on individuals with SMI is significantly greater (31,32).

Although many factors contribute to the poor physical health of people with SMI (33), the increased morbidity and mortality seen in this population are largely due to a higher prevalence of modifiable risk factors, many of which are related to individual lifestyle choices (31). However, this is not the whole story. It seems that the somatic well being of people with a (severe) mental illness has been neglected for decades (15), and still is today (7,34-39,40,41). There is increasing evidence that disparities not only in health care

access and utilization, but also in health care provision contribute to these poor physical health outcomes (33-39). A confluence of patient, provider, and system factors has created a situation in which access to and quality of health care is problematic for individuals with SMI (31). This is not totally surprising as we are today in a situation in which the gaps, within and between countries, in access to care are greater than at any time in recent history (42). Therefore, this growing problem of medical comorbidities and premature death in people with SMI needs an urgent call to action.

This paper highlights the prevalence of physical health problems in individuals with SMI. Furthermore, contributing factors are considered that impact on the physical health of these people, such as psychotropic medications (antipsychotics, antidepressants and mood stabilizers), individual lifestyle choices (e.g., smoking, diet, exercise), psychiatric symptoms, as well as disparities in the health care. This is a selective, rather than a systematic review of clinical data on physical health problems in people with SMI, as we did not include all physical diseases. We searched MEDLINE (1966 – August 2010) for epidemiological, morbidity and mortality data on the association between physical illnesses and schizophrenia, bipolar disorder and major depressive disorder. We com-

bined the MeSH terms of these psychiatric disorders with the different MeSH terms of major general physical disease categories. We included pertinent reviews to identify prevalence figures and factors contributing to the excess morbidity and mortality rates. Reference lists of reviews were searched for additional relevant studies. Moreover, if necessary to obtain more specific information, for some of the general physical disease categories (e.g., respiratory diseases), we also used specific physical illnesses as a search term.

PHYSICAL DISEASES LINKED TO SMI AND/OR PSYCHOTROPIC TREATMENT

Obesity

Obesity is becoming a significant and growing health crisis, affecting both developed and developing countries (43,44). People with obesity have shorter life spans and are at increased risk for a number of general medical conditions, including type 2 diabetes mellitus, DM (relative risk, RR >3), cardiovascular disease, CVD (RR >2-3), dyslipidemia (RR >3), hypertension (RR >2-3), respiratory difficulties (RR >3), reproductive hormone abnormalities (RR >1-2) and certain cancers (e.g., colon) (RR >1-2) (22,45-49,50).

Several methods are available to assess overweight and obesity. Body mass index (BMI) is a direct calculation based on height and weight (kg/m²). A BMI ≥25 kg/m² corresponds to overweight, a BMI ≥30 kg/m² to obesity (31). BMIs ≥30kg/m² are known to shorten life expectancy (48,51). However, based on evidence for higher morbidity and mortality risk at BMIs below 30 Kg/m² in Asian popu-

lations, the threshold for the definition of overweight in these populations is modified to a BMI ≥23 Kg/m² and the threshold for obesity to a BMI ≥25 Kg/m². Waist circumference (WC), measuring abdominal or central adiposity, is emerging as a potentially more valid and reliable predictor of risk for CVD, type 2 DM, and other metabolic risk-related conditions, compared with BMI (31). Accumulating evidence argues that lower cutoff points for WC should be used for Asians, as this population is prone to obesity-related morbidity and mortality at shorter WCs (52-56). The International Diabetes Federation (IDF) provides sex-and race-specific criteria in defining WC to identify people with central obesity, thus adjusting this criterion to make it also useful in non-Caucasian populations (Table 2). However, long-term prospective studies are still required to identify more reliable WC cut points for different ethnic groups, particularly for women (57).

Obesity in SMI patients

SMI and obesity overlap to a clinically significant extent (45). Increasing evidence suggests that persons with SMI are, compared to the general population, at increased risk for overweight (i.e., BMI =25-29.9, unless Asian: BMI =23-24.9), obesity (i.e., BMI ≥30, unless Asian: BMI ≥25) and abdominal obesity (see Table 2) (63-75), even in early illness phase and/or without medication (76-78). The risk of obesity in persons with SMI, however, varies by diagnosis. People with schizophrenia have a 2.8 to 3.5 increased likelihood of being obese (79). Several Canadian and US studies reported rates of obesity (BMI ≥30) in patients with schizophrenia of 42-60% (63,79,80). On the other hand, those with major depres-

Table 1 Physical diseases with increased frequency in severe mental illness (from 15)

Disease category	Physical diseases with increased frequency
Bacterial infections and mycoses	Tuberculosis (+)
Viral diseases	HIV (++) , hepatitis B/C (+)
Neoplasms	Obesity-related cancer (+)
Musculoskeletal diseases	Osteoporosis/decreased bone mineral density (+)
Stomatognathic diseases	Poor dental status (+)
Respiratory tract diseases	Impaired lung function (+)
Urological and male genital diseases	Sexual dysfunction (+)
Female genital diseases and pregnancy complications	Obstetric complications (++)
Cardiovascular diseases	Stroke, myocardial infarction, hypertension, other cardiac and vascular diseases (++)
Nutritional and metabolic diseases	Obesity (++) , diabetes mellitus (+), metabolic syndrome (++) , hyperlipidemia (++)

(++) very good evidence for increased risk, (+) good evidence for increased risk

Table 2 Ethnicity-specific cutoff values of waist circumference indicating abdominal obesity (see 57-62)

	European, sub-Saharan Africans, Mediterranean and Middle Eastern populations	South Asians, Chinese, and ethnic South and Central Americans	Japanese	Northern Americans
Men	≥94 cm	≥90 cm	≥90 cm	≥102 cm
Women	≥80 cm	≥80 cm	≥82-85 cm	≥88 cm

sion or bipolar disorder have a 1.2 to 1.5 increased likelihood of being obese (BMI ≥ 30) (44,69,70,81,82). Clinical research has suggested that up to 68% of treatment-seeking bipolar disorder patients are overweight or obese (83). One study found an obesity rate (BMI ≥ 30) of 57.8% among those with severe depression (84).

In patients with SMI, as in the general population, obesity is associated with lifestyle factors (e.g., lack of exercise, poor diet), but also with illness-related (negative, disorganized and depressive symptoms) and treatment-related factors, including weight liability of certain psychotropic agents. Adverse effects, such as sedation, should also be considered as potential contributors to weight gain in addition to, still not fully elucidated, medication induced effects on appetite and food intake (45,73,50,85-87).

Obesity and psychotropics

Weight gain during acute and maintenance treatment of patients with schizophrenia is a well established side effect of antipsychotics (AP), affecting between 15 and 72% of patients (26,50,77,88-98). There is growing evidence for similar effects in patients with bipolar disorder (65,83,99). There is a hierarchy for risk of weight gain with AP that has been confirmed in different studies and meta-analyses (88,92,100-106). Weight gain is greatest with clozapine and olanzapine (107,108), while quetiapine and risperidone have an intermediate risk. Aripiprazole, asenapine, amisulpride and ziprasidone have little effect on weight. A recent systematic review of randomized, placebo controlled trials of novel AP in children and

adolescents (<18 years old) identified the same hierarchy for risk of weight gain for this vulnerable population (109). Among the conventional AP, so-called low-potency agents, such as chlorpromazine and thioridazine, have a higher risk than high-potency drugs, such as haloperidol (110-112). No agent, however, should be considered as truly weight-neutral, as the proportion of individuals experiencing $\geq 7\%$ weight gain is greater with any atypical AP than with placebo (92), and all AP have been found to cause significant weight gain in AP-naïve or first-episode patients (113-115). Even amisulpride, ziprasidone and low-dose haloperidol demonstrated notable weight gain of 9.7 kg, 4.8 kg and 6.3 kg respectively at endpoint in a 12-month trial of AP in first-episode patients (102). Equally, antidepressants (AD) such as paroxetine (116), and mood stabilizers, such as lithium and valproate (117-119), have been associated with weight gain (Table 3).

The high interindividual variability in medication-induced weight gain suggests that genetic factors influence the risk to gain weight (50,122). Studies of genetic predictors of weight gain under AP therapy have mainly but not exclusively (131) focused on HTR2C (132-135) and LEPR (135,136) gene polymorphisms. Although the results are promising, the role of genetic factors in predicting this severe side effect remains an option for the future.

Metabolic syndrome

Obesity is also associated with the metabolic syndrome (MetS), a clustering of abnormalities that confers a 5-6-fold

Table 3 Weight gain liability of psychotropic agents used in SMI (see 45,63-65,87,95,99,104,120,121-130)

Drug class	Weight loss	Relatively weight neutral	Weight gain
Antidepressants	Bupropion Fluoxetine	Citalopram	<i>Substantial</i>
		Duloxetine	Amitriptyline
		Escitalopram	Imipramine
		Nefazodone	Mirtazapine
		Sertraline	
		Venlafaxine	<i>Intermediate</i>
			Nortriptyline Paroxetine
Anticonvulsants/ Mood stabilizers	Topiramate Zonisamide	Lamotrigine	<i>Substantial</i>
		Oxcarbazepine	Lithium Valproate
			<i>Intermediate</i> Carbamazepine Gabapentin
Antipsychotics	Aripiprazole (in pre-treated individuals) Molindone (in pre-treated individuals) Ziprasidone (in pre-treated individuals)	Amisulpride	<i>Substantial</i>
		Aripiprazole	Chlorpromazine
		Asenapine	Clozapine
		Fluphenazine	Olanzapine
		Haloperidol	
		Lurasidone	<i>Intermediate</i>
		Perphenazine	Iloperidone
		Ziprasidone	Quetiapine
			Risperidone
			Thioridazine Zotepine

increased risk of developing type 2 DM and a 3-6 fold increased risk of mortality due to coronary heart disease (137-144).

There is also evidence supporting the hypothesis that the MetS or components of the MetS may be important etiologic factors for certain cancers (e.g., colon cancer) (145,146).

Although some controversy exists whether the MetS is a true syndrome (57,147-149), and despite differences in specific criteria among the definitions (Table 4), there is agreement that the major characteristics of the syndrome include central obesity, hypertension, dyslipidemia, glucose intolerance or insulin resistance (45,137,150). Studies show large variations in prevalence estimates of the MetS across definitions, countries or regions, gender, ethnicity, and age groups (137). Countries in North and South America (151-154) reported a relatively higher prevalence than other countries or regions in the world (137).

MetS in SMI patients

The MetS is highly prevalent among treated patients with schizophrenia. Depending on used MetS criteria, gender, ethnicity, country, age groups and AP treatment, percentages vary considerably (between 19.4% and 68%) (155-167). However, there is little debate that people with schizophrenia exhibit a higher MetS prevalence than their peers in the general population across the world (168). MetS rates in patients with bipolar disorder and schizoaffective disorder have been reported to be 22-30% (143,169,170) and 42% (171), respectively.

Table 5 summarizes the potential of various AP medication to cause or exacerbate the metabolic syndrome. Nevertheless, lifestyle and behavioral patterns (smoking, physical inactivity, dietary habits) also play important roles in the prevalence of the MetS in SMI populations (118,168,176).

Disparities in health care

The proportion of SMI patients not receiving tests for assessing metabolic risk factors, even for factors relatively simple and easy to measure, such as obesity and blood pressure, is high (141,177-181). At present, neither psychiatrists nor primary care physicians carefully screen or monitor patients receiving AP medication for metabolic risk factors (173). Even after FDA (Food and Drug Administration) and ADA (American Diabetes Association)/APA (American Psychiatric Association) recommendations for novel AP, the frequency of baseline glucose and lipid testing showed little change. Several large-scale pharmacoepidemiologic studies of individuals initiating a novel AP (with non-psychiatric large control groups) reported low mean baseline metabolic testing rates, varying between 8% and less than 30% (181-183) and follow-up assessments done in only 8.8% of patients. Likewise, most children starting treatment with novel

AP do not receive recommended glucose and lipid screening. In a related study in children receiving AP treatment, similarly low metabolic monitoring rates were found (184). The MetS remains, thus, widely underdiagnosed and undertreated among patients with SMI.

Diabetes mellitus

Three to four percent of the world's population have DM, which leads to a markedly increased risk of blindness, renal failure, amputation and cardiovascular disease, and reduces life expectancy by 10 or more years. Currently, 70% of people with DM live in developing countries, and while DM is increasing across the world, its greatest increase will be in these countries. By 2030 more than 80% of people with DM will live in developing countries (195).

There are well-defined biological and behavioral risk factors for type 2 DM (195). The most important of these are overweight and obesity (RR: 4.10-17.5)(196), particularly abdominal obesity, and physical inactivity (RR: 1.12-2.18) (196-205). Other behavioral risk factors include certain dietary patterns (over and above any effect on obesity), such as diets low in whole grains and other sources of fibre, as well as smoking (206).

Identifying people at high risk of DM is important because it has been demonstrated that intensive interventions in this group can reduce the incidence of DM. In individuals at high risk, a combination of moderate weight loss, increased physical activity and dietary advice can lead to a 60% reduction in DM incidence (207,208).

DM in SMI patients

Evidence suggests that the prevalence of DM in people with schizophrenia as well as in people with bipolar disorder and schizoaffective disorder is 2-3 fold higher compared with the general population (103,209-216). The risk of DM in people with depression or depressive symptoms is 1.2-2.6 times higher compared to people without depression (217-225).

The reason for the increased risk of DM in SMI patients is multifactorial and includes genetic and lifestyle factors as well as disease and treatment specific effects. An increase in well-established DM risk factors in these patients partially accounts for much of the increased risk (16,226). However, additional factors (disease, treatment) are important as well, and research suggests that, compared to the general population, the prevalence of DM in schizophrenia patients is 4 to 5 times higher in different age groups (15-25: 2% vs. 0.4%; 25-35: 3.2% vs. 0.9%; 35-45: 6.1% vs. 1.1%; 45-55: 12.7% vs. 2.4%; 44-65: 25% vs. 5.8%) (227).

Table 4 Working definitions of the MetS (see 57,185-194)

Criteria	WHO (1998,1999)	EGIR (1999)	NCEP ATP III (2001,2004)	AACE/ACE (2003)	IDF (2005)	IDF & AHA/NHLBI (2009)
Required factor	IGT, IFG or DM type 2, and/or insulin resistance	Insulin resistance or hyperinsulinemia	None	At least one of the specified risk factors (e.g., obesity, sedentary lifestyle, age>40)	Central obesity	None
	plus any 2 or more of the following	plus any 2 of the following	but any 3 or more of the following	plus 2 or more of the following	plus any 2 of the following	but any 3 or more of the following
Additional factors						
Obesity	Waist-to-hip ratio >0.90 (men) Waist-to-hip ratio >0.85 (women) and/or BMI>30 kg/m ²	WC≥94 cm (men) WC≥80 cm (women)	WC≥102 cm (men) WC≥88 cm (women)	BMI>25 kg/m ² or WC>102 cm (men) WC>89 cm (women) (10-15% lower for non-Caucasians)		Elevated WC and country-specific definitions as defined by the IDF and AHA/NHLBI until more data are available
Triglycerides	≥150 mg/dL (≥1.7 mmol/L) and/or	>177 mg/dL (>2.0 mmol/L)	≥150 mg/dL (≥1.7 mmol/L) or on elevated triglycerides Rx	>150 mg/dL	≥150 mg/dL (≥1.7 mmol/L) or on lipid abnormality Rx	≥150 mg/dL (≥1.7 mmol/L) (Rx for elevated triglycerides is an alternate indicator)
HDL - cholesterol	<35 mg/dL (<0.9 mmol/L) (men) <39 mg/dL (<1.0 mmol/L) (women)	<40 mg/dL (<1.0 mmol/L) (men and women) or on dyslipidemia Rx	<40 mg/dL (<1.03 mmol/L)(men) <50 mg/dL (<1.29 mmol/L) (women) or on reduced HDL-cholesterol Rx	<40 mg/dL (men) <50 mg/dL (women)	<40 mg/dL (<1.03 mmol/L) (men) <50 mg/dL (<1.29 mmol/L) (women) or on lipid abnormality Rx	<40 mg/dL (<1.0 mmol/L)(men) <50 mg/dL (<1.3 mmol/L)(women) (Rx for reduced HDL-cholesterol is an alternate indicator)
Blood pressure	≥160/90 mm Hg (later modified as ≥140/90 mm Hg)	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg or on hypertension Rx	>130/85 mm Hg	≥130/85 mm Hg or on antihypertensive Rx	≥130/85 mm Hg (antihypertensive Rx in a patient with a history of hypertension is an alternate indicator)
Glucose	IGT, IGF (≥110 mg/dL) (≥6.1 mmol/L), or DM type 2	IGT or IFG (≥110 mg/dL) (≥6.1 mmol/L) (but not DM)	≥110 mg/dL (≥6.1 mmol/L) (includes DM) (later modified as ≥100 mg/dL) (≥5.6 mmol/L) or on elevated glucose Rx	110-125 mg/dl	≥100 mg/dL (≥5.6 mmol/L) or previously diagnosed type 2 DM	≥100 mg/dL (≥5.6 mmol/L) (Rx of elevated glucose is an alternate indicator)
Other	Microalbuminuria (urinary albumin excretion rate ≥20 µg/min or albumin:creatinine ratio ≥20 mg/g) (later modified as ≥30 mg/g)					

WHO: World Health Organization; EGIR: European Group for the Study of Insulin Resistance; NCEP ATP III: National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); AACE/ACE: American Association of Clinical Endocrinologists/American College of Endocrinology; IDF: International Diabetes Federation; AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute; IGT: impaired glucose tolerance; IFG: impaired fasting glucose; DM: diabetes mellitus; BMI: body mass index; WC: waist circumference; Rx: treatment; HDL: high-density lipoprotein.

DM and psychotic medications

Atypical AP seem to have a stronger diabetogenic risk than conventional AP (96,228,229), the risk being 1.3 fold higher in people with schizophrenia taking atypical AP compared with those receiving conventional AP (230). However, the risk of DM-related adverse events differs between atypical

AP. Of the atypical AP, specifically olanzapine (231-234) and clozapine (232,234,235) and, to a lesser extent, quetiapine (236) and risperidone (237), are associated with an increased risk of DM (80) in people who have schizophrenia or bipolar disorder (238,239). A recent large-scale pharmacoepidemiologic study (including 345,937 patients who purchased antipsychotics and 1,426,488 unexposed individuals)

Table 5 Approximate relative likelihood of metabolic disturbances with AP medication (172-175)

Medication	MetS
Chlorpromazine	High (? , limited data)
Clozapine	High
Olanzapine	High
Quetiapine	Moderate
Amisulpride	Mild
Iloperidone	Mild (? , limited data)
Risperidone	Mild
Sertindole	Mild
Asenapine	Low (? , limited data)
Aripiprazole	Low
Haloperidol	Low
Lurasidone	Low (? , limited data)
Perphenazine	Low
Ziprasidone	Low

found low to moderate, but significantly increased rates of incident DM compared with the general population for clozapine (RR=1.45), olanzapine (RR=1.29) and risperidone (RR=1.23). Rates increased two or more times with ziprasidone and sertindole. Aripiprazole, amisulpride and quetiapine did not have a significantly increased rate (240).

In the only study to date in first-episode patients, DM development was promoted in patients with schizophrenia by initial treatment with olanzapine (hazard ratio, HR=1.41) and mid-potency conventional AP (HR=1.60), as well as by current treatment with low-potency conventional AP (odds ratio, OR=1.52), olanzapine (OR= 1.44) and clozapine (OR=1.67). Current aripiprazole treatment reduced DM risk (OR= 0.51) (241). An analysis of the FDA's DM-related adverse events database (ranging from new-onset hyperglycemia to life-threatening ketoacidosis), found the following adjusted reporting ratios for DM relative to all drugs and events: olanzapine 9.6 (9.2-10.0); risperidone 3.8 (3.5-4.1); quetiapine 3.5 (3.2-3.9); clozapine 3.1 (2.9-3.3); ziprasidone 2.4 (2.0-2.9); aripiprazole 2.4 (1.9-2.9); haloperidol 2.0 (1.7-2.3) (242). However, a systematic review of 22 prospective, randomized, controlled trials found no difference in the incidence of glycaemic abnormalities between placebo cohorts and AP medication cohorts, as well as no significant difference between any of the AP medications studied in terms of their association with glycaemic abnormalities (243). Although the latter analysis was restricted to mostly short-term trials, this inconsistency of findings suggests that medication effects interact with patient, illness, cohort and study-specific factors.

AD may also increase the risk of DM, probably partly due to side effects such as sedation, increased appetite, and weight gain (244-248). However, although increasing, specific data on the risk of DM associated with the use of AD are sparse. Given the heterogeneity and small sample sizes of the few currently available studies, it is unclear whether or not specific AD themselves may increase the risk of DM. Nevertheless, it seems that an increased risk of DM is associated with the concurrent use of tricyclic AD and serotonin

reuptake inhibitors (SSRIs) (OR=1.89) (249), the long-term use of both tricyclic AD (incidence rate ratio, IRR=1.77) and SSRIs (IRR=2.06) in at least moderate daily doses (250), as well as the use of AD medication in high-risk patients (251).

Furthermore, although understudied, certain mood stabilizers, especially valproate, have been associated with an elevated risk for the development of insulin resistance (252,253), conferring a risk for DM, which is possibly related to weight gain (254), and/or fatty liver infiltration (255), but also to valproate itself (256).

Disparities in health care

There is evidence that diabetes patients with mental health conditions are less likely to receive standard levels of diabetes care (35,257,258). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study, non-treatment rate for DM was 45.3% (35). One study (n=76,799), examining the impact of mental illness on DM management, found the unadjusted OR to be 1.24 (1.22-1.27) for no hemoglobin A(1c) testing, 1.25 (1.23-1.28) for no low-density lipoprotein cholesterol testing, 1.05 (1.03-1.07) for no eye examination, 1.32 (1.30-1.35) for poor glycemic control, and 1.17 (1.15-1.20) for poor lipaemic control (257). Despite clear guidance and a high prevalence of undiagnosed DM, screening rates for metabolic abnormalities in people with SMI remain low, which may lead to prolonged periods of poor glycaemic control (259-263). Delayed diagnosis results in prolonged exposure to raised blood glucose levels, which can, among other things, cause visual impairment and blindness, damage to kidneys with the potential consequence of renal failure, and nerve damage (264).

Diabetic ketoacidosis

Although diabetic ketoacidosis (DKA), a potentially fatal condition related to infection, trauma, myocardial infarction or stroke (265), occurs most often in patients with type 1 DM, it may be the first obvious manifestation of type 2 DM. Symptoms include: increased thirst and urination, nausea and vomiting, abdominal pain, poor appetite, unintended weight loss, lethargy, confusion and coma.

The incidence of DKA is nearly (266) or more (267) than 10-fold greater in those with schizophrenia compared to the general population. Cases of DKA have been reported with the atypical AP clozapine (235,268), olanzapine (233,269), quetiapine (236), risperidone (237), aripiprazole (270-272) and ziprasidone (242). However, not all atypical AP appear to have the same propensity to cause this complication (273). The incidence of DKA for each atypical AP over a 7-year period was as follows: clozapine, 2.2%; olanzapine, 0.8%; and risperidone, 0.2% (267). However, higher incidence rates for clozapine and olanzapine can be due to reporting and detection biases (more DKA cases may be re-

ported for these agents since doctors in general are more careful about clozapine and olanzapine and therefore detect and report such cases with these agents more frequently). Within the class of conventional AP, cases of DKA have been reported with chlorpromazine (274,275), but no such cases have been reported for other conventional AP. The mortality of reported cases of DKA varies between 15.4% and 48% (233,235-237), which is up to ten times higher than the 4% rate in the general population (276).

Cardiovascular diseases

The term cardiovascular diseases (CVD) refers to any disease that affects the cardiovascular system. Coronary heart disease and cerebrovascular disease are the principal components of CVD and make the largest contribution to its global burden (277,278). CVD accounts for 17.1 million or 29% of total worldwide deaths (279). While there are downward trends in CVD mortality in most developed countries due to successful secondary prevention, the mortality rates in developing countries are rising (280). A staggering 82% of worldwide CVD deaths take place in developing countries (279). Global trade and food market globalization have led to a transition toward a diet that is energy dense and nutrient poor. The resultant increases in obesity are accompanied by physical inactivity. In addition, tobacco consumption is increasing at alarming rates in developing countries (281). Finally, people in developing countries have less access to effective and equitable health care services which respond to their needs (279).

The conventional risk factors for CVD are smoking, obesity, hypertension, raised blood cholesterol and DM. Many other factors increase the risk of CVD, including unhealthy diet, physical inactivity and low socioeconomic status (282, 283). Table 6 shows the summary prevalence of CVD risk factors in developed and developing countries, based on the World Health Organization (WHO) comparative risk factor survey data. The risk of late detection of CVD risk factors and consequent worse health outcomes is higher among people from low socioeconomic groups due to poor access

to health care. This gradient exists in both rich and poor countries (284,285).

CVD in SMI patients

The preponderance of evidence suggests that patients with major depression, bipolar disorder and schizophrenia are at significantly higher risk for cardiovascular morbidity and mortality than are their counterparts in the general population (2,9,11,23,28,29,287-295). Moreover, in SMI patients, CVD is the commonest cause of death (2,25,33, 218,289,290,296-300).

The prevalence of CVD in people with schizophrenia and bipolar disorder is approximately 2- to 3-fold increased, particularly in younger individuals (5,16,25,29,297,299,301,302). A recent review of all published larger (>100 patients) studies between 1959 and 2007 found the mortality risk for CVD to be 35% to 250% higher among persons with bipolar spectrum disorders compared to the general population (6). People with depression have a 50% greater risk of CVD (22). Besides the fact that depression is an independent risk factor for aggravating morbidity and mortality in coronary heart disease (303), the main factor mediating the link between depression and coronary events seems to be lack of physical activity (304).

The aetiology of this excess CVD is multifactorial and likely includes genetic and lifestyle factors as well as disease specific and treatment effects (16). People with SMI have significantly higher rates of several of the modifiable risk factors compared with controls. They are more likely to be overweight or obese, to have DM, hypertension, or dyslipidemia and to smoke (25,95,229,178,305-308). The excess CVD mortality associated with schizophrenia and bipolar disorder is widely attributed to the 1-5 fold RR of the modifiable CVD risk factors in this group of patients compared with the general population (Table 7).

Coronary heart disease in SMI patients

Coronary heart disease refers to the failure of coronary

Table 6 Economic development and risk factors for cardiovascular disease in WHO subregions (see 280,286)

	Poorest countries in Africa, America, South-East Asia, Middle East	Better-off countries in America, Europe, South-East Asia, Middle East, Western Pacific	Developed countries of Europe, North America, Western Pacific
Mean body mass index	19.9 - 26.0	22.9 - 26.0	23.4 - 26.9
Physical inactivity (% with no physical activity)	11 - 23	15 - 24	17 - 20
Low fruit and vegetable intake: average intake per day (grams)	240 - 360	190 - 350	290 - 450
Blood pressure (mean systolic pressure mmHg)	125 - 133	124 - 133	127 - 138
Mean cholesterol (mmol/L)	4.8 - 5.1	4.6 - 5.8	5.1 - 6.0

Table 7 Estimated prevalence and relative risk (RR) of modifiable risk factors for cardiovascular disease in schizophrenia and bipolar disorder compared to the general population (see 4,305,309)

Modifiable risk factors	Schizophrenia		Bipolar disorder	
	Prevalence (%)	RR	Prevalence (%)	RR
Obesity	45-55	1.5-2	21-49	1-2
Smoking	50-80	2-3	54-68	2-3
Diabetes mellitus	10-15	2-3	8-17	1.5-3
Hypertension	19-58	2-3	35-61	2-3
Dyslipidemia	25-69	≤5	23-38	≤5
Metabolic syndrome	37-63	2-3	30-49	2-3

circulation to supply adequate circulation to cardiac muscle and surrounding tissue, a phenomenon that can result in a myocardial infarction. During the 21st century, coronary heart disease will remain the leading cause of death in developed countries, will become the leading cause of death in developing countries, and therefore, will emerge as the leading cause of death in the world (25). The risk of coronary heart disease seems to be 2-3.6-fold higher in patients with schizophrenia (25,299). One large study found that the ten-year coronary heart disease risk was significantly elevated in male (9.4% vs. 7.0%) and female (6.3% vs. 4.2%) patients who have schizophrenia compared to controls ($p=0.0001$) (101). People with bipolar disorder have a 2.1 fold higher risk (299). The RR of myocardial infarction in people with major affective disorder was found to be 1.7 to 4.5 (310-313). Depression is an even stronger risk factor for cardiac events in patients with established coronary heart disease: prospective studies have shown that depression increases the risk of death or nonfatal cardiac events approximately 2.5-fold in patients with coronary heart disease (314).

Cerebrovascular disease in SMI patients

Cerebrovascular disease is a group of brain dysfunctions related to disease of the blood vessels supplying the brain, and can result in a cerebrovascular accident or stroke. The risk of cerebrovascular accident seems to be 1.5 to 2.9 fold higher in patients with schizophrenia (40,41,299,302,315, 316) and 2.1 to 3.3 fold higher in patients with bipolar disorder (299,317). The RR of developing cerebrovascular accident for patients with major affective disorder was found to be 1.22 to 2.6 (318,319). Obesity, DM, CVD as well as depressive symptoms are recognized as risk factors for cerebrovascular accident (317,320).

CVD and psychotropics

In addition to weight gain and obesity related mechanisms, there appears to be a direct effect of AP that contributes to the worsening of CVD risk (96,97,121,321). A recent publication demonstrated that atypical AP D₂ antagonism

could have a direct effect on the development of insulin resistance (322). Evidence was found that higher AP doses predicted greater risk of mortality from coronary heart disease and cerebrovascular accident (299).

Overall, SSRIs appear safe in cardiac populations, with few cardiac side effects (287,311), while studies have found an increased risk of adverse cardiac events in patients using tricyclic AD (311,323,324). Tricyclic AD commonly increase heart rate by over 10%, induce orthostatic hypotension, slow cardiac conduction, and increase the risk of arrhythmias. Although it can have some cardiac conduction effects, in general, lithium can be safely used in cardiac patients (287).

Sudden cardiac death and psychotropics

Patients with schizophrenia have been reported to be three times as likely to experience sudden cardiac death as individuals from the general population (325,326). In patients with AP monotherapy, a similar dose-related increased risk of sudden cardiac death was found for both conventional and atypical AP, with adjusted RRs of 1.31 vs. 1.59 (low dose, chlorpromazine equivalents <100mg), 2.01 vs. 2.13 (moderate dose, chlorpromazine equivalents 100-299mg) and 2.42 vs. 2.86 (high dose, chlorpromazine equivalents ≥300mg), respectively (327). In large epidemiological studies, a dose dependent increased risk of sudden cardiac death has been identified in current users of tricyclic AD (328).

There is a consensus that QTc values >500 msec, or an absolute increase of 60 msec compared with drug-free baseline, puts a patient at significant risk of torsade de pointes, ventricular fibrillation and sudden cardiac death (94,329, 330). Most AP and some AD may be associated with QTc prolongation (331). Patients using AP have higher rates of cardiac arrest or ventricular arrhythmias than controls, with ratios ranging from 1.7 to 5.3 (332-335). AP associated with a greater risk of QTc prolongation include pimozide, thioridazine and mesoridazine among the conventional AP (94,335,336) and sertindole and ziprasidone among the atypical AP (94,337). However, the largest randomized study to date ($n=18,154$) did not find a statistically significant difference in the risk of sudden cardiac death between ziprasidone and olanzapine treated patients with schizophrenia

(338,339). Similarly, another large randomized study (n=9,858) observed no significant differences between sertindole and risperidone recipients in cardiac events, including arrhythmias, requiring hospitalization. However, cardiac mortality in general was higher with sertindole (337). These large randomized studies, which focused on a low incidence serious side effect, suffer from the problem that they did not enrich samples for cardiac risk, so that they lack power and, possibly, generalizability. Cases of torsade de pointes have been reported with thioridazine, haloperidol, ziprasidone, olanzapine, and tricyclic AD. Although SSRIs have been associated with QTc prolongation, no cases of torsade de pointes have been reported with the use of these agents. There are no reported cases of lithium-induced torsade de pointes (328).

Disparities in health care

SMI patients have the highest CVD mortality but the least chance of receiving many specialized interventions or circulatory medications. Evidence suggests that people with schizophrenia are not being adequately screened and treated for dyslipidemia (up to 88% untreated) and hypertension (up to 62% untreated) (35,306,340-343). The care of these patients shows a significant deficit in the monitoring of cholesterol values and the prescription of statins (25,35,40,344). They also have low rates of surgical interventions, such as stenting and coronary artery bypass grafting (40,41,291, 297,345). A poorer quality of medical care contributes to excess mortality in older people with mental disorders after heart failure (346). Another important barrier is the lack of seeking medical care by SMI patients themselves, even during acute cardiovascular syndromes (25).

Viral diseases

Patients with SMI are at increased risk for a variety of chronic viral infections, of which the most serious are the diseases associated with human immunodeficiency virus (HIV) and hepatitis C virus.

HIV positivity

The prevalence of HIV positivity in people with SMI is generally higher than in the general population, but varies substantially (1.3-23.9%) (347-370). The high frequency of substance abuse, sexual risk behaviors (e.g., sex without a condom, trading sex for money and drugs), and a reduced knowledge about HIV-related issues contribute to this high HIV prevalence (364,371-376). Therefore, it is important that patients with SMI are tested for HIV (377). However, studies investigating HIV testing rates among individuals with a SMI indicate that fewer than half of these patients (percentages ranging from 17% to 47%) have been tested in the past year (378-394).

Since many patients with SMI are exposed to atypical AP, which have been associated with metabolic abnormalities, and since patients infected with HIV and on highly active antiretroviral therapy may also develop metabolic abnormalities, this group of patients is at particularly high risk for developing MetS and ultimately CVD (395).

Hepatitis

Across different continents, markedly elevated rates of hepatitis virus infection have been reported in persons with SMI compared to the general population (364,396-403). The largest study to date found prevalence rates of hepatitis B virus (23.4%) and hepatitis C virus (19.6%) in SMI patients to be approximately 5 and 11 times the overall estimated population rates for these infections. Overall, an estimated 20-25% of persons with SMI are infected with hepatitis C virus (360,404-407).

The most common transmission routes for persons with SMI are drug-use behaviors and sexual behaviors related to drug use (404-406). Therefore, especially patients with SMI and substance use disorders (including dependency) should have routine screening and treatment for hepatitis C virus infection to prevent associated morbidity and mortality (400,407,408). Interventions exist that are specifically designed to facilitate integrated infectious disease programming in mental health settings for people with SMI and to overcome provider- and consumer-level barriers at a modest and specified cost (409). A recent study showed that the assignment of people with SMI to the "STIRR" (Screening, Testing, Immunization, Risk reduction counseling, medical treatment Referral) intervention had high levels (over 80%) of participation and acceptance of core services (testing for hepatitis C, immunization against hepatitis, knowledge about hepatitis) (407).

Respiratory tract diseases

Up until 50 years ago, respiratory diseases, such as pneumonia and tuberculosis, accounted for the majority of deaths amongst people with SMI who lived in institutions (2). Today, respiratory diseases are still more prevalent in people with SMI (8,410-417).

Tuberculosis

Studies consistently show a higher incidence of tuberculosis among patients with schizophrenia compared with the general population (422-426). In some countries, tuberculosis still occurs so frequently that mental hospitals have special wards for people with both tuberculosis and schizophrenia (15). If untreated, up to 65% of people with active tuberculosis will die of the disease. However, chemotherapy is

effective and the vast majority of people with drug-susceptible forms of tuberculosis are cured if properly treated (427).

Pneumonia

A nationwide, population-based study found schizophrenia to be associated with a 1.37 times greater risk of acute respiratory failure and a 1.34-fold greater risk of mechanical ventilation (428). Filik et al (414) found that people with SMI have a higher prevalence of angina and respiratory symptoms and impaired lung function when compared with the general population. Significant barriers to prompt and appropriate medical care for pneumonia still persist for patients who have schizophrenia (428).

Chronic obstructive pulmonary disease

The prevalence of chronic obstructive pulmonary disease, i.e. chronic bronchitis and emphysema, is significantly higher among those with SMI than comparison subjects (429-433). In a study of 200 outpatients in the US, 15% of those with schizophrenia and 25% of those with bipolar disorder had chronic bronchitis, and 16% of people with schizophrenia and 19% of people with bipolar disorder had asthma. These rates were significantly higher than those of the matched controls from the general population. The authors also found that, even when smoking was controlled for as a confounder, both people with schizophrenia and bipolar disorder were more likely to suffer from emphysema (430). Although the association remains unclear, a higher incidence of chronic obstructive pulmonary disease in the past two decades has been associated with the side effects of phenothiazine conventional AP (434).

Cancer

Cancer risk in SMI patients

Given that obesity and unhealthy lifestyle behaviors are known risk factors for a number of cancer types (149,435-438), one would expect to see higher cancer rates in patients with SMI. However, studies exploring the relationship between SMI and all cancer types together have shown conflicting results (30,439). Some studies have demonstrated a decreased cancer risk in schizophrenia (440-448). On the other hand, other studies found an increased (9,21,28,449-451) or no different (292,419,452,453) overall risk of cancer in patients with schizophrenia compared to the general population. In the population of bipolar spectrum disorders, deaths from cancer are not higher (8,288,416,417,454-456) or only slightly elevated (417,418,456) compared with the general population, despite the higher number of risk factors for cancer (such as obesity) in this population. This discrep-

ancy of results may be a result of various confounding factors that could artificially lower the rates of diagnosed and reported cancer in SMI populations. For example, people with SMI are less likely to receive routine cancer screening (457-460). Furthermore, patients with SMI have a shorter life expectancy, so they may die from cardiovascular reasons before reaching the expected age of death from cancer (30). Another tentative hypothesis is that AP have antitumour properties (448) or that the disease itself has a possible protective effect, including a tumor suppressor gene or enhanced natural killer cell activity (461,462). Nevertheless, a problem with most of the existing data base analyses is that etiologically disparate cancer types were lumped together. An important analysis of cause-specific excess deaths associated with underweight, overweight, and obesity in the general population found that obesity was associated with an increased mortality from cancers considered obesity-related but not with mortality from other cancers (463).

Cancer risk and psychotropics

Because of the possible, but still controversial, role of prolactin in breast cancer, the assumption has been made that exposure to prolactin-raising dopamine antagonists could result in breast cancer. The current study database on AP and breast cancer risk is very limited (464). The majority of the studies in which the risk of breast cancer has been investigated in patients treated with conventional AP (465-468) did not uncover an increased risk of breast cancer, an exception being the cohort study by Wang et al (469).

Musculoskeletal diseases

Osteoporosis in SMI patients

Schizophrenia, schizoaffective states, major depression and bipolar disorder are known to be associated with low bone mineral density (BMD) (470). In comparison with the general population, untreated patients with schizophrenia appear to have an increased risk of developing osteoporosis. On the one hand, this is because of the disease itself, on the other hand, because of risk factors related to their lifestyle (e.g., smoking, reduced physical activity, alcohol abuse, vitamin D and calcium deficiency, polydipsia) (470-476). Although the association between depression and loss of BMD has been reported inconsistently, most studies have found low BMD in patients with depressive symptoms or major depressive disorder (477-483). Two recent meta-analyses confirmed that depression is associated with low BMD and should be considered as an important risk factor for osteoporosis, although this increased risk may be mediated by AD (484,485). However, physiologic changes and the adoption of poor health behaviors are two prominent ways in which depression is hypothesized to directly affect BMD (486).

Osteoporosis and psychotropics

Although it has been suggested that raised prolactin levels provoked by AP medication can lead to an increased risk of osteoporosis in patients with schizophrenia (471, 487), clinical data implicating AP-induced hyperprolactinemia as a possible major risk factor for bone loss are limited and contradictory (488,489). Some studies (490-493) found a relationship between the use of prolactin-raising medication and low BMD in patients with chronic schizophrenia, while others (474,489,494-498) failed to find a relationship between prolactin, AP and osteoporosis. Nevertheless, the available data seem to indicate that hyperprolactinemia with associated hypogonadism may be a risk factor (488), leading to bone mineral loss in women as well as men (499).

The majority of studies directly examining the relationship between AD and BMD in humans report that the use of these medications is associated with low BMD (486). However, this finding seems to be restricted to the SSRI class of AD (500-502).

Data describing the epidemiology of osteoporotic fracture and psychotropics in patients with SMI are limited. Regarding AP, conflicting results exist (503). Some of these studies have reported higher prevalence rates of osteoporotic fractures in patients with chronic schizophrenia, entirely or partly independent of the use of AP (504,505). Other studies (506-510) have found significant increases (OR=1.2-2.6) in the risk of fractures associated with AP. For AD, a dose-response relationship was observed for fracture risk (504,508). SSRIs seem to be associated with the highest adjusted odds of osteoporotic fractures (OR=1.5) (504,505, 508). A meta-analysis showed a 33% increased risk of fractures with SSRIs compared to non-SSRI AD. The RR of fractures in this meta-analysis was 1.60 for AD and 1.59 for AP (511). Although lithium has a potentially negative impact on bone metabolism (470), it is associated with lower fracture risk (OR=0.6) and, thus, seems to be protective against fractures (504,505).

Urological, male/female genital diseases and pregnancy complications

Sexual dysfunction in SMI patients

Sexual dysfunction in SMI patients has received little attention from clinicians (512,513). This low awareness has a significant negative impact on patients' satisfaction with treatment, adherence, quality of life and partner relationships (450). Although there are relatively few systematic investigations concerning sexual disorders in schizophrenia (514), sexual dysfunction in schizophrenia is, compared to normal controls, estimated to be more frequent (515-519) and to affect 30-80% of women and 45-80% of men (512,515, 520-523). This dysfunction can be secondary to the disease itself and to comorbid physical disorders, or be an adverse

event of AP (520,524,525). Sexual dysfunction is also a common symptom of depression (526-530). Up to 70% of patients with depression may have sexual dysfunction (466). Approximately 25% of patients with major depression may experience problems with erection or lubrication (531).

Patients with SMI are likely to engage in high-risk sexual behavior, putting them at risk of sexually transmitted diseases. However, findings suggest that sexual health education for these people tends to produce a reduction in sexual risk behavior (532).

Sexual dysfunction and psychotropics

Psychotropic drugs are associated with sexual dysfunction (514). To date, only few studies (534-547) have directly compared the sexual functioning associated with different atypical AP. These studies suggest that the relative impact of AP on sexual dysfunction can be summarized as: paliperidone = risperidone > haloperidol > olanzapine ≥ ziprasidone > clozapine ≥ quetiapine > aripiprazole (503,520,536). Conventional AP cause less sexual dysfunction than risperidone but more than the other novel AP (520,522).

AD therapy (except for mirtazapine, nefazodone and bupropion) frequently induces or exacerbates sexual dysfunction, which occurs in approximately 50% of patients (548). Although sexual dysfunction has been reported with all classes of AD (549), SSRIs are associated with higher rates (550-552). Published studies suggest that between 30% and 60% of SSRI-treated patients may experience some form of treatment-induced sexual dysfunction (553,554).

Pregnancy complications, SMI and psychotropics

There is an extensive literature reporting an increased occurrence of obstetric complications among women who have schizophrenia (15). During pregnancy, it is important to evaluate the safety of psychotropic drugs. Most women with a SMI cannot stop taking their medication, as this would interfere with their activities of daily living, especially taking care of an infant (555). There is a paucity of information, with a lack of large, well designed, prospective comparative studies during pregnancy. However, no definitive association has been found up to now between the use of AP during pregnancy and an increased risk of birth defects or other adverse outcomes (555,556). Among AD, SSRIs and, possibly, serotonin and noradrenaline reuptake inhibitors (SNRIs) have been associated with preterm labor, respiratory distress, serotonin rebound syndrome, pulmonary hypertension and feeding problems in the neonate (557-559). Furthermore, a number of mood stabilizers have been associated with fetal malformations, including carbamazepine and valproate (560,561). Current evidence seems to suggest that Fallot's tetralogy is not considerably elevated with lithium compared to the rate in the general population (560).

Stomatognathic diseases

Oral health in SMI patients

Dental health has been consistently found to be poor in people with SMI (562-573). A study using an overall dental status index (DMF-T) in chronically hospitalized patients with mental disorders (mostly schizophrenia) found a mean score of 26.74 (out of a possible 32), one of the highest reported in the literature (571). According to another study, only 42% of patients with schizophrenia brush their teeth regularly (at least twice a day) (573). This poor dental health leads to functional difficulties. In one large study (n=4,769), 34.1% of the patients with SMI reported that oral health problems made it difficult for them to eat (572).

Factors which influence oral health include: type, severity, and stage of mental illness; mood, motivation and self-esteem; lack of perception of oral health problems; habits, lifestyle (e.g., smoking), and ability to sustain self-care and dental attendance; socio-economic factors; effects of medication (dry mouth, carbohydrate craving); and attitudes and knowledge of dental health teams concerning mental health problems (569,574).

Oral health and psychotropics

AP, AD and mood stabilizers all cause xerostomia (575). This reduction in salivary flow changes the oral environment and leads to caries, gingivitis and periodontal disease (576).

Disparities in health care

Oral health status is a frequently disregarded health issue among SMI patients (498), with low rates of dental examination within the past 12 months (569,577-579). In one study of a mixed psychiatric population, 15% had not been to a dentist in the last 2 years (579), while in another only 31% of schizophrenia patients had visited a dentist during a three year period (577). In the latter study, non-adherence to annual dental visits was predicted by substance abuse diagnosis, involuntary legal status, living in an institution, admission to a psychiatric facility for a minimum of 30 days, and male gender, whereas clozapine treatment, novel AP treatment, at least monthly outpatient visits, and age > 50 years were associated with a lower risk for inappropriate dental care.

Taken together, these findings confirm the urgent need for an intervention program to improve oral health outcomes among patients with SMI, by facilitating access to dental care and addressing modifiable factors such as smoking and medication side effects (571,572), especially because oral diseases are preventable and social inequity in oral health avoidable (580). Moreover, improving dental health status and care are relevant, as poor dental status is associated with endocarditis and reduces social and work opportunities.

Other physical health conditions in people with SMI

This review is by no means exhaustive. We speculate that perhaps most medical illnesses occur with greater frequency in SMI, which in itself serves as a vulnerability factor (587).

Haematological diseases, which may in themselves be primary problems in patients with SMI, have frequently been described in the literature as potential serious complications of psychotropic medications. AP (e.g., clozapine, haloperidol, olanzapine, phenothiazines, quetiapine, risperidone, ziprasidone), AD (e.g., amitriptyline, clomipramine, imipramine) as well as lithium are associated with blood dyscrasias. Clozapine (approximately 0.8%) and phenothiazines (chlorpromazine approximately 0.13%) are the most common causes of drug-related neutropenia/agranulocytosis. AD are rarely associated with agranulocytosis. With appropriate management, the mortality from drug-induced agranulocytosis in Western countries is 5-10% (before the use of antibiotics this percentage was 80%) (582).

Some physical conditions, although important, are rarely studied, underreported and not systematically assessed. Although a common side effect of AP that can be severe and lead to serious consequences and even death, constipation has been given relatively little attention. The most reported complications of this physical condition are paralytic ileus, faecal impaction, bowel obstruction and intestine/bowel perforations. Constipation has most widely been reported for clozapine, although it can be associated with other AP as well. Prevalence of constipation in randomized controlled trials for different AP is: zotepine 39.6%, clozapine 21.3%, haloperidol 14.6% and risperidone 12% (583). Next to medication effects, lifestyle and diet factors can contribute to the occurrence of constipation in people with SMI (sedentary life, low physical activity, diet low in fibre, limited fluid intake) (584). Clinicians should actively and systematically screen and monitor symptoms and possible complications of constipation (585-588).

CONCLUSIONS

In summary, many physical disorders have been identified that are more prevalent in individuals with SMI. In addition to modifiable lifestyle factors and psychotropic medication side effects, poorer access to and quality of received health care remain addressable problems for patients with SMI. Greater individual and system level attention to these physical disorders that can worsen psychiatric stability, treatment adherence, and life expectancy as well as quality of life will improve outcomes of these generally disadvantaged populations worldwide. The barriers to somatic monitoring and interventions in persons with SMI will be summarized in the second part of this educational module, where monitoring and treatment guidelines as well as recommendations at the system level (state and health care institutions) and individual level (clinicians, patients, family) will be provided.

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