



Review

Humanistic burden in schizophrenia: A literature review



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ABSTRACT

Objectives of the study and background: Schizophrenia is a complex disease that affects 1% of the population. This disease has a considerable impact not only on patients' health and well-being but also on their surrounding environment. The costs of the disease's management remain large for individuals and society. While literature on the economic impact of schizophrenia is abundant, few studies have focused on its humanistic burden. This does not only concern patients, but also caregivers, relatives, neighbours and others in a patient's daily life. This burden appears through several dimensions, including treatment side effects and the impact on caregivers and features of the patient's environment. The aim of this review is to consider, compile and describe the humanistic burden of schizophrenia as documented in the literature.

Materials and methods: We conducted a literature review assessing the worldwide disease burden of schizophrenia, taking into account all humanistic burden topics. The search considered several databases, including Embase, Medline, Cochrane Library, The German Institute of Medical Documentation and Information (DIMDI) and the ISPOR conference websites.

Results: The search identified 200 literature reviews, covering several dimensions of humanistic burden and documenting many issues. Main findings included the high death rates that may be explained by long-lasting negative health habits, disease- and treatment-related metabolic disorders, and consequent increased frequencies of cardiovascular diseases. Co-existing depression was found to have adverse consequence on the course of schizophrenia progression, morbidity and mortality. Cognitive impairment also adds to the burden of schizophrenia. Social impairment is worsened by underestimated stigmatisation and lack of corresponding awareness within the professional and social spheres. Finally, caregiver burden was found to be considerable.

Discussion: Humanistic burden among patients with schizophrenia is substantial potentially impacted by co-morbid depressive symptoms, caregiver burden and cognitive impairment. Effects of treatment on humanistic burden in addition to economic burden need to be explored in future trials.

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1. Objectives of the study and background

Schizophrenia is a disorder of brain function, affecting one's thoughts, feeling and acts. Symptoms develop either progressively

or appear abruptly and vary from one patient to another. The disease evolves in cycles of remissions and relapses. Symptoms consist of separation from reality with delusion formation, hallucinations, emotional dysregulation and disorganized behaviour. Over time, a

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slow decline in mental function and social relationships occurs. This leads to a marked personality change, social isolation, occupational disability, cognitive impairment and poor health. Schizophrenia is also a major cause of suicide (Carlborg et al., 2010). Currently, there are no curative treatments for schizophrenia (Van Os et al., 2006; Andreasen et al., 2005).

The worldwide prevalence of schizophrenia is about 1% (Leucht et al., 2007). The World Health Organization (WHO) estimated that schizophrenia was the 5th (respectively 6th) leading worldwide cause of global disease burden in 2004 among males (respectively females), with 2.8% (respectively 2.6%) of total Years Lived With Disability (YLD) (WHO, 2004).

Schizophrenia is a financial burden on society because of the potential for institutionalization and chronic use of treatments. It is described as a disease with large costs for individuals and society. While literature on the economic impact of schizophrenia is abundant (de Silva et al., 2012; Abouzaid et al., 2010; Willis et al., 2010), few studies have focused on its humanistic burden, which not only concerns patients, but also caregivers, relatives, neighbors, and other individuals in a patient's daily life.

We developed this paper with the objective of identifying all existing literature reviews on the humanistic burden of schizophrenia and providing a comprehensive overview. Our aim was quantification, but also to highlight potential areas of unmet need.

2. Material and methods

2.1. Humanistic dimensions of schizophrenia

The humanistic burden of schizophrenia involves several dimensions of life. Since no studies have documented the key dimensions to determine the overall schizophrenia humanistic burden, we have referred to experts' opinion. Experts suggested focusing on quality of life, depression, treatment side effects, family or caregiver burden, cognitive functioning and social impairment, mortality, suicide, homelessness, morbidity, stigmatisation, violence, and lifestyle, including abuse, physical performance and abortion/pregnancy. Most of these dimensions are overlapping, and all are linked. For example impaired cognitive functioning can lead to stigma and lack of empowerment, which may lead to depression, causing physical, emotional and economic distress that is likely to negatively affect a patient's quality of life and ultimately to provoke suicide in some cases. In this paper, dimensions will be described separately but these overlaps will be taken into account.

2.2. Search strategy

A systematic literature review was conducted in order to identify all relevant literature reviews on each dimension of humanistic burden of schizophrenia. Search strategies with different search terms for each dimension of humanistic burden were defined and the following databases were used: Embase, Medline, Cochrane library, DIMDI, and grey literature, including Google Scholar and the ISPOR website. We expanded these initial database search results by screening the bibliographies of all relevant reports and by performing electronic searches for further relevant articles by the first author of any identified study.

The initial database search was conducted by two researchers who then independently screened titles, abstracts and, where appropriate, the full text of all identified references to minimize the possibility of discarding potentially relevant reports. Potential references were included if they were literature reviews considering at least one dimension of the humanistic burden of patients with schizophrenia. There was no restriction on language.

The searches identified 3545 publications that met the inclusion criteria, out of which 3368 were excluded (not a schizophrenia-specific literature review). Finally, 177 reviews were selected, and 23 other literature reviews were found in grey literature.

Table 1 presents the number of articles preselected and selected considering all databases together.

In total, 200 literature reviews were included; the results were extracted and summarized.

3. Results

This section describes our findings for each dimension of humanistic burden and draws out commonalities found.

3.1. Quality of life (QoL)

Although QoL improvement represents one of the main objectives of much modern medicine, and QoL questionnaires are currently widely used in schizophrenia, no strict definition exists. As reported by Awad et al., the concept has come to represent the ultimate outcome of the interaction between the patient and the illness, its treatment, its psychosocial impact and its consequences (Awad and Voruganti, 2004). Lehman et al. reported that there are three dimensions of QoL: subjective positive experience and happiness, ability to function, and availability of certain lifestyles and material resources (in Katschnig, 2000). Other publications have stated that QoL measures general satisfaction or health related disturbance.

Pinikahana et al. reported that QoL in schizophrenia may be affected by two different types of levers: those that affect perception, such as pain or depression (which are associated with cognitive distorters that may alter perceived reality), and those that alter expectations, such as accommodation to adverse circumstances (Pinikahana et al., 2002).

Most reviews described the importance of improved QoL for better social reintegration and stigmatisation reduction. Braga et al. showed a higher prevalence of anxiety and depression in correlation with lower QoL (Braga et al., 2005). QoL improvement could be achieved by physical activities: Schmitz et al. reported that physical activities improved QoL, resulting in less co-morbidity like overweight, less depression and improvement of personal strengths (Schmitz et al., 2004). Recently Awad stated that more focused research is needed to demonstrate the role of QoL, not only as an outcome in itself but also as a contributor to other outcomes (Awad and Voruganti, 2012). One publication reported that QoL could be considered as an important predictor of relapse (Boyer et al., 2013).

Table 1

Humanistic burden literature review: number of articles included by dimension.

Key words	Identified references#	Selected references#	Grey literature
Quality of life	731	27	
Depression	146	8	
Treatment side effects	9	2	12
Family burden or caregiver burden	587	9	
Cognitive functioning and social impairment	1101	40	
Mortality/suicide	1137	45	
Homelessness	13	3	
Morbidity	312	15	
Stigmatisation	91	3	7
Violence	127	16	
Lifestyle including abuse	19	9	2
Physical performance	558	5	
Abortion/pregnancy	3	0	2
Total	3545	177	23

Question of who should fill out the QoL questionnaire were raised. There is evidence that patients with schizophrenia can adequately provide a subjective measure of their QoL, unless they are in a psychotic state. Nevertheless, [Viertö et al., 2012](#) noted that most of their patients were not able to assess their situation, leading to a very large range of QoL values ([Viertö et al., 2011](#)). Authors argued that some cognitive ability is required to answer existing questionnaires, suggesting that accuracy, reliability and consistency are difficult to obtain with the use of QoL questionnaires in schizophrenia. More recently, [Baumstark et al.](#) reported that cognitive decline did not compromise the reliability or validity of self-reported QoL measures ([Baumstark et al., 2013](#)).

Although limitations in QoL measurement for schizophrenia, as well as potential doubts about the reliability of self-report in patients with schizophrenia, make it difficult to accurately measure the burden of the disease ([Awad and Voruganti, 2004](#)), it remains clear that the QoL of patients with schizophrenia is worse than that of the general population, and worse than that of many patients with physical and other mental disorders ([Bobes et al., 2007](#)).

3.2. Depression

Depression is a common co-morbidity in schizophrenia and is described in the literature in conjunction with other disease outcomes, such as decreased QoL or higher risk of suicide ([Siris, 2001](#)). Depressive symptoms can vary in magnitude and may occur at any time during the course of the illness.

The prevalence of depression is higher in patients with schizophrenia than in the general population, but there was variability in the depression rates report in the literature. [Mulholland et al.](#) reported that prevalence of depressive symptoms in schizophrenia ranged from 13% to 80% ([Mulholland and Cooper, 2000](#)). [Siris](#) reported similar rates of depression prevalence, ranging from 25% to 81% ([Siris, 2001](#)). This wide variation in prevalence estimates may be explained by the different definitions of depression used in schizophrenia.

[Conley et al.](#) used data from the U.S. Schizophrenia Care and Assessment Program (US-SCAP) study, covering 2327 patients with schizophrenia between July 1997 and September 2003 ([Conley et al., 2007](#)). Assessments were performed at enrolment and at 12-month intervals. The study found that 39.4% of patients were depressed at enrolment, with poor mental and physical health, a lower level of medication adherence, more substance-related problems, and poorer social and family relationships and poor QoL compared to the general population. Moreover, patients with depressive symptoms used relapse-related mental health services more frequently than the cohort of patients with schizophrenia without depressive symptoms.

[Conley et al.](#) also addressed the problem of suicidal thinking in schizophrenia and found a rate higher of it in depressed patients compared to non-depressed patients. Safety concerns were measured, and statistically significant differences for schizophrenia with depression in contrast to non-depressed patients were found.

In a study of 249 inpatients with schizophrenia admitted over a 4-year period, the German Research Network on Schizophrenia reported a significantly higher rate of 'suicidality' for patients depressed on admission compared to patients not depressed on admission (36.7%, $n = 90$, vs. 18.4%, $n = 159$). More depressed patients than non-depressed patients also attempted suicide during hospitalization (3 vs. 1), but the difference did not reach statistical significance. The authors concluded that patients with depressive symptoms should be monitored closely, given the burden of negative symptoms, impairments in well-being and functioning, and the threat of suicide partly due to the significantly greater insight into their disease ([Schennach-Wolff et al., 2011](#)).

Depression in patients with schizophrenia poses a challenge for their social reintegration, since depressed patients might simply be too handicapped by their symptoms: social withdrawal and reduction in work and activities are core symptoms of depression. Depression further adds to the humanistic burden in schizophrenia with the challenges posed by its treatment and by the fatal consequences of related suicide. Depression deepens the psychopathological, social and health impairment posed by schizophrenia, and degrades patient wellbeing.

3.3. Treatment side effects

Treatment side effects merit consideration as a distinct humanistic issue. It is well-known that first generation antipsychotics (FGA) can especially cause mild to severe problems with body movements, such as restlessness, tremors, and rigid muscles. Second generation antipsychotics (SGA) have reduced this burden. Nevertheless they have their own issues: over the years different surveys have shown that weight gain, metabolic syndrome and cardiovascular disease are all related to the side effects of SGAs and to unhealthy behaviour of patients caused by their illness ([Seeman, 2009](#); [Clark et al., 2011](#); [Sevy et al., 2001](#)).

The most harmful side effects reported are weight gain, diabetes, metabolic syndrome, sexual dysfunction, osteoporosis, and physical impairments such as tardive dyskinesia.

[De Hert et al.](#) reported data on prevalence and relative risk of modifiable cardiovascular disease risk factors for patients with schizophrenia, compared to the general population, independently of SGAs ([De Hert et al., 2009](#)):

- 10–15% for diabetes with RR = 2
- 45–55% for obesity with a relative risk (RR) ranging between 1.5 and 2
- 19–58% for hypertension with RR between 2 and 3
- 25–69% for dyslipidemia with RR ≤ 5
- 37–63% for metabolic syndrome with RR between 2 and 3

These numbers are consistent with statistics reported in other literature reviews ([Ismail, 2008](#)).

[Seeman](#) reported antipsychotic medication resulted in increased prolactin secretion ([Seeman, 2009](#)). This complication is mostly associated with FGAs, which likely raise prolactin levels 10-fold above pre-treatment values in both men and women. Women are more likely to experience related symptoms such as galactorrhoea, sexual dysfunction, atrophic changes in the urethra and vaginal mucosa, reduced vaginal lubrication and dyspareunia, loss of libido, ovarian dysfunction, infertility, oligomenorrhoea, and amenorrhoea. This represents a particular burden for women of childbearing age.

[Baggaley](#) conducted a comprehensive study to examine the recent evidence of sexual dysfunction: results showed that 30%–80% of patients with schizophrenia were affected (30–80% of women and 45–80% of men) ([Baggaley, 2008](#)); 68% of patients reported reduced libido. FGAs were the cause of 70% of sexual dysfunction for both women and men receiving the medication for 12 months. The issues reported were consistent when patients received SGAs. This represents an inevitable treatment related burden of the disease, since patients cannot be left without treatment.

Sexual dysfunction contributes to poor QoL, negative attitude to therapy, and treatment non-compliance. Unsurprisingly sexual dysfunction had a negative impact on the relationship of couples when one partner was diagnosed with schizophrenia. Sexual dysfunction can be measured by the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) ([Montejo and Rico-](#)

Villademoros, 2008). This is another humanistic burden to be clearly diagnosed, discussed and treated while the patient complies with the treatment of schizophrenia.

FGAs have been associated with an incidence of tardive dyskinesia of 5% per year in adults and 25%–30% in elderly patients. The weighted mean annual incidence risk of tardive dyskinesia associated with SGA across all different SGA and age groups was 2.1% (Correll et al., 2004).

Patients experiencing adverse side effects are likely to reject their treatment and to decrease their level of compliance, which causes more relapses, more clinical admissions, and worsening of disease symptoms (Voruganti et al., 2000). Many reviews have highlighted the high unmet need for safer, more tolerable and more efficient treatments for schizophrenia, especially ones that will avoid the main side effects such as metabolic syndrome, tardive dyskinesia and sexual dysfunction. The effect of current treatments on humanistic burden has not been sufficiently defined, and needs to be explored further.

3.4. Family burden/caregiver burden

Schizophrenia affects the physical, psychological, emotional, social and financial life of patients' caregivers (Rafiyah, 2011): 41% of patients with schizophrenia still live with their parents, or have moved back in with their parents (Jungbauer et al., 2004); 12% of caregivers are the patient's siblings; and 7% of caregivers are a spouse or partner (http://www.nami.org/Content/NavigationMenu/SchizophreniaSurvey/Download_Report.htm).

Caregiver burden can be associated with work overload, sleep disturbance, financial problems, less spare time etc. Stigmatisation and social isolation by neighbours or other acquaintances can be seen as a substantial part of the caregiver burden, referred to as environmental burden. It was reported that many neighbours are fearful of violence caused by patients with schizophrenia (Lögdberg et al., 2004). A reported 32% of the burden related to caregiver problems arises from young patient age, awareness of the patient's suicidal ideation, and concern about family resources (McDonnell et al., 2003).

It is not uncommon for patients to require 24-h care and the caregivers suffers, particularly those who are relatives of the patient. Caregivers can feel overloaded and may show symptoms of burnout. The lack of spare time, special care requirements for medication intake, the efforts needed to ensure eating or physical health — the cumulative burden on the caregiver is significant, and is often underestimated. The burden may be exacerbated by limited financial and healthcare resources (Caqueo-Urizar et al., 2009). However, independent of social status, all publications reported a reduced QoL for the caregiver if the patient's QoL was also reduced.

The caregiver burden often leads to loss of social contact outside the family. In the United States, a National Alliance on Mental Illness (NAMI) survey of caregivers for patients with schizophrenia found that 41% of caregivers had provided care for more than ten years, and 19% of them for more than 40 h per week. Fifty-five percent of caregivers found it a challenge to find time to take care of their own health, 90% of caregivers were worried for the future of their child or loved one with schizophrenia, and more than 70% of caregivers felt sad, protective or frustrated when they heard others talking about the person in their care (NAMI, 2008). Because of the intense care required, some relatives are forced to quit their jobs or to reduce their working hours. The proportion of caregivers giving up work ranged from 1.2% for first-episode to 2.5% for highly dependent patients (NAMI, 2008).

Substantial evidence demonstrates that the humanistic burden of schizophrenia extends beyond patients to caregivers. The impact

on the caregiver is worthy of consideration in estimating the humanistic burden of the disease.

3.5. Cognitive impairment

Cognitive impairment is a core feature of schizophrenia and is established as reliable clinical predictor of functional impairment in the disease (Backer and Howard, 2007). Cognitive deficits appear as a lack of attention, declarative memory, and higher-order problem-solving. Speed of processing, working and long-term memory, executive function, and social cognition can also be affected. These capacities are essential for tasks in school or employment. During a crisis, individuals may fail their tests at school or lose their jobs. Cognitive dysfunction appears in approximately 70–85% of in-patients (Allardyce and van Os, 2008).

Functioning or social impairment can be a result of cognitive impairment. It appears as a lack of social behaviours related to chronicity, such as emotional withdrawal and reduction of interpersonal interaction (Cook and Razzano, 2000).

Episodic memory dysfunction may explain some behavioural abnormalities associated with schizophrenia, notably, inadequate functional outcomes in everyday life. Patients with a social cognitive deficit are unable to communicate effectively and this contributed to increased social isolation. Patients with a social cognitive deficit may also experience stigmatisation and discrimination (Shrivastava et al., 2011).

All of these factors require health care professionals to consider the humanistic burden related to the cognitive and functional/social impairments associated with schizophrenia whenever making treatment decisions or other judgements regarding patient care.

3.6. Mortality/suicide

The overall mortality rate is twice to three times as high for patients with schizophrenia as for the general population (Bushe et al., 2010).

A Swedish study reports that life expectancy was reduced in patients with schizophrenia: at age 40 years, conditional life expectancy was 7 years less for patients with schizophrenia or affective psychosis when compared to general population. (Hannerz et al., 2001) The main causes of mortality are suicide, cancer and cardiovascular disease, with evidence that cancer mortality rates are similar to cardiovascular mortality rates. (Bushe et al., 2010).

It has been reported that although antipsychotic treatment is linked with a higher mortality rate from cardiovascular disease, it reduces overall mortality compared to no treatment. Kopenen et al. reported part of the high death rates may be explained by long-lasting negative health habits, disease- and treatment-related metabolic disorders, and consequent increased frequencies of cardiovascular diseases (Koponen et al., 2008). Approximately one-third of the excess mortality in schizophrenia is due to unnatural causes (Hawton et al., 2005; Ward et al., 2006; Brown, 1997). Mortality risk in offspring of parents with psychotic disorders, including schizophrenia, is also higher than in the general population. Webb et al. conducted a meta-analysis, finding an overall risk ratio of 1.89 (95% CI 1.36–2.62) (Webb et al., 2005). Brown et al. investigated different mortality conditions in schizophrenia. The mortality rate was higher in patients with substance abuse and lower for patients who were married or employed (Brown et al., 2000).

Between 4% and 13% of patients with schizophrenia attempt suicide (Carlborg et al., 2010; Hor and Taylor, 2010; Palmer et al., 2005; Pompili et al., 2007). Hawton et al. examined the risk factors for suicide in schizophrenia (Hawton et al., 2005). It was reported that the evidence of increase risk of suicide was mainly due

to previous depressive disorders, among other factors such as young age, male gender, white race, never married, good pre-morbid function, a history of substance abuse, suicide attempts, and high level of education. Mortality in schizophrenia, and especially suicide, are major features of the humanistic burden of the disease and there is a need, especially in young patients, to implement prevention programs addressing social isolation, substance abuse, depression, hopelessness and disappointment about lowered expectations for the future, which are also aspects of the humanistic burden of schizophrenia. Today, clozapine is the only antipsychotic medication that has demonstrated efficacy for the management of suicidality in schizophrenia (Hor and Taylor, 2010).

3.7. Homelessness

Schizophrenia is over-represented in homeless populations when compared to non-homeless populations. Being homeless worsens the QoL in persons with schizophrenia who already have particularly low QoL levels, suggesting that homelessness amongst patients with schizophrenia is a double jeopardy (Auquier et al., 2013).

Salkow et al. reported a weighted average prevalence of 11% of schizophrenia in homeless population, with higher rates of schizophrenia in younger persons, women, and the chronically homeless (Salkow and Fichter, 2003). Folsom and Jeste reported that the prevalence of schizophrenia in homeless people ranged between 2% and 45% in different countries (Folsom and Jeste, 2002). These authors also reported that almost half of the homeless patients with schizophrenia received no or little treatment for schizophrenia or other related diseases.

Homelessness is strongly associated with cognitive impairments. Deficits in personal memory, judgement, or planning can result in poor problem-solving and social skills. Poor social behaviour skills could be the reason of some landlords denies housing to people with cognitive impairments.

It is also noteworthy mentioning that healthcare and housing management for homeless people with mental disorders is currently not sufficient. Interestingly, several approaches have been investigated for homeless people in developed countries. Recent reviews of the literature suggested that Housing First programs provided satisfactory health outcomes and well-being for people with mental illness (Wright and Kloos, 2007).

3.8. Schizophrenia comorbidity

Schizophrenia co-morbidities can be associated with the side effects of the medication, or with the unhealthy lifestyle of the patients.

Leucht et al. reported higher prevalence for HIV infection and hepatitis, osteoporosis, altered pain sensitivity, sexual dysfunction, obstetric complications, cardiovascular diseases, overweight, diabetes, dental problems, and polydipsia among patients with schizophrenia, compared to the general population (Leucht et al., 2007).

Weight gain in schizophrenia is significantly correlated to impaired QoL. Citrome and Vreeland reported that the prevalence of morbid obesity (BMI of at least 40) among patients with schizophrenia was 2.8% in men and 6.9% in women (Citrome and Vreeland, 2009). In the 1-year European First-Episode Schizophrenia Trial, weight gain greater than 7% from baseline was observed in 86% of patients randomized to olanzapine, 65% for those on quetiapine, 37% for those on ziprasidone, and 53% for those on haloperidol (Alvarez-Jiménez et al., 2006).

It is difficult to motivate any patient with physical deficits to participate in sport or other physical activities. Because of

overweight and obesity, approximately 60% of patients with schizophrenia are physically inactive. Schmitz et al. (Schmitz et al., 2004) and Vancampfort et al. (Vancampfort et al., 2011) reported that reduced physical activity is associated with a reduced QoL and higher risk for developing many of the aforementioned comorbidities.

Patients with mental disorders have increased rates of diabetes and other diseases with complications, but are often not able to manage the complexity of doctor visits and appropriate medication intake. In general, patients with diagnosed stable schizophrenia are treated by GPs. Unfortunately GPs are not well informed about the specific health care management needs of patients with schizophrenia.

It is also worth mentioning that patients with schizophrenia are at risk of undetected somatic comorbidity, especially at late and more developed disease stages.

3.9. Stigmatisation

Apart from the illness itself, the stigma surrounding schizophrenia places a major burden on patients. According to Link and Phelan, stigma exists when the following interrelated components converge (Link and Phelan, 2001): people distinguish and label human differences. Dominant cultural beliefs link labelled persons to undesirable characteristics – to negative stereotypes. Labelled persons are placed in distinct categories so as to accomplish some degree of separation of 'us' from 'them'. Finally, labelled persons are exposed to negative emotional reactions and experience status loss and discrimination. In principle, three different forms of discrimination can be distinguished: individual discrimination, discrimination internal to the affected person himself/herself (or 'self-stigma'), and structural discrimination.

Individual discrimination refers to behaviours of one group that are intended to have a harmful or at least differential effect on the members of another group. A frequently used measure to quantify this form of discrimination is the desire for social distance, i.e. the unwillingness of people to engage persons with schizophrenia in activities such as hiring them for babysitting or renting them a room. Among all mentally ill people, with the exception of patients with substance use disorders, people with schizophrenia face the strongest rejection by the public (Angermeyer and Dietrich, 2006). In a qualitative study carried out in Germany, people with schizophrenia, relatives, and mental health professionals from outpatient centres all reported that the stigma of schizophrenia was a major barrier to employment (Schulze and Angermeyer, 2003).

A systematic review and meta-regression analysis of time-trend analyses of public beliefs and attitudes about mental illness, based on representative national population samples, showed that while considerable advances in mental health literacy have been achieved over the last two decades, this has not translated into better social acceptance of people with mental illness. In fact, the desire for social distance from persons with schizophrenia has even increased (Schomerus et al., 2012).

Another form of discrimination operates through the stigmatized person himself/herself. Once the cultural stereotype is in place, it can affect labelled persons in important ways that do not involve obvious forms of discriminatory behaviour on the part of other people around the stigmatized person. Many persons with mental illness know which stereotypes about their group prevail in society, for instance that they are incompetent. If they agree with these stereotypes this may lead to negative emotions, especially low self-esteem and self-efficacy, and in the end, they may fail to pursue work or independent living opportunities (Rüsch et al., 2005).

Structural discrimination is defined as institutional practices and policies that work to the disadvantage of the stigmatized group even in the absence of individual discrimination. Structural discrimination includes the policies of private or governmental institutions that intentionally restrict the opportunities of people with mental illness (Corrigan et al., 2004). In the U.S., approximately one-third of the 50 states restrict the rights of an individual with mental illness to hold elective office, participate in juries, and vote. Another example is how people with mental illness are portrayed in the media. Survey analyses in several English-speaking countries have shown that newspapers frequently frame mental illness in a stigmatizing way. Most articles discuss people with mental illness, particularly those suffering from schizophrenia, in terms of dangerousness and violent crime (Corrigan et al., 2004). Structural discrimination also includes major institutions' policies that are not intended to discriminate but whose consequences nevertheless hinder the options of people with mental illness (Corrigan et al., 2004). As concerns health care, there is strong evidence that people with a diagnosis of a mental illness, and particularly those with schizophrenia, have less access in the U.S. to primary health care (Levinson et al., 2003) and also receive inferior care for diabetes and cardiovascular disease (Desai et al., 2002; Druss et al., 2000).

These factors illustrate how deep the human impact of schizophrenia can be, in addition to the intrinsic aspects of the disease. We believe that stigmatization is still underestimated in clinical practice, and that there is insufficient awareness of this social burden.

3.10. Violence

Only a small proportion of societal violence is due to patients with schizophrenia. Of patients diagnosed with schizophrenia, 99.97% will not commit serious violence (Walsh et al., 2002). However schizophrenia is associated with an increased risk for non-violent and violent crime and with aggressive behaviour towards others (Bo et al., 2011). In one study, the likelihood of having committed at least one violent crime was 7 times as high among patients with schizophrenia as among people without mental illness (Tiihonen et al., 1997).

Kelly has argued that schizophrenia is a consequence of belonging to a lower socio-economic group, and therefore patients from a lower socio-economic group tend to have a longer duration of untreated psychosis prior to first presentation to health services, and this is associated with more severe illness and poor treatment outcomes (Kelly, 2005). Hodgins observed that the largest group of violent offenders with schizophrenia showed no antisocial behaviour prior to the onset of the illness and then repeatedly engaged in aggressive behaviour towards others, which made it difficult to predict patient behaviour (Hodgins, 2008).

Patients with schizophrenia are frequently found in socially deprived areas, which may lead to a worsening of the illness, as well as an increased chance of social isolation from the local community. Violence is often a likely result of inadequate treatment with fewer positive treatment outcomes. The causes of violence must be identified in order to allow customized treatment for patients, and appropriate training must be available to caregivers. The prevention of violence is associated with an improvement in the social and economic environment of patients with schizophrenia.

3.11. Lifestyle including substance abuse

It is very well accepted that patients with schizophrenia have lower rates of employment, marriage, and independent living than general population do (Nanko and Moridaira, 1993). The rate of

developing close, intimate interpersonal relationships is very low and much impaired as a result of the illness. Moreover schizophrenia makes self-reliant and gainful employment difficult for patients with schizophrenia, leading to a lack of independence in meeting basic needs (food, shelter, clothing, material goods etc.).

It is not clear why patients with schizophrenia are more likely to be substance users. Some reports suggest that the patients want to diminish the side effects of the disease or medical treatment (Winterer, 2010): Nicotine releases dopamine, while classic antipsychotics block dopaminergic transmission (Burda et al., 2010).

Substance abuse in people across the schizophrenia disorder spectrum is well described, with a prevalence of up to 60% (Swartz et al., 2006). Alcohol, drugs and nicotine are associated with comorbidity and social isolation, followed by treatment non-compliance and irregular medication intake, which increases the symptoms of schizophrenia.

Smoking is much more prevalent in patients with schizophrenia, 70–80%, in contrast to 20–30% in the general population (Winterer, 2010). Hjorthø et al. reviewed the literature and reported that a widely used substance is cannabis, with prevalence rates ranging from 27% to 42% in patients with schizophrenia (Hjorthø et al., 2009).

Alcohol use disorders (AUD) are also common in patients with schizophrenia. A review by Koskinen et al. reported a median AUD prevalence of 9.4%, with a median lifetime prevalence of 20.6% (Koskinen et al., 2009). Approximately a fifth of patients with schizophrenia are diagnosed with AUD at some point in their life (Culhane et al., 2008). The risk of a patient developing AUD was related to the patient being violent (odds ratio = 2.1), having low level of education (OR = 1.3), or having had a parent with AUD (OR = 1.9) (Jones et al., 2011).

Wobrock and Soyka reported that comorbid substance-use disorder in patients with schizophrenia was associated with poor clinical and functional outcomes (Wobrock and Soyka, 2009). They concluded that screening all patients with schizophrenia for substance misuse could be an important tool to improve outcomes. Before any treatment can be started, clinicians must try to find out the reasons for substance misuse. Additional treatment with antidepressants, depending on the patient's psychopathology, as well as with anti-craving agents, should be considered for therapeutic interventions (Wobrock and Soyka, 2009). Treatment of schizophrenia-related substance abuse is an important aspect of reducing the humanistic burden of the disease.

3.12. Abortion/pregnancy

Seeman reported that patients with schizophrenia were older at their first pregnancy relative to control cases and, over their lifetime, patients had fewer children, attesting to the fertility impairment that results from high levels of prolactin (Seeman, 2009). In addition, there is a higher risk of diabetes for female patients. The risk of a congenital malformation was increased by an OR of 1.2 for each 1 SD unit increase in glycosylated haemoglobin (GHb). At normal GHb concentrations, the absolute risk of congenital abnormality was approximately 2%.

One review reported that patients with schizophrenia were also more likely to have a therapeutic abortion compared to the general population (Romans, 2010). In Canada, patients were also more likely to have had multiple partners, and 50% of patients had sex with at least one partner in the past year. A third indicated that they would not insist on condom use (Chuang and Atkinson, 1996).

The antipsychotic medications used to treat schizophrenia have a number of side effects. Patients who do not receive treatment may increase the risk that patients will act on delusions or hallucinations, to the point that the patient's safety and/or the safety of

the foetus is endangered. In addition Seeman reported “sedating antipsychotics raise(s) the risk of embolic phenomena during pregnancy, and postpartum” (Seeman, 2009).

4. Discussion

This review describes and quantifies the findings of 200 literature reviews assessing the humanistic burden of schizophrenia. This review focused specifically on schizophrenia, but it is likely that most of the dimensions of humanistic burden considered could also be discussed more generally in the context of psychiatric disorders. It has been shown that schizophrenia is associated with a broad humanistic burden, which needs to be considered appropriately; it is then of importance to consider the broader context in order to optimize clinical and social outcomes from treatment.

The humanistic burden in schizophrenia is considerable, and concerns not only the patient but also his/her surrounding environment: caregiver burden remains considerable and treatment side effects have to be taken into consideration in the management of schizophrenia. Depression negatively affects the course of the disease, often with fatal consequences. Its management and the social reintegration of patients are a challenge for professionals. Cognitive impairment is known to add to the disease burden, and as a core symptom and specific disorder of schizophrenia, this neuropsychological dysfunction must be precisely defined and targeted for remediation if patients are to be treated effectively. The related social impairment is worsened by an underestimated stigmatisation and lack of corresponding awareness within the professional and social bodies. Early intervention and action to reduce stigmatisation helps to re-socialize patients and their families. Family education related to disease progression and the necessary interventions and treatments could be important family-related supports.

Lifestyle, morbidity and mortality in schizophrenia are also indicators of the overall burden of the disease; quality of life and other social aspects of a patient's life can be significantly degraded if they are not taken into account as part of antipsychotic treatment. Mortality is mainly due to suicide, and although the main causes of suicide are known, the treatments are very complex and are not always successful. There is a need, especially in young patients, to implement prevention programs addressing social isolation, substance abuse, depression, hopelessness and disappointment about lowered expectations for the future.

Above all there is a need for safe and effective antipsychotic treatments.

As reported by Awad et al., there has been significant growth in the number of publications about QoL in schizophrenia. Although a number of concerns previously outlined continue to be an issue, many publications discussed relations between humanistic burden and QoL. Each dimension considered in this article, such as depression, cognitive impairment, or co-morbidities may significantly impact QoL, and it is of importance to continue research on that topic. Nevertheless, it may be of interest to focus on how QoL may impact other outcomes, and how to integrate QoL data in clinical care.

This review has explored several issues that still remain to be solved, such as agreement on definitions of terminology. Although progress has been made toward better understanding of schizophrenia and despite the availability of multiple antipsychotics in the past decade, the humanistic burden of the disease remains high. Patients strongly need to be supported through appropriate non-pharmacological interventions that do exist but are still inadequately used, and through the development of new pharmacological interventions that will minimize the drug-related

burden, and at least improve patients' functioning and quality of life.

Ideally, an exhaustive review would have required search and selection of all individual articles on the subject, and not only literature reviews. Therefore the main limitation of this review is that there might be several relevant articles that were not included. Nevertheless, we believe that the description and quantification provided gives a sufficiently thorough overview of the overall humanistic burden of schizophrenia, despite the challenges of identifying and summarizing findings of 200 reviews in a single publication.

In conclusion, this review highlights the existing need to provide patients and their families with supportive interventions, to improve public health education, and to target interventions in the areas of employment, financial and other support for persons with mental disorders. This would help to overcome the limitations that the illness imposes in these areas, ensure better treatment and management outcomes, and above all reduce the humanistic burden of schizophrenia.

Contributors

A. Millier, D. Chauhan and N. Cadi-Soussi designed the study and wrote the protocol. A. Millier and U. Schmidt managed the literature searches and analyses. A. Millier wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

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