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Mortality in mental disorders: are we approaching to close the gap respect to other medical specialties? The case of schizophrenia

Summary

Objectives

To selectively review data on the effect of antipsychotic treatment on mortality in schizophrenia.

Methods

The authors performed a search of relevant registry-based and population-based studies, systematic reviews and meta-analyses, randomized controlled trials directly or indirectly assessing the impact of antipsychotic treatment on mortality in schizophrenia.

Results

Antipsychotics, particularly long-acting preparations such as paliperidone palmitate, might be beneficial in reducing mortality risk in schizophrenia.

Conclusions

Although data on the effect of antipsychotics on mortality are encouraging, the field of psychiatry is still far from achieving results in line with what observed in other areas of medicine (for instance in oncology and cardiology). Only the implementation of accurate clinical monitoring and a stronger engagement of the medical field in the care of people affected by mental disorders, will overcome the scandal of the underestimation of their physical health problems and the undeniable disparities they meet when specific treatments for physical disorders with an important impact on survival are needed.

Key words

Schizophrenia • Antipsychotics • Long-acting injectable • Mortality • Stigma • Treatment gap • Physical comorbidity

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Schizophrenia is a severe and lifelong disorder characterized by periods of largely partial remission alternated with periods of relapse in approximately three-quarters of cases¹. Approximately 80% of patients relapse within 5 years of the initial episode² and symptomatic remission rates, evaluated according to defined stringent criteria, are as low as 23% among chronic patients^{3,4}. Schizophrenia is a cause of significant disability⁵ due to a frequently impaired functioning⁶. The latter is explained by a highly complex interplay between illness-related variables, personal resources and contextual variables^{7,8}. In turn, impaired functioning seems to be the main factor explaining the quite low rate of recovery (14%) found on average among patients affected by schizophrenia⁹. Taking into account these data, the tremendous human, economic and social costs of the illness are not surprising. Schizophrenia has a heavy socio-economic burden worldwide, being the 8th leading cause of disability-adjusted life years (DALYs) in the age group 15-44 years, and accounting for 1.1% of total DALYs and 2.8% of total years lived with disability (YLDs)¹¹. The eco-

conomic burden of the illness has been estimated to range from 0.02% to 1.65% of gross domestic product¹². In Europe, the annual cost per patient ranges from €533 in Ukraine to €13,704 in the Netherlands¹³. In Italy, the total economic burden has been estimated at €2.7 billion, with 50.5% due to indirect costs and 49.5% to direct costs¹⁴. Although the economic impact of schizophrenia is remarkable and to some extent quantifiable, the so-called “humanistic burden” caused by subjective suffering, stigma, discrimination and poor quality of life of patients and families, is virtually inestimable¹⁵. In addition to these undoubtedly high and well-known illness-related problems, the reduction in life expectancy, an extremely serious burden of schizophrenia, seems to have been somewhat overlooked, if not by the scientific literature, certainly by the extended field of medicine and by the public opinion. Indeed, research data show a markedly high physical comorbidity and relevant premature mortality in individuals affected by schizophrenia, with a 15-20 year shorter life expectancy compared to the general population¹⁶. This gap has been prevalently attributed to natural causes of death, among which appear prominent those attributable, in particular, to cardiovascular diseases¹⁷. Unhealthy lifestyles, such as smoking, inadequate diet, sedentary habits, lower healthcare fostered by social stigma against people with mental illnesses, drug side effects, and biological factors such as genetic predisposition and accelerated aging have been indicated as determinants of the increasing mortality gap between people affected by schizophrenia and the general population. Indeed, in recent years a 37% increase of the standardized mortality ratio (SMR) has been observed in schizophrenia, with a rise from the 2.2 recorded in pre-1970s studies to the 3.0 of post-1970s reports¹⁸. At variance with schizophrenia, increased life expectancy has been observed for a number of severe medical conditions including breast cancer¹⁹, HIV/AIDS²⁰, and, in particular, ischemic heart disease and acute myocardial infarction, with mortality for the latter being reduced by 60-80% over the last 30 years in Europe^{21,22}. The latter trends are highly impressive when compared to data specifically relating to schizophrenia and other severe mental disorders, which display a much lower decline in mortality from circulatory diseases (from 35% to 42%) than for the general population²³.

It is an acknowledged fact that mortality is the strongest outcome measure in medicine, hence representing a gold standard of clinical performance; however, psychiatry has invariably encountered difficulty in demonstrating the potential efficacy of the therapeutic methods applied in improving this end-point, with the sole exception of the lowering of suicide mortality in schizophrenia due to clozapine²⁴, and in mood disorders due

to lithium salts²⁵. The reduction of mortality has long represented a relevant indicator of outcome in mental health, a field where policies and services are evaluated, amongst other indicators, by their effectiveness in reducing suicide rates. Unnatural deaths, however, provide only a partial picture of the life expectancy of a vulnerable population, given that natural causes of death contribute prevalently to increased mortality. The possibility of reducing overall mortality in patients with severe mental disorders, and particularly schizophrenia, has long been questioned, with data collected in recent years (Tab. I) suggesting that psychiatry is gradually closing the gap with other medical specialties. Indeed, data from observational studies have shown that the use of antipsychotics is associated with a lower mortality in treated patients²⁶⁻³⁴, compared to untreated individuals. Further, evidence emerging from meta-analyses and systematic reviews of randomized controlled trials (RCTs) shows lower mortality rates during antipsychotic treatment than during placebo³⁵⁻³⁷. Conversely, a recent meta-analytic study investigating long acting injectable antipsychotics (LAI) reported no difference versus placebo in the incidence of all-cause death and death due to suicide³⁸. However, in a subgroup meta-analysis of only short duration RCTs (≤ 13 weeks), LAIs exhibited a lower incidence for all-cause deaths compared to placebo³⁸. It should be noted that the increasing mortality gap observed in schizophrenia has been partly attributed to side effects of antipsychotics, with particular reference to induced weight gain and metabolic syndrome and the consequent increased of cardiovascular risk³⁹. Strong support was provided to the notion of a beneficial effect of antipsychotic treatment on mortality by a very recent prospective study of more than 29,000 patients affected by schizophrenia followed for 5-7 years; the results revealed an approximately 40% lower mortality rate amongst schizophrenia patients taking antipsychotics compared to those who were not receiving these treatments⁴⁰. Moreover, the use of LAI antipsychotics was associated with an approximately 30% lower risk of death compared with oral use of the same medication; extrapolation of these results would correspond to a difference of approximately 10% in absolute risk over a 15-20 year time span⁴⁰. The latter finding suggests that the excessive mortality recorded for patients affected by schizophrenia is more likely associated with a lack of antipsychotic therapy rather than with the presence of antipsychotic treatment. Furthermore, the use of second generation LAIs, in particular paliperidone palmitate, might lower mortality rates in schizophrenia⁴⁰. The time has arrived for psychiatry to overcome premature mortality of people suffering from severe mental disorders such as schizophrenia. Research data tell us that antipsychotics do not exert a

TABLE I. Effect of treatments on mortality in schizophrenia.

Authors, year of publication, country, (reference)	Study design	Sample	Main findings
Tiihonen J et al., 2009, Finland ²⁶	Registry based prospective cohort study	2,230 schizophrenic patients consecutively hospitalized for the first time	During an average follow-up of 3.6 years mortality was markedly raised in patients not taking antipsychotics (Adjusted RR 12.3, 95% CI 6.0 to 24.1) and the risk of suicide was high (37.4, 5.1 to 276).
Tiihonen J et al., 2009, Finland ²⁷	Registry based prospective cohort study	66,881 schizophrenic outpatients	Long-term cumulative exposure (7-11years) to any antipsychotic. Treatment is associated with lower mortality than is no drug use (HR 0.81, 95% CI 0.77-0.84)
Tiihonen J et al., 2011, Finland ²⁸	Registry based prospective cohort study	2,588 schizophrenic patients consecutively hospitalized for the first time	Use of any antipsychotic compared with no antipsychotic was associated with lower mortality (adjusted hazard ratio = 0.45, 95% CI = 0.31-0.67).
Tiihonen J et al, 2012, Finland ²⁹	Registry based prospective cohort study	2,588 schizophrenic patients consecutively hospitalized for the first time	Compared with antipsychotic monotherapy, concomitant use of 2 or more antipsychotics was not associated with increased mortality (HR, 0.86; 95% CI, 0.51-1.44). Antidepressant use was not associated with a higher risk of mortality (HR, 0.57; 95% CI, 0.28-1.16) and was associated with markedly decreased suicide deaths (HR, 0.15; 95% CI, 0.03-0.77). Benzodiazepine use was associated with a substantial increase in mortality (HR, 1.91; 95% CI, 1.13-3.22)
Tiihonen J et al., 2016, Sweden ³⁰	Registry based prospective cohort study	all individuals 16-65 years of age with a schizophrenia diagnosis (n = 21,492)	Compared with no exposure, both moderate (adjusted hazard ratio = 0.59, 95% CI = 0.49-0.70) and high (adjusted hazard ratio = 0.75, 95% CI = 0.63-0.89) antipsychotic exposures were associated with substantially lower overall mortality. Moderate antidepressant exposure was associated with a lower mortality adjusted hazard ratio (0.85, 95% CI = 0.73-0.98), and high exposure, even lower (adjusted hazard ratio = 0.71, 95% CI = 0.59-0.86). Exposure to benzodiazepines showed a dose-response relationship with mortality (hazard ratios up to 1.74 [95% CI = 1.50-2.03])
Torniainen M et al., 2015, Sweden ³¹	Registry based prospective cohort study	All individuals with schizophrenia diagnoses before year 2006 (n = 21,492), aged 17-65 years, and persons with first-episode schizophrenia during the follow-up (n = 1,230)	The highest overall mortality was observed among patients with no antipsychotic exposure (hazard ratio [HR] = 6.3, 95% CI: 5.5-7.3), followed by high exposure (> 1.5 DDD/day) group (HR = 5.7, 5.2-6.2), low exposure (< 0.5 DDD/day) group (HR = 4.1, 3.6-4.6), and moderate exposure (0.5-1.5 DDD/day) group (HR = 4.0, 3.7-4.4) The highest excess overall mortality was observed among first-episode patients with no antipsychotic use (HR = 9.9, 5.9-16.6)
Baandrup L et al., 2010, Denmark ³²	Population-based nested case-control study	27,633 patients with ICD-8- and ICD-10-diagnosed schizophrenia or other mainly non-affective psychoses aged 18-53 years	Risk of natural death did not increase with the number of concurrently used antipsychotic agents compared with antipsychotic monotherapy (no antipsychotics: adjusted odds ratio[OR] = 1.48 [95% CI, 0.89-2.46]; 2 antipsychotics: OR = 0.91 [95% CI, 0.61-1.36]; 3 or more antipsychotics: OR = 1.16 [95% CI, 0.68-2.00])

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Authors, year of publication, country, (reference)	Study design	Sample	Main findings
Crump C et al., 2013, Sweden ³³	Registry based prospective cohort study	8,277 patients with schizophrenia, followed for 7 years (2003-2009) for mortality and comorbidities diagnosed in any outpatient or inpatient setting nationwide	Patients affected by schizophrenia had an elevated mortality from ischemic heart disease (adjusted hazard ratio for women, 3.33 [95% CI = 2.73-4.05]; for men, 2.20 [95% CI = 1.83-2.65]) and cancer (adjusted hazard ratio for women, 1.71 [95% CI = 1.38-2.10]; for men, 1.44 [95% CI = 1.15-1.80]). Lack of antipsychotic treatment was associated with elevated mortality
Vanasse A et al., 2016, Canada ³⁴	Retrospective cohort study using administrative data	18,869 adult patients with SZ and starting antipsychotic drugs between January 1998 and December 2005	Quetiapine and not using any antipsychotics were associated with an increased risk of mental and physical health events as compared to other drugs
Baxter AJ et al., 2016, International study ³⁵	Meta-review of 16 systematic reviews of controlled studies		Antipsychotic and antidepressant medications had some protective effect on mortality, subject to treatment adherence
Khan A et al., 2007, USA ³⁷	Review of FDA safety data from clinical trials conducted from 1982 to 2002	16,791 adult patients with schizophrenia	The mortality rate for patients assigned to placebo treatment was significantly higher ($p < 0.05$) than for either the investigational antipsychotic (OR = 0.23, 95% CI = 0.13 to 0.45) or the active control group (OR = 0.19, 95% CI = 0.08 to 0.45)
Khan A et al., 2014, USA ³⁸	Review of FDA safety data from clinical trials conducted from 1990-2011	92,542 adult patients with a diagnosis of schizophrenia, depression, bipolar disorder, anxiety disorders, or attention-deficit/hyperactivity disorder	Compared with the general adult population, patients with schizophrenia had the highest mortality risk (3.8-fold increase), followed by patients with depression (3.15-fold increase) and bipolar disorder (3.0-fold increase). The mortality risk was not increased when patients were assigned to psychotropic agents rather than placebo except for heterocyclic antidepressants
Kishi T et al., 2016, Japan ³⁹	Categorical meta-analysis of 52 RCT	17,416 patients with schizophrenia	Neither pooled nor individual LAI-Aps differed from the placebo regarding the incidences of all-cause death (pooled LAI-APs: RR = 0.64, $p = .37$) and death due to suicide (pooled LAI-APs: RR = 0.98, $p = .98$). Only short-duration RCTs (≤ 13 wk), pooled LAI-APs exhibited a trend toward lower incidence of all-cause death than placebo (RR = 0.29, $p = .08$)
Taipale H et al, Sweden, 2017 ⁴⁰	Registry based prospective cohort study	All patients aged 16-64years with schizophrenia in Sweden ($n = 29,823$ in total; $n = 4,603$ in the incident cohort)	The lowest cumulative mortality was observed for second generation (SG) long-acting injection (LAI) use (7.5%). Adjusted hazard ratios (aHRs) compared to SG LAI use were 1.37 (95%CI 1.01-1.86) for first generation (FG) LAIs, 1.52 (1.13-2.05) for SG orals, 1.83 (1.33-2.50) for FG orals, and 3.39 (2.53-4.56) for nonuse of antipsychotics. The lowest mortality was observed for once-monthly paliperidone LAI (0.11, 0.03-0.43), oral aripiprazole (0.22, 0.15-0.34), and risperidone LAI (0.31, 0.23-0.43). In pairwise comparison, LAIs were associated with 33% lower mortality than equivalent orals (0.67, 0.56-0.80)

class-specific effect on mortality. Indeed, it seems that Lai preparation of paliperidone might have a distinct impact on this relevant outcome. However, even if used optimally, antipsychotics alone are likely not sufficient in modulating mortality risk in schizophrenia. As clinicians we must pay a greater attention to prevention through interventions on lifestyles as well as through an accurate monitoring of the physical health of our patients. But, again, even this is not enough. Taking care of the health of people with mental disorders is not just the focus of psychiatrists. We do need help from specialists in the other areas of medicine. This implies that we should do our best to overcome their fears and prejudices toward the mentally ill. The new frontier is to engage the rest of the medical field in the care of people affected

by mental disorders, in order to overcome the scandal of the underestimation of their physical health problems and the undeniable disparities they meet when specific treatments for physical disorders with an important impact on survival are needed⁴¹⁻⁴³.

Conflict of Interest

BC participated as a consultant in scientific boards and as a speaker in industry sponsored courses or symposia supported by Janssen Italy, Lundbeck Italy, Otsuka Italy, ACRAF Angelini ; FP participated as a speaker in Industry sponsored courses or symposia supported by Janssen Italy and Otsuka Italy. MM and MGO declare no conflict of interest

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