



Review

Direct healthcare cost of schizophrenia – European overview

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ABSTRACT

Purpose: To provide an overview on the magnitude of the impact of schizophrenia on the healthcare system in Europe and to gain a better understanding on the most important factors influencing the variation of costs.

Methods: Studies reporting costs and healthcare utilization among patients with schizophrenia were searched in MEDLINE (via Scopus), EMBASE (via Scopus) and Cochrane Database of Systematic Reviews on 19th January 2017.

Results: Twenty-three studies, from the 1075 references initially identified, were included in this review. The annual cost per patient ranged from €533 in Ukraine to €13,704 in the Netherlands. Notably drug costs contributed to less than 25% of the direct healthcare cost per patient in every country, which might be explained by similar pharmaceutical prices among countries due to the reference pricing system applied in Europe. Inpatient costs were the largest component of health service costs in the majority of the countries. Despite methodological heterogeneity across studies, four major themes could be identified (age, severity of symptoms, continuation of treatment/persistence, hospitalization) that have substantial impact on the costs of schizophrenia.

Conclusions: Schizophrenia represents a substantial cost for the healthcare system in Europe driven by the high cost per patient. Substantial savings could potentially be achieved by increasing investment in the following areas: (1) reducing the number of hospitalizations e.g. by increasing the efficiency of outpatient care; (2) working out interventions targeted at specific symptoms; (3) improving patient persistence and adherence in antipsychotic therapy.

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1. Introduction

Schizophrenia represents one of the leading public health issues in psychiatry. The median (10–90 percentile) of point prevalence of schizophrenia was found to be 460 (190–1000), and the incidence was found to be about 15.0 (7.7–43.0)/100,000 in a systematic review that included studies from several regions of the World [1]. A comprehensive study including data from member states of the European Union (EU-27) plus Switzerland, Iceland and Norway [2] estimated that the prevalence of psychotic disorders is 1.2% in the EU population, and the estimated number of persons affected in 2011 was 5 million.

Existing antipsychotics can achieve full remission only in about 30% of schizophrenia patients and about 20–30% are resistant [3] showing a significant unmet need. Antipsychotics cause typical adverse effects (e.g. extrapyramidal symptoms, altered glucose metabolism) especially when administered in combinations [4]. Both the high rate of resistance and the need for adverse effect treatment result in an additional burden on health systems.

Individuals with schizophrenia use a substantial amount of healthcare services. This condition imposes a significant economic burden on both the patients and their families, and on society as a whole [5]. The interpretation of the cost-of-illness studies for schizophrenia can be difficult, due to the diversity in study design, reporting and the change in prices. The most recent systematic literature review, published in 2017, gives a comprehensive overview on the global economic burden of schizophrenia [6] from a societal perspective. The study shows high differences in

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the total societal cost across the globe varying from \$US5818 in Thailand to \$US 94,587 in Norway. We believe that a more detailed overview of the direct healthcare costs among schizophrenia patients in Europe might provide additional insight into the cost drivers and the factors explaining the variation of treatment costs across patient groups within a given country. This information can highlight certain aspects of the disease and processes of care where improvements are needed, and thus inform those involved in the planning of healthcare services and prioritizing research.

The development of systems of mental healthcare in Western Europe is characterized by a common trend toward deinstitutionalization, less inpatient treatment and improvement of community services [7]. The structure and capacity planning of inpatient care has been changed dynamically in recent years, leading to the strengthening of outpatient care provisions which reduce hospital bed days. The development of health care provision in the Central and Eastern European (CEE) countries shows more inconsistencies. Recently, mental health policy began to change, new mental health legislation focusing on human rights was taken into effect and a deinstitutionalization process took place. However, in some CEE countries decrease in the number of psychiatric beds was not accompanied by adequate development of outpatient care and so it is often limited to drug prescription [8,9]. Consequently, in some countries recent trends in pharmaceutical therapies may have more influence on the direct costs of schizophrenia.

Our review included relatively recent papers published from 2010. Our aim was to balance between the requirements of HTA agencies preferring up-to-date data and to have sufficient information to draw conclusion. When initial date for inclusion was selected we considered that major policy and treatment changes with potentially significant impact on direct health care cost, including deinstitutionalization of patients, shift toward generic and/or long acting injectable drugs were implemented earlier than 2010. Hence the period since 2010 could reasonable be considered fairly homogenous period in the management of schizophrenia.

The objective of this overview was to provide an overview on the magnitude of the impact of schizophrenia on the healthcare system in Europe and to gain a better understanding on the most important factors influencing the variation of costs. More, specifically the review aims to address the following questions:

- What is the total direct healthcare cost per patient with schizophrenia in European countries?
- What is the relationship between European countries' economic wealth (GDP per capita) and direct healthcare cost per patient with schizophrenia?
- What are the most important factors associated with the variations in cost of schizophrenia across patient groups?

2. Methods

2.1. Databases and literature search strategy

The systematic literature search was conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [10], an external quality control benchmark. The literature search was performed in 19th January 2017 using MEDLINE (via Scopus), EMBASE (via Scopus) and Cochrane Database of Systematic Reviews.

The search strategy was built up as a combination of search strings related to the economic burden of schizophrenia. The detailed search strategy with number of hits can be found in [Appendix A](#). The literature search was limited to English language

papers published between 2011 and 2017. Due to the overlap of coverage between the databases, search results were de-duplicated first, followed by a title and abstract-based screening conducted by two independent reviewers (T.A., G.K). Disagreements were resolved by a third, principal researcher (A.T.Z.).

Studies were included if the *population* of interest had a clinical diagnosis of schizophrenia at any age and the study contained any cost or resource use data related to the treatment of schizophrenia. No restrictions on study *interventions*, *comparators* and study *outcomes* were used during the systematic literature review. Search results were considered in two steps. Initially, titles and abstracts of all articles were screened using the following exclusion criteria: (1) article is without abstract; (2) article is not English language paper; (3) article is editorial, letter or review; (4) article is case study/case series or the total sample number is <100; (5) article does not report data relevant to the research topic. Due to the potential limitations of electronic search strategies, reference lists of the excluded reviews were also checked for additional relevant studies. Articles deemed relevant were checked for eligibility in full-text. Publications were excluded if met any of the following criteria (1) in language other than English; (2) conference abstract or study protocol; (3) no European focus; (4) no relevant data; (5) data collection closed before the end of 2005 (i.e. if a study did not present any cost or resource use related from the period after December 31, 2005); (6) the number of the included persons < 100; (7) review article; (8) data referred from other included articles.

2.2. Data extraction

A standardized data extraction form was developed and then checked for suitability. The following information was extracted from each included study: (1) the first author and year of publication; (2) the study perspective (i.e., societal, healthcare, third party payer or patient as sub-perspectives); (3) epidemiological approach (i.e., prevalence or incidence based); (4) study design (i.e., prospective or retrospective); (5) the country; (6) the cost calculation method: bottom-up (assessing the individual cost of persons with schizophrenia) or top-down (using national or regional statistics to withdraw the cost of the disease); (7) the year of analysis, pricing year and currency; (8) the diagnostic criteria for schizophrenia; (9) the characteristics of the study sample; (10) data on healthcare utilization (i.e., resource use data on inpatient care); and (11) data on direct healthcare costs (i.e., the resource consumption in the healthcare sector associated with the provision of healthcare interventions: e.g. the cost of hospital stays, outpatient visits and drugs). Costs and resource use estimates were extracted with regards to the related follow-up period, unit, and currency.

Data was retrieved per study arm from included studies that had a comparative design investigating differences in the cost of treatment across study groups. Based on these subgroup analyses we identified important factors and cost drivers that explain the variation of treatment costs across patient groups with schizophrenia.

2.3. Reporting cost estimates

To compare costs across studies, the costs were extrapolated to calculate annual costs per patient where necessary. Cost data reported in US dollars were converted into euro (€) using the average US dollar/euro exchange rate reported by the European Central Bank (https://www.ecb.europa.eu/stats/policy_and_exchange_rates/key_ecb_interest_rates/html/index.en.html) for the year of costing. Cost estimates were reported in two ways, reflecting the different purpose of our analyses: (1) The direct healthcare cost of

schizophrenia was compared to other country specific figures such as population or GDP in the given year. In these analyses cost estimates were considered for the given year, because inflating cost to a specific year would have distorted the ratios included in the analyses (e.g. expenditure per 100,000 head, total cost per GDP or cost per patient to GDP per capita ratio). The value of the denominator can be influenced by several other factors (such as GDP growth or population change) which are irrelevant in our context, therefore we omitted uplifting costs and other indicators (GDP, population) to a specific year. (2) We also compared the cost per patient across countries. In order to ensure comparability of the results costs were inflated to a common year (2012, representing the latest year of costing among the included studies).

2.4. Assessment of methodological quality of included studies

A quality assessment of the included studies was performed with the checklist used by Larg et al. [11]. The purpose of the assessment was to check the validity of study methods considering the disease-specific cost and resource-use estimation. The

checklist consists of 3 sections; general analytical framework (11 checking questions), used methodology (7 checking questions) and conducted analysis and reporting (10 checking questions). Each included article was assigned an overall score calculated as the share of yes answers divided by the total number of 'yes', 'no' or 'unclear' answers. The detailed checklist can be found in [Appendix B](#).

3. Results

3.1. Search result

After deduplication, a total of 1076 titles and abstracts were reviewed, and 77 full articles were retrieved, from which 66 papers were identified through the screening process and 11 papers were included from the reference lists of published review/overview papers [6,12–25]. Of these, 23 met the predefined inclusion criteria and were included. A flow diagram of the systematic literature search, based on the PRISMA template [10], is presented in [Fig. 1](#).

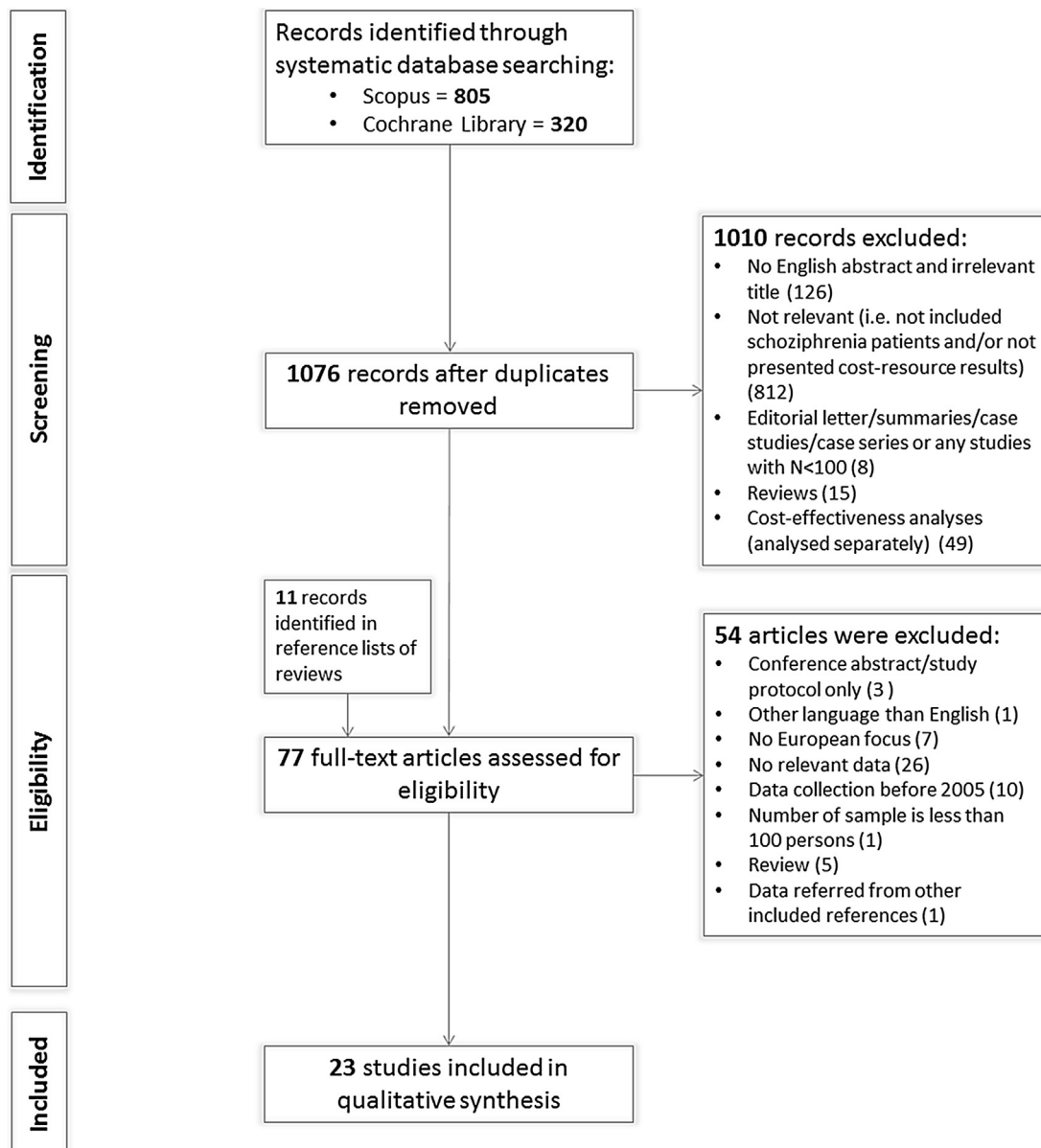


Fig. 1. The flow diagram of the systematic literature search.

3.2. Summary of included studies

Seventeen studies had two or more study arms comparing different patient groups, while six studies had a non-comparative design. The majority of the included studies assessed both the costs and healthcare utilization of schizophrenia, while six studies examined only resource use in association with the disease. The classification of each study is presented in [Appendix C.1](#).

Five studies had societal [26–30], nine had healthcare system [31–39], and nine had a third-party-payer perspective [40–48]. Eighteen studies had a retrospective [26–31,35,37–42,44–48], five studies had a prospective design [32–34,36,43], and all studies had a prevalence based approach. Although a publication date since 2010 was necessary for any study to be included according to the criteria, the oldest data analyzed in a study was from 1998 [44] and the latest data was from 2013 [35,38,45]. The countries covered by the studies are summarized in [Appendix C.2](#).

From the 23 studies, 3 did not specify the disease classification criteria used to identify patients with schizophrenia. Fifteen studies used ICD-10 [26–31,35,38–42,44,46,48], while 5 papers applied DSM-IV-based patient inclusion criteria [32,33,36,37,47]. Differences were found when considering the included ICD-10 codes. From the 15 studies using ICD-10, 4 were restrictive by limiting their study population to only those patients who had disease diagnoses ICD – F20 [28,42,46,48], while the remaining 11 studies applied a broader disease definition, admitting codes varying from F20 to F29 [26,27,29–31,35,38–41,44].

The details of the cost studies included are presented in [Table 1](#). Note that irrespective of the perspective described in the study (e.g. societal, healthcare system etc.) only direct healthcare costs were presented in our review, making data more comparable across studies.

In total 13 articles had good quality with overall scores ranging between 72% and 97%. There was no article with lower total scores than 46% or lower score than 33% in any of the domains. Data presented in lower quality articles were concerned acceptable to be included in the analysis.

3.3. Direct healthcare cost of schizophrenia

3.3.1. Total cost per country

Estimates for total direct healthcare costs for European countries were provided in five studies [28–30,36,41] presented in [Table 2](#). According to Olesen [29] the total European cost of schizophrenia in 2010 was €29 billion. The data suggest that the total cost of schizophrenia relative to the country population is threefold higher in Germany and Norway compared to France. The proportional direct cost of schizophrenia relative to the GDP is the highest in Germany (0.28%), although the EU27 countries plus Iceland, Norway and Switzerland show a similar percentage (0.21%) on average. This might be due to the relatively high prevalence (1.2%) reported by Olesen [29] compared to prevalence estimates in other studies. Comparability of data is limited due to the difference in the year of costing, cost calculation method and the estimated prevalence.

3.3.2. Cost per patient

Cost estimates from 8 studies [26,28–30,36,39,40,47] considering 8 countries and 1 study referring to the total EU27 supplemented by Iceland, Norway and Switzerland are presented in [Table 3](#) in terms of cost in € and the proportion of inpatient, outpatient, drug and other costs. The review revealed large differences in the total direct healthcare cost of schizophrenia among countries. The average annual direct medical cost per patient was estimated to be €5800 [29] in Europe. The annual cost per patient ranged from €533 in Ukraine [39] to €13,704 in the

Netherlands [47]. Notably drug costs contributed to less than 25% of the direct healthcare cost per patient in every country, while inpatient costs were the largest component of health service costs in the majority of the countries.

Ukraine is classified as a lower-middle-income country according to the World Bank Country Classification,¹ while all other countries included in the analyses are classified as high-income countries. This difference is reflected in the direct healthcare cost of schizophrenia in Ukraine compared to the EU countries listed in [Table 3](#).

To improve the cross-country comparability of the costs of schizophrenia, we plotted the results from studies providing a direct per capita cost estimate against the GDP per capita estimate of the respective country (we limited this comparison to studies using samples representative of a larger population of the given country). A moderate relationship was found between costs and economic wealth: GDP per capita explains about half of the variation in cost per patient estimates (see R^2 in [Fig. 2](#)).

3.4. Inpatient care related resource use

Average length of stay shows heterogeneity across the studies (see [Table 4](#)). Where total group-specific data were available, the duration of hospital stay ranged between 32.62 [28] and 107.7 days [44], representing a threefold difference. UK-specific length of stay was reported by 2 studies [42,44] that show a twofold difference; the average length of stay was 107.7 and 47.7 days. This might be explained by the different disease definitions used in the two papers. Comparative studies show that young age [28], antipsychotic polypharmacy [31] and oral antipsychotics (compared to LAI antipsychotics) [27] also tend to increase length of hospitalization. In Eastern Europe, the average duration ranges between 15.5 (Estonia) and 33.9 days (Serbia) according to Szkultecka-Debek [38]. Greatest number of admission frequency (mean 3.7/month) was associated with the use of LAI antipsychotics [32]. This outstanding value may be explained by several reasons: (1) a small subgroup sample size of 7 persons; (2) unfavorable baseline characteristics of the examined patient population; (3) psychiatric and general hospitalization frequencies were examined separately and the latter – that we also report in our review – may include a greater extent of services than hospitals usually provide in the form of inpatient care.

3.5. Factors associated with the variations in the direct healthcare costs

Seven comparative studies were identified investigating substantial factors that explain the differences of treatment costs among patient groups with schizophrenia. A large sample German study [48] found that the annual overall treatment cost of hospitalized patients (€16,073) was threefold higher compared to the non-hospitalized group (€3754). Direct healthcare costs were also found to be strongly related to the global assessment of functioning (GAF) score of the patient in a study with a large sample size in Sweden [26]. The study highlights that patients with serious to severe impairment (GAF score < 50) have 236% (€9315 per patient per year) higher treatment costs compared to those with no or slight symptoms (GAF score ≥ 70). According to the study of Sicras-Mainar et al. [37], patients with negative symptoms used 23% (€382 per patient per year) more healthcare resources over a period of 12 months, regarding especially primary care assistance (compared to patients without negative symptoms). In another German study [28], that analyzed a large patient sample,

¹ <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>.

Table 1
Annual direct healthcare cost of schizophrenia per patient per study group.

Reference – first author (year)	Country	Currency (as reported)	Perspective	Costing method	Year of costing	Sample population ^b	Study arm	Number of patients	Cost estimates ^d				
									Inpatient cost (%)	Outpatient cost (%)	Drug cost (%)	Other direct cost (%)	Total direct healthcare cost (€ per patient per year)
Baandrup (2012)	Denmark	EUR	Healthcare system	Top-down ^a	2009	Patients of two municipalities: Esbjerg (114,148 inhabitants) and Viborg (91,405 inhabitants)	Antipsychotic polypharmacy 2007	400	63%	21%	NR	NR	24,246
							Antipsychotic monotherapy 2007	183	69%	20%	NR	NR	16,353
							Antipsychotic polypharmacy 2008	423	56%	27%	NR	NR	17,204
							Antipsychotic monotherapy 2008	235	54%	28%	NR	NR	1261
							LAI antipsychotics	92	3%	3%	36%	58%	16,884
Bernardo (2011)	Spain	EUR	Healthcare system ^a	Bottom-up ^a	2010	Patients with perceived risk of nonadherence to oral antipsychotic therapy	LAI risperidone – subgroup	79	NR	NR	39%	NR	17,844
							LAI fluphenazine – subgroup	6	NR	NR	0%	NR	1126
							LAI zuclopenthixol – subgroup	7	NR	NR	1%	NR	10,852
							90 days before enrollment	637	27%	29%	30%	14%	4685
Cortesi (2013)	Italy	EUR	Patients' and third-party-payer's	Bottom-up ^a	2007	Schizophrenia patients throughout Italy	1st follow-up	614	23%	26%	35%	16%	4939
							2nd follow-up	603	21%	23%	34%	22%	5139
							3rd follow-up	587	17%	23%	36%	24%	4838
							All patients	2161	46%	37%	17%	0%	9728
Ekman (2013)	Sweden	EUR (=9.23 SEK)	Societal	Bottom-up	2009	Patients of Northern Stockholm Psychiatry serving 317,131 inhabitants	Men	1153	42%	39%	19%	0%	9412
							Women	1008	50%	35%	15%	0%	10,088
							GAF ≥ 70	122	32%	56%	12%	0%	3949
							GAF 50–69	652	41%	47%	12%	0%	801
							GAF < 50	104	51%	35%	14%	0%	13,264
Esposti (2012)	Italy	EUR	Societal ^a	Top-down ^a	2007, 2008	4 Local Health Units in the regions Emilia-Romagna, Toscana and Lazio, with about 1,480,000 beneficiaries	12 months before switching (to oral antipsychotic)	157	47%	5%	8%	40%	5943
							12 months after switching (to LA-risperidone)	157	24%	5%	45%	26%	5386
Esposti (2014)	Italy	EUR	Third-party-payer	Bottom-up ^a	2008, 2009	Patients enrolled from databases of 16 Local Health Units, approximately 7.5 million health assisted individuals	Schizophrenia	7457	27%	NR	27%	NR	4157
							Bipolar disorder	5486	47%	NR	35%	NR	3301

Table 1 (Continued)

Reference – first author (year)	Country	Currency (as reported)	Perspective	Costing method	Year of costing	Sample population ^b	Study arm	Number of patients	Cost estimates ^d				
									Inpatient cost (%)	Outpatient cost (%)	Drug cost (%)	Other direct cost (%)	Total direct healthcare cost (€ per patient per year)
Frey (2014)	Germany	EUR	Third-party-payer	Econometric ^a	2008	Patients of a large sickness fund (Techniker Krankenkasse, 7.9 million residents)	Schizophrenia group – third-party-payer	8224	48%	6%	14%	32%	12,251
							Control group – third-party-payer	8224	23%	34%	11%	32%	1382
			Societal	Bottom-up	2008	Patients of a large sickness fund (Techniker Krankenkasse, 7.9 million residents)	Schizophrenia group – societal	8224	49%	6%	13%	32%	12,169
							Control group – societal	8224	23%	35%	11%	31%	1412
Herbild (2013)	Denmark	USD	Healthcare system	Bottom-up ^a	2010	20% of patients characterized as extreme metabolizers, this rate is higher than would be expected from the general patient population	PGx group (treatment after the results of genotyping for CYP2D6 and CYP2C19)	103	NR	NR	17%	NR	17,565 ^c
							Control group (treatment as usual)	104	NR	NR	15%	NR	20,564
Hirjak (2016)	Germany	EUR	Healthcare system	Bottom-up ^a	2013 ^a	Patients who underwent treatment at the Department of General Psychiatry in Heidelberg in 2013	Schizophrenia	118	NR	NR	2%	NR	677
							Schizoaffective disorder	71	NR	NR	2%	NR	9889
Olesen (2012)	EU27 + Iceland, Norway, Switzerland	EUR (PPP)	Societal perspective ^a	Bottom-up & top-down	2010	EU27, Iceland, Norway and Switzerland	All patients	Approx. 5,000,000	NR	NR	NR	NR	5805
Pletscher (2015)	Switzerland	EUR (=1.21 CHF)	Societal ^a	Bottom-up	2012	Population of Northern part of canton of Zurich, 5.3% of the Swiss population	All patients	1666	66%	8%	14%	12%	9507
Sarlon (2012)	France	EUR	Healthcare system	Bottom-up ^a	Drug costs: 2007 Other costs: 1999–2000	Catchment areas of northern France (Lille), central France (Lyon and Clermont-Ferrand) and southern France (Marseille and Toulon)	All patients	288	39%	7%	16%	38%	7068
							Users of health services	280	267%	7%	16%	–190%	7104
Sicras-Mainar (2014)	Spain	EUR	Healthcare system ^a	Bottom-up	2012	Patients from six outpatient centers managed by Badalona Serveis Assistencials covering a population of 120,000 inhabitants	All patients	112	NR	20%	49%	NR	1783

Table 1 (Continued)

Reference – first author (year)	Country	Currency (as reported)	Perspective	Costing method	Year of costing	Sample population ^b	Study arm	Number of patients	Cost estimates ^d				
									Inpatient cost (%)	Outpatient cost (%)	Drug cost (%)	Other direct cost (%)	Total direct healthcare cost (€ per patient per year)
Van der Lee (2016)	Netherlands	EUR	Third-party-payer ^a	Top-down	2009–2011	All insured covered by Dutch Health Insurer Agis, 1.2 million residents in the central more urbanized part of the country	Negative symptoms present	588	NR	19%	51%	NR	2009
							Without negative symptoms	532	NR	20%	48%	NR	1627
							All patients	7392	46%	23%	7%	24%	13,705
							Group 1: continuous medical care for 3 years	54	29%	32%	10%	29%	12,162
							Group 2: continuous medical care for 2 years	936	73%	9%	2%	16%	21,503
Zaprutko (2015)	Poland	EUR (= PLN 4.07)	Healthcare system ^a	Bottom-up	2012	Adult patients hospitalized in Karol Jonscher Hospital of Poznan University of Medical Sciences (Poland)	Group 3: continuous medical care for 1 year	560	80%	4%	1%	15%	17,862
							Group 4: patients without continuous medical care (whole follow-up period 2009–2011)	496	84%	NR	0%	NR	11,095
	Ukraine	EUR (= UAH 10.55)	Healthcare system ^a	Bottom-up	Adult patients hospitalized in Psychiatric Hospital of Lviv National Medical University (Ukraine)	Polish center/all patients	50	91%	NR	7%	NR	3211	
						Ukraine center/all patients	58	92%	NR	6%	NR	534	
Zeidler (2012)	Germany	EUR	Third-party-payer	Top-down	2006	Large statutory health insurance (with approx. 6 million insured persons in 2006)	Stable patients (schizophrenia-specific costs)	8497	0%	22%	75%	3%	1489
							Unstable patients (schizophrenia-specific costs)	1449	86%	3%	10%	1%	12,533
							Stable patients (overall costs)	8497	33%	19%	41%	7%	3754
							Unstable patients (overall costs)	1449	84%	5%	10%	1%	16,073

CHF: Swiss franc; EUR: euro; GAF: global assessment of functioning; LAI: long-acting injectable; PGx: pharmacogenetic testing; PLN: Polish zloty; PPP: purchasing power parity; NR: not reported; UAH: Ukrainian hryvnia.

^a Assumed based on the presented methodology since information was not explicitly stated in the study.

^b Studies not presenting estimations for the total population or using a non-representative sample were excluded.

^c Converted from USD to EUR (1 EUR = 1.33 USD as of 2010, annual average exchange rate, European Central Bank).

^d The table represents the ratio of inpatient, outpatient and drug cost compared to the total cost, while other costs (such as community care, GP etc.) were omitted due to incomparability of data across studies. As a result the cost elements presented here do not necessarily add up to 100%.

Table 2

Total annual direct healthcare cost of schizophrenia by countries.

Reference – first author (year)	Country	Year of costing	Perspective	Cost calculation method	Total direct healthcare cost (million €)	Population size (in study year) ^b	Expenditure per 100,000 head per year (million €)	GDP (million €, year of costing) ^b	Proportion of direct healthcare cost relative to total GDP
Frey (2014)	Germany	2008	Societal ^a	Bottom-up	5028 (prevalence = 0.57%) 7057 (prevalence = 0.8%) 29,007 (PPP)	82,110,000	6.12 (prevalence = 0.57%) 8.59 (prevalence = 0.8%) 5.64 (prevalence = 1.2%)	2,561,740	0.20% (prevalence = 0.57%) 0.28% (prevalence = 0.8%) 0.21%
Olesen (2012)	EU27, Iceland, Norway and Switzerland	2010	Societal ^a	b-up & t-down	1581	514,000,000	2.48 (prevalence = 0.5%) 5.3 (prevalence = 0.17%) 3.70 (prevalence = 0.39%)	1,945,669	0.08%
Sarlon (2012)	France	2007	Healthcare system ^a	Bottom-up ^a	263 ^c	63,826,000	5.3 (prevalence = 0.17%) 3.70 (prevalence = 0.39%)	358,274	0.07%
Evensen (2015)	Norway	2011	Healthcare system ^a	Top-down	296	4,953,000	3.70 (prevalence = 0.39%)	517,411	0.06%
Pletscher (2015)	Switzerland	2012	Societal ^a	Bottom-up		7,997,000			

^a Assumed based on the presented methodology of this review since information was not explicitly stated in the study.^b Source: Eurostat: <http://ec.europa.eu/eurostat/data>.^c Total mental health treatment cost, converted from USD, 1 EUR = 1.39 USD, as of 2011, annual average exchange rate, European Central Bank.**Table 3**

Average annual direct healthcare cost of schizophrenia per patient by countries.

Reference – first author (year)	Country	Year of costing	N	Direct healthcare cost ^b		Cost contribution to total cost %				GDP per capita € (actual year)
				€ per patient (year of costing)	€ per patient (inflated to 2012)	Inpatient costs	Outpatient cost	Drug cost	Other direct cost	
Van der Lee (2016)	Netherlands	2010	7392	13,704 ^c	16,072	46%	23%	7%	25%	37,920
Frey (2014)	Germany	2008	8224	12,251	12,813	48%	6%	14%	31%	31,276
Ekman (2013)	Sweden	2009	2161	9728	10,403	46%	37%	17%	0%	33,092
Pletscher (2015)	Switzerland	2012	1666	9507	9507	66%	8%	14%	12%	65,348
Sarlon (2012)	France	2007	288	7068 ^d	7604	39%	7%	16%	38%	31,500
Olesen (2012)	EU27, Iceland, Norway and Switzerland	2010	NR	5805	6075	NR	NR	NR	NR	26,441
Esposti (2014)	Italy	2008, 2009	7457	4157	4749	27%	NR	25%	NR	26,712
Zaprutko (2015)	Poland	2012	50	3211	3211	91%	NR	7%	NR	10,277
Zaprutko (2015)	Ukraine	2012	58	533	533	92%	NR	6%	NR	3025

^a Assumed based on the presented methodology since information was not explicitly stated in the study.^b Health specific harmonised index of consumer prices (HICPs) was used to inflate all costs to the common year of 2012.^c Originally reported data referred to 3 years.^d Originally reported data referred to 6 month.

Note: studies not presenting estimations for the total population or using a non-representative sample were not displayed in this table.

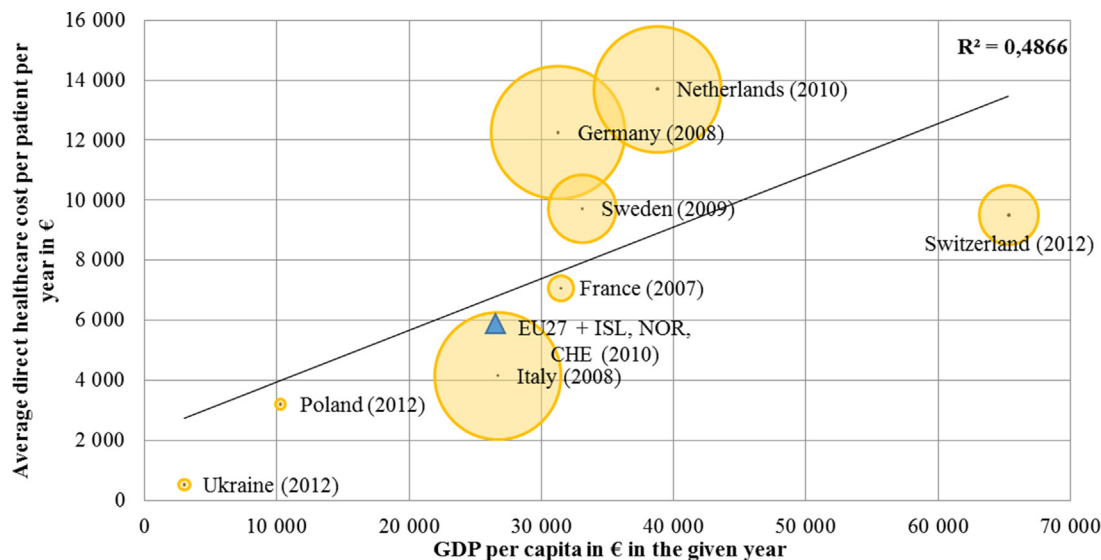
**Fig. 2.** The association between GDP per capita and average direct healthcare cost per patient. Note: The line depicts the best fit based on the linear regression of annual direct healthcare costs on actual GDP per capita in € in the given year. The size of the bubbles reflects the sample size of the study. The data for EU27 plus Iceland, Norway and Switzerland study are marked with a triangle because no data was available on the sample size.

Table 4
Hospitalization – resource use by study group where data was available.

First author (year)	Country	Analysis year (follow-up period)	Study arms (no. of sample)	Hospitalization			
				Average length of stay per admission (days)	Inpatient days ^a	Number of admissions ^b	Percentage of hospitalized patients
Frey (2014)	Germany	2008	Schizophrenia group (8224)	32.62			
			Control group (8224)	7.05			
			ATT ^c age ≤25 (NR)	29.6			
			ATT ^c age 26–45 (NR)	27.6			
			ATT ^c age 46–65 (NR)	23.3			
			ATT ^c age > 65 (NR)	16.9			
Szkulcka-Dębek (2016)	Croatia Estonia Hungary Poland Slovak Republic Slovenia Serbia	2013	Total (961)	25.3		1.0/year	
			Croatia (123)	29.4		1.6/year	
			Estonia (150)	17.2		0.7/year	
			Hungary (150)	15.5		0.8/year	
			Poland (165)	28.3		1.2/year	
			Slovakia (81)	19.6		0.7/year	
			Slovenia (172)	31.7		0.7/year	
			Serbia (120)	33.9		1.0/year	
Evensen (2015) Baandrup (2012)	Norway Denmark	2012 2007–2008 (2 years of follow-up)	Total (8399)		23.8/year		
			Antipsych. polypharmacy 2007 (400)		35.8/year	1.1/year	
			Antipsych. monotherapy 2007 (183)		26.5/year	0.6/year	
			Antipsych. polypharmacy 2008 (423)		22.6/year	1.1/year	
			Antipsych. monotherapy 2008 (235)		15.8/year	0.7/year	
Bernardo (2011)	Spain	2008–2009 (1 year of follow-up)	LAI antipsychotics (92)			3.7/month	
Cortesi (2013)	Italy	2006–2007 (1 year of follow-up)	90 days before enrollment (637)			0.6/month	11.90%
			1st follow-up (12 ± 2 weeks after enrollment) (614)			0.2/month	7.20%
			2nd follow-up (36 ± 2 weeks after enrollment) (603)			0.1/month	6.60%
			3rd follow-up (52 ± 2 weeks after enrollment) (587)			0.1/month	8.40%
Esposti (2012)	Italy	2006–2008 (1 year of follow-up)	12 months before switching (oral antipsychotic) (157)	15		0.7/year	43.90%
			12 months after switching (to LA-risperidone) (157)	12		0.37/year	20.40%
Esposti (2014)	Italy	2008–2009 (1 year of follow-up)	Schizophrenia (follow-up 12 months) (7457)	15.5			17.90%
			Bipolar disorder (follow-up 12 Months) (5486)	4.2			26.20%

Table 4 (Continued)

First author (year)	Country	Analysis year (follow-up period)	Study arms (no. of sample)	Hospitalization			
				Average length of stay per admission (days)	Inpatient days ^a	Number of admissions ^b	Percentage of hospitalized patients
Hirjak (2016)	Germany	2013	Schizophrenic patients (118)	33.07			
Uggerby (2011)	Denmark	2006	Institutionalized (2188) Non-institutionalized (20,207) Total (22,395)		24.9/year 20.4/year 20.8/year		
Zaprutko (2015)	Poland; Ukraine	2010–2011 (1 year of follow-up)	Polish center/all patient (50) Polish center/men (25) Polish center/women (25) Ukraine center/all patient (58) Ukraine center/men (25) Ukraine center/women (33)	54.64 65.64 43.64 38.43 34.8 41.18			
Pillay (2011)	United Kingdom	1998–1999 and 2008–2009 (11 years of follow-up)	Patients with schizophrenia – 2008–2009 (NR)	107.7			
Novick (2012)	Denmark Italy Portugal Spain Ireland Great Britain	NR (3 years of follow-up)	Oral typical antipsychotics (6 months before the index visit) (262) Oral typical antipsychotics (0–6 months) (262) Oral typical antipsychotics (6–12 months) (262) Oral typical antipsychotics (12–18 months) (262) Depot typical antipsychotics (6 months before the index visit) (262) Depot typical antipsychotics (0–6 months) (262) Depot typical antipsychotics (6–12 months) (262) Depot typical antipsychotics (12–18 months) (262)			0.76/6months 0.32/6months 0.26/6months 0.09/6months 0.85/6months 0.20/6months 0.18/6months 0.10/6months	34.8% of total oral typicals 22.2% of total oral typicals 15.7% of total oral typicals 7.7% of total oral typicals 39.6% of total depot typicals 13.3% of total depot typicals 10.8% of total depot typicals 8.1% of total depot typicals

Table 4 (Continued)

First author (Year)	Country	Analysis year (follow-up period)	Study arms (no. of sample)	Hospitalization			Percentage of hospitalized patients
				Average length of stay per admission (days)	Inpatient days ^a	Number of admissions ^b	
Jacobs (2015)	United Kingdom	2006 to 2011 (5 years of follow-up)	2006/07 (NR)	48			
			2007/08 (NR)	47			
			2008/09 (NR)	49			
			2009/10 (NR)	47.7			
			2010/11 (NR)	46.1			
			Pooled schizophrenia population (38,216)	47.7			
Carlton (2012)	France	1998–2002	Total population Users of health services		5.72/6months 39.10/6months		

NR: not reported.

^a Mean value.^b Excess resource use attributable to schizophrenia.^c ATI: average treatment effect on the treated.

the difference in the excess resource use attributable to schizophrenia for elderly (aged > 65 years) patients was found to be 66% higher (€18,007) than the excess cost (€10,530) attributed to schizophrenia in the overall population in 2008. In a cost-consequence study Esposti (2012) found that the mean cost per patient one year after switching to depot-injection (Larisperidone) from oral antipsychotic decreased by 9% (€557) compared to the year before. The incremental cost of polypharmacy compared to monotherapy calculated based on the data presented by Baandrup et al. [31] was €7893 and €4594 in 2007 and 2008, respectively. Van Der Lee [47] found that compliance to elective pharmaceutical therapy is associated with less acute treatment events, inpatient care and reduced costs of healthcare for patients with schizophrenia, accounting for €5700 to €9300 savings per patient annually. The factors investigated by the included comparative studies are summarized in Table 5.

4. Discussion

The direct healthcare cost of schizophrenia was investigated in a limited number of cost studies, which were considered to be of good quality and representative for a country population. The analysis provides evidence for an association between a direct per capita cost estimate and a GDP per capita estimate of various countries. The review highlights that despite the modest prevalence of schizophrenia in Europe – varying between 0.4 and 1.2% – [2,49–51] the total cost of the disease is substantial in the investigated countries due to the high cost per patient. The review also identified important cost drivers and factors associated with the variation in the treatment cost.

Hospital stay represents the most important direct cost of schizophrenia. The share of hospitalization cost among direct medical costs varied from 27% to 92% depending on the country being considered. The large difference in the share of hospitalization cost among direct medical costs might be explained by substantial differences in the analyzed healthcare systems. The comparability of the data regarding the hospital admissions and inpatient stays are very limited due to several reasons. There are substantial differences in the analyzed healthcare systems, such as health policy objectives and resources devoted to mental health care. There are also dissimilarities across the countries in their basic conceptual approach and preferences regarding the management of a disease. Furthermore socio-cultural factors (living alone, addictive behaviors, role of caregivers etc.) or educational differences and resource issues can also explain the differences observed in the results of inpatient admission indicators. However, no obvious differences in the inpatient care related resource use could be detected based on the identified surveys in the contrast of Western versus Eastern European countries, probably because the most significant development in the psychiatric care of Eastern European countries took place in deinstitutionalization [8,9] similar to the trend in the Western European countries.

The high costs of inpatient care also highlight the importance of preventing relapses that need hospitalizations. Treatment costs were strongly related to the global assessment function (GAF) score of the patient, suggesting that improvements in global functioning e.g. by means of more effective treatment for severe symptoms might reduce hospitalizations and the cost of schizophrenia. Another study [52], investigating the cost drivers of schizophrenia in six European countries, suggests that each additional negative symptom (PANSS) increases the total healthcare costs by 1.5%. However, evidence on the impact of negative symptoms on schizophrenia related to healthcare costs is still scarce. The notable difference in the excess resource use attributable to schizophrenia for elderly (aged > 65 years) patients

Table 5
Factors associated with incremental costs of schizophrenia among different patient groups.

Cost determinant	Investigated factor	Cost/patient/year	Comparator factor	Cost/patient/year	Incremental cost/patient/year	Incremental rate	Country	Reference, first author (year)
Hospitalization	Hospitalization	€16,073	Non-hospitalization	€3754	€12,319	328%	Germany	Zeidler (2012)
Symptoms	GAF score 50–69 (mild to serious symptoms)	€8010	GAF score \geq 70 (no or slight symptoms)	€3949	€4061	103%	Sweden	Ekman (2013)
	GAF score < 50 (serious symptoms to severe impairment)	€13,264	GAF score \geq 70 (no or slight symptoms)	€3949	€9315	236%	Sweden	Ekman (2013)
	Outpatients with negative symptoms	€2009	Outpatients without negative symptoms	€1627	€382	23%	Spain	Sicras-Mainar (2014)
Age	Disease-specific incremental cost ^a for elderly patients with schizophrenia (age > 65)	€18,007	Disease-specific incremental cost ^a for all patients with schizophrenia	€10,869	€7138	66%	Germany	Frey (2014)
Continuation of treatment/persistence	Switching to depot injection	€5386	Oral antipsychotic	€5943	€–557	–9%	Italy	Esposti (2012)
	Antipsychotic polypharmacy (2007, 2008)	€24,246 €17,204	Monotherapy (2007, 2008)	€16,353 €12,610	€7893 €4594	48% 36%	Denmark	Baandrup (2012)
	Persistent patients up to 3 years (continuous care)	€12,162	Non-persistent patients (<2 years of continuous care)	€21,503	€–9341	–43%	Netherlands	Van der Lee (2016)
	Persistent patients up to 3 years (continuous care)	€12,162	Non-persistent patients (<1 year of continuous care)	€17,862	€–5700	–32%	Netherlands	Van der Lee (2016)

GAF: global assessment of functioning.

^a Compared to patients without schizophrenia.

supports the view that the growing share of elderly people implies substantially higher treatment costs for economies in Europe. One of the most important predictors of hospitalization was found to be patient persistence with the assigned drug treatment, relatively modest interruptions of continuity of care may be associated with worse outcome and higher health care costs [39,47]. Several factors were identified in the reviewed studies that can influence non-adherence and non-persistence with antipsychotic therapy. In the real-world clinical practice setting, depot formulations of typical antipsychotics were shown to be more effective than oral formulations [43,27] when prescribed for non-persistent outpatients previously receiving oral therapy, as indicated by increased persistence and therefore less hospitalization due to relapses. Another important factor associated with non-compliance of patients was polypharmacy [31]. Combining treatment with multiple antipsychotics could increase the risk of distressing side effects, lead to greater non-compliance and reduce the level of functioning, which again could increase the risk of readmission and give rise to higher costs of treatment. Discontinuation of treatment was found to be responsible for a large proportion of treatment costs in hospitalized patients with schizophrenia, therefore improving persistence and adherence in antipsychotic therapy can thus lead to cost savings by reducing the frequency and duration of hospital stay.

Based on the above findings, substantial improvement in the allocation of financial resources could potentially be achieved by increasing investment in the following areas: (1) reducing the number of hospitalizations e.g. by increasing the efficiency of outpatient care; (2) working out interventions targeted at specific symptoms; (3) improving patient persistence and adherence in antipsychotic therapy.

Our results are comparable with previous reviews presenting data on the cost of schizophrenia. The cost per patient data in Gustavsson's study [53] regarding France (€7068) is the same as the cost reported in the current review, while the data for Germany

(€5848) is about half of the amount (€12,251) reported recently by Frey [28]. The study conducted by Salize [52] shows a high variation in costs compared to our review. The costs presented for Sweden (€21,020), Germany (€16,868) and Switzerland (€36,978) are notably higher than in the studies included in our review, which may be due to different costing methodologies. Salize [52] included sheltered accommodation in total costs which represented a large proportion of the overall costs in these countries. This cost was not taken into account in our review considering it is not a direct medical cost. The review conducted by Chong et al. [54] gives detailed information on the methodological issues of COI studies and presents only aggregated data that does not include cost per patient. The most recent systematic literature review was published in 2017, shortly after our literature search was completed. Jin et al. included nine studies [26,28,30,36,41,55–58] from European countries adopting a societal perspective. The studies published in 2010 or later [26,28,30,36,41] were also identified by us, however we included in our review further studies that used healthcare perspective. Our findings related to cost drivers were similar: age, global assessment of functioning score, and hospitalizations were found to be important factors associated with higher costs. In addition we identified based on the results of the included comparative studies that continuation of treatment, persistence [27,31,47] and negative symptoms [37] also play significant role in influencing the total direct healthcare cost of schizophrenia.

The review has some limitations. Only papers in English language were selected for the review. Inclusion of further publications in other languages may improve the validity of major conclusions. Large differences could be identified in the total direct healthcare cost of schizophrenia among countries. Besides the diverse economic conditions of the investigated countries this might also be due to the different methodological approaches used in the studies. Several studies sampled patients from inpatient facilities and thus probably included the most severely impaired and expensive

patients [26–28,32,35,37,39]. Studies used different approaches (top-down, bottom-up and econometric) for the estimation of resource consumption. Although each method is valid and appropriate, the resources allocated to the disease were identified differently, which can lead to disparities in the estimation of costs. The included cost-of-illness studies had a variety of perspectives, each of which included slightly different cost items leading to different and wide range of results for the illness of schizophrenia. These perspectives measured costs to the society, healthcare system and third-party payers. Each perspective provides useful information about the costs to a particular group, although it is weakening the comparability of our findings. Purchasing power parity was not used in the analyses because in our view it does not explain the healthcare related price differences across countries appropriately (e.g. it is not used in the external reference pricing system neither). However, the association between GDP per capita and average direct healthcare cost per patient was investigated in this study to expose in what extent the economic wealth of a country explains the variation in the cost per patient.

There is a lack of generalizable information on the impact of emergence of new treatment, therefore we think that further research is needed to collect more evidence on the effects of new-generation medications.

Central and Eastern European countries are short of up-to-date COI studies. No information is available on all European countries therefore no comprehensive comparisons and analyses could be made on the cost of schizophrenia. There were only a few studies that gave estimations on country-specific total direct healthcare cost by taking into account the population and disease prevalence.

5. Conclusion

Our overview, focusing on the factors influencing the direct health care costs of schizophrenia in European countries could identify several major factors (hospitalization, symptoms, age, persistence and adherence) that have substantial impact on direct healthcare costs of schizophrenia indicating potential solutions that could contribute to a more efficient allocation of available treatment resources.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.eurpsy.2017.10.008>.

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