TECHNICAL COMMENTARY

Burden

Introduction

The burden of schizophrenia includes direct costs, indirect costs, and intangible costs. Direct costs are estimated by the amount of services used and the price of treatment. Indirect costs are estimated by the average reductions in potential future earnings of both patients and caregivers. Intangible costs are those that may be associated with the illness, such as trauma and depression.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that

some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found nine systematic reviews that met our inclusion criteria[3-11].

- Moderate to high quality evidence suggests worldwide burden of schizophrenia contributes 13.4 (95%UI 9.9 to 16.7) million years of life lived with disability to the burden of global disease.

- Moderate quality evidence suggests the global cost of schizophrenia varies worldwide; ranging from US$94 million in Puerto Rico to US$102 billion in the USA (0.02-1.65% of GDP). Indirect costs associated with productivity loss due to absenteeism, unemployment or premature mortality, contributed 50 to 85% of overall

costs. Hospitalisation costs account for the greatest proportion of direct illness costs.

- Moderate quality evidence suggests the average annual indirect cost of schizophrenia in Europe per patient is €20,664, with indirect costs contributing 44% to 58% of overall costs. Increased symptom severity was associated with increased indirect cost.

- Moderate quality evidence suggests the average annual healthcare costs for a person with medication-resistant schizophrenia is USD162,186 compared to USD8,733 for the general USA population.

- Moderate quality evidence finds the cost of relapse in the USA costs between US$6,033 and US$32,753 per relapse, and between US$8,665 and US$18,676 per relapse in Europe and Australia. Re-hospitalisation costs between US$6,383 and US$28,767 in the USA, between US$1,615 and US$39,088 in Europe, Japan and New Zealand, and between US$2,217 and $14,923 in other regions.

- Moderate to low quality evidence suggests psychosocial burden associated with schizophrenia include: stigma, marginalisation, discrimination, social withdrawal, disengagement, loneliness, fear, despair, helplessness, problems with relationships and interpersonal skills, frustrations with mental health services, problems with self-esteem and over protection, unmet needs for social reciprocity, constancy, hope and understanding, problems with finding and keeping work, and having a place to live. Facilitating factors to overcome these difficulties are: providing empathetic living spaces, work spaces and routine environments, meaningful occupations and supported employment, exercise for socialisation as well as for health reasons, trust, knowledge in advance of what is happening, training for health workers to

listen more and work in partnership and family support.

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Burden

Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, McGrath JJ, Whiteford HA

Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016

Schizophrenia Bulletin 2018; 44: 1195-203

View review abstract online

Comparison	Worldwide burden of schizophrenia.
Summary of evidence	**Moderate to high quality evidence (very large samples, unable to assess consistency, appears precise, direct) suggests worldwide burden of schizophrenia contributes 13.4 (95%UI 9.9 to 16.7) million years of life lived with disability to the burden of global disease.**

Burden of schizophrenia	
129 population-level studies Schizophrenia contributed 13.4 (95%UI 9.9 to 16.7) million years of life lived with disability to the burden of global disease. Both prevalence and disease burden peaked around 30 to 40 years of age.	
Consistency in results[‡]	Unable to assess; no measure of consistency is reported.
Precision in results[§]	Appears precise.
Directness of results[‖]	Direct

Chong HY, Teoh SL, Wu DB, Kotirum S, Chiou CF, Chaiyakunapruk N

Global economic burden of schizophrenia: a systematic review

Neuropsychiatric Disease and Treatment 2016; 12: 357-73

View review abstract online

Comparison	Global economic cost of schizophrenia.

Summary of evidence	Moderate quality evidence (unable to assess consistency or precision, large sample, direct) suggests the global annual economic cost of schizophrenia ranges from US$94 million in Puerto Rico to US$102 billion in the USA (0.02-1.65% of GDP), with indirect costs contributing 50 to 85% of these costs.
Economic outcomes	
56 population-level studies Annual costs for the schizophrenia ranged from US$94 million in Puerto Rico to US$102 billion in the USA. Indirect costs contributed to 50%–85% of the total costs associated with schizophrenia. The economic burden of schizophrenia was estimated to range from 0.02% to 1.65% of the gross domestic product of each country. Studies were mostly conducted in high-income countries.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Fasseeh A, Nemeth B, Molnar A, Fricke FU, Horvath M, Koczian K, Gotze A, Kalo Z

A systematic review of the indirect costs of schizophrenia in Europe

European journal of public health 2018; 28: 1043-9

View review abstract online

Comparison	Indirect cost of schizophrenia in Europe.
Summary of evidence	Moderate quality evidence (unable to assess consistency or precision, large sample, direct) suggests the average annual indirect cost of schizophrenia in Europe per patient is €20,664, with indirect costs contributing 44% to 58% of overall costs. Increased symptom severity was associated with increased indirect cost.
Economic outcomes	
9 population-level studies Mean annual indirect cost of schizophrenia in Europe = 20,664 Euros (range 119 to 62,034) per patient	

The average share of indirect cost was 44%, while papers that included both the cost of productivity loss by patients and by caregivers had a higher mean of 58%. Severe symptom severity caused a 2.5-fold increase in indirect costs.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Hartley S, McArthur M, Coenen M, Cabello M, Covelli V, Roszczynska-Michta J, Pitkanen T, Bickenbach J, Cieza A **Narratives Reflecting the Lived Experiences of People with Brain Disorders: Common Psychosocial Difficulties and Determinants** **PLoS ONE 2014; 9(5): e96890. doi:10.1371/journal.pone.0096890** View review abstract online	
Comparison	**Psychosocial difficulties associated with schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (unable to assess consistency or precision, small to medium-sized sample, direct) suggests the greatest psychosocial difficulties associated with schizophrenia are: stigma, marginalization, discrimination, social withdrawal, disengagement, loneliness, fear, despair, helplessness, problems with relationships and interpersonal skills (affecting family, intimate and occupational relationships), frustrations with mental health services, problems with self-esteem and overprotection, un-met needs for social reciprocity, constancy, hope and understanding, problems with finding and keeping work, and having a place to live.** **Facilitating factors to overcome these difficulties are: providing empathetic living spaces, work spaces and routine environments, meaningful occupations, exercise for socialization as well as for health reasons, supported employment, trust, knowledge in advance of what is happening, training for health workers to listen more and work in partnership and family support.**
Psychosocial difficulties	

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11 studies, (N = 182) from Australia, Canada, Italy, Spain, and USA

Greatest psychosocial difficulties were: stigma, marginalization, discrimination, social withdrawal, disengagement, loneliness, fear, despair, helplessness, problems with relationships and interpersonal skills (affecting family, intimate and occupational relationships), frustrations with mental health services, problems with self-esteem and overprotection, un-met needs for social reciprocity, constancy, hope and understanding, problems with finding and keeping work, and having a place to live.

Facilitating factors to overcome these difficulties were: providing empathetic physical and social spaces, such as living spaces, work spaces and routine environments, meaningful occupations, often outside the home such as exercise (noted to be both a way to socialize and become healthier), supported employment, trust, knowledge in advance of what is happening, training for health workers to listen more and work in partnership and family support.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC

The social and economic burden of treatment-resistant schizophrenia: a systematic literature review

International Clinical Psychopharmacology 2014; 29(2): 63-76

View review abstract online

Comparison	**Annual total healthcare costs for people with treatment-resistant schizophrenia vs. average annual healthcare costs in the USA.**
Summary of evidence	**Moderate quality evidence (unable to assess consistency or precision, large sample, direct) suggests the average annual healthcare costs for people with medication-resistant schizophrenia is USD162,186 compared to USD8,733 for the general USA population.**

Healthcare costs
65 studies, N = 4,985
Treatment-resistant schizophrenia: USD162,186

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USA average: USD8,733	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Knapp M, Mangalore R, Simon J

The global costs of schizophrenia

Schizophrenia Bulletin 2004; 30(2): 279-293

View review abstract online

Comparison	**Estimated cost of schizophrenia worldwide.**
Summary of evidence	**Moderate to low quality evidence (unable to assess consistency or precision, large samples, indirect) suggests the global cost of schizophrenia varies worldwide, in the 1990's costing Australia up to $114 million and the USA up to $15 billion annually. Hospitalisation costs account for the greatest proportion of direct illness costs.**

Economic outcomes

National total costs of schizophrenia:

Australia: 2 studies estimate the national total costs of schizophrenia (1976-1990) to range from $56-114.3 million. The annual cost per patient was estimated at $33,560.

USA: 3 studies estimate the national total costs of schizophrenia (1975-1990) to range from $8.5-15.2 billion. The annual cost per patient was estimated at $13,000-$31,000.

Canada: 1 study estimated the national total costs of schizophrenia (1996) to be $1.23 billion. The annual cost per patient was estimated at $11,300.

United Kingdom: 3 studies estimate the national total costs of schizophrenia (1990-1997) to range from £84 million – £1.8billion. The annual cost per patient was estimated at £23,000.

Cost of inpatient services:

Australia: 1 study estimated the hospitalisation cost to be 28% of direct health care costs.

USA: 1 study estimated the hospitalisation cost to be 68% of direct health care costs.

Canada: 1 study estimated the hospitalisation cost to be 54% of direct health care costs.	
United Kingdom: 3 studies estimated the hospitalisation cost to range from 51-74% of direct health care costs.	
Europe: 12 studies estimated the hospitalisation cost to range from 16-93% of direct health care costs.	
Cost of medications:	
USA: 1 study estimated the medication cost to be 2.3% of direct health care costs.	
Canada: 1 study estimated the medication cost to be 4.7% of direct health care costs.	
United Kingdom: 3 studies estimated the medication cost to range from 2-5% of direct health care costs.	
Europe: 8 studies estimated the medication cost to range from 1-13% of direct health care costs.	
Nigeria: 1 study estimated the medication cost to be 61% of direct health care costs.	
Cost of lost productivity:	
USA: 2 studies estimated the annual cost of lost productivity to range from $9-12 billion.	
Canada: 1 study estimated the annual cost of lost productivity to be $1.23 billion.	
United Kingdom: 3 studies estimated the annual cost of lost productivity to be £82 million.	
Family impact costs:	
USA: 2 studies estimated the family costs to be 17% of indirect health care costs.	
United Kingdom: 1 study estimated the family costs to be 2.3% of indirect health care costs.	
Europe: 3 studies estimated the family costs to be 12-85% of indirect health care costs.	
Nigeria: 1 study estimated the family costs to be 48% of indirect health care costs.	
Cost of criminal justice system:	
USA: 1 study estimated the costs of the justice system to be $464 million.	
Canada: 1 study estimated the costs of the justice system to be $70 million.	
United Kingdom: 3 studies estimated the costs of the justice system to be £1.3 million.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Indirect; estimated costs

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Pennington M, McCrone P

The Cost of Relapse in Schizophrenia

PharmacoEconomics 2017; 35: 921-36

[View review abstract online](#)

Comparison	Estimated cost of relapse and re-hospitalisation.
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) finds the cost of relapse in the USA costs between US$6,033 and US$32,753 per relapse, and between US$8,665 to US$18,676 per relapse in Europe and Australia. Re-hospitalisation costs between US$6,383 to US$28,767 in the USA, between US$1,615 to US$39,088 in Europe, Japan and New Zealand, and between US$2,217 to $14,923 in other regions.**

Cost of relapse and re-hospitalisation

Any relapse

16 studies, N = 54,101

USA: cost per relapse = US$6,033 to US$32,753 over 12 to 15 months

Europe and Australia: cost per relapse = US$8,665 to US$18,676 over 6 to 12 months

The relative cost increase associated with relapse ranged from 103% to 1137% of costs for patients who had not relapsed.

Hospitalisation

43 studies, N > 1million

USA: cost per hospitalisation = US$6,383 to US$28,767

Europe, Japan and New Zealand: cost per hospitalisation = US$1,615 to US$39,088

Other countries: cost per hospitalisation = US$2,217 to $14,923

There were no significant changes in costs over time.

There was a significant association between hospitalisation cost and gross domestic product of each country.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.

Directness of results	Direct

Sun SX, Liu GG, Christensen DB, Fu AZ

Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States

Current Medical Research and Opinion 2007; 23(10): 2305-2312

View review abstract online

Comparison	**Estimated cost of antipsychotic non-adherence in the USA.**
Summary of evidence	**Moderate quality evidence (unable to assess consistency or precision, large samples, direct) suggests the cost of re-hospitalisation due to non-adherence may range from US$1392 million to US$1826 million in one year (based on 2005 estimates).**

Costs of non-adherence

7/7 studies (N = not reported) showed that antipsychotic non-adherence was related to an increase in hospitalisation rate (relapse), hospital days or hospital costs.

The estimated 2005 US national re-hospitalisation costs related to antipsychotic non-adherence were reported in 3 studies, and ranged from US$1,392 million to $1,826 million.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[12].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardized mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[12].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[13]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

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‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I² is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[12];

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[14].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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