TECHNICAL COMMENTARY

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Infectious diseases

Introduction

Infectious diseases include the human immunodeficiency virus infection (HIV), and hepatitis viruses, such as hepatitis B and hepatitis C. Schizophrenia is associated with an increased risk of these infectious diseases when compared to the general population, which may be explained by more high-risk behaviours.

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 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 prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews rated as having 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 or if there is a dose dependent response. We have also taken into account sample size and whether results are 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 five systematic reviews that met our inclusion criteria[3-7].

- Moderate to low quality evidence finds medium-sized increased rates of hepatitis B and C in people with schizophrenia compared to controls without schizophrenia.
- Moderate quality evidence suggests the overall prevalence of HIV is ~8%, hepatitis B is ~16%, and hepatitis C is ~7% in people with any severe mental illness. HIV prevalence rates are similar in males and females, while males are more likely than females to have hepatitis B or C.
- Moderate to low quality evidence shows prevalence rates of HIV and hepatitis vary across regions; HIV = 1.5% in Asia, 1.9% in Europe, 2.7% in Central and South America,

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

6% in North America, and 19.2% in Africa. Hepatitis B = 2.2% in North America, 2.6% in Central and South America, 2.7% in Europe, and 9.7% in Asia. Hepatitis C = 3.0% in Central and South America, 3.1% in Oceania, 4.4% in Asia, 4.9% in Europe, and 17.4% in North America. Authors report these rates are higher than general population rates in regions with low overall prevalence rates, but similar in regions with high overall prevalence rates.

- Moderate quality evidence shows the lifetime prevalence of HIV testing is on average around 57% in people with a severe mental illness.
- Moderate quality evidence finds an increased rate of toxoplasmosis or toxocariasis in people with schizophrenia.

Ayano G, Tulu M, Haile K, Assefa D, Habtamu Y, Araya G, Yohannis Z

A systematic review and meta-analysis of gender difference in epidemiology of HIV, hepatitis B, and hepatitis C infections in people with severe mental illness

Annals of General Psychiatry 2018; 17

View review abstract online

Comparison	**Overall and gender differences in the prevalence of HIV and hepatitis in people with a severe mental illness. The sample also included people with bipolar disorder and other psychoses.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent, imprecise, direct) suggests the overall prevalence of HIV is ~8%, hepatitis B is ~16%, and hepatitis C is ~7% in people with a severe mental illness. HIV prevalence rates are similar in males and females, while males are more likely than females to have hepatitis B or C.**
HIV and hepatitis	
Overall prevalence of HIV; 13 studies, N = 9,855, prevalence = 7.59%, 95%CI 4.82 to 11.75, I^2 = 96%, $p < 0.001$ *No significant differences in the prevalence of HIV in women (8.25%) vs. men (7.04%);* OR = 1.42, 95%CI 0.96 to 2.10, $p > 0.05$, I^2 = 57%, $p = 0.007$ *Overall prevalence of hepatitis B;* 4 studies, N = 1,083, prevalence = 15.63%, 95%CI 7.19 to 30.69, I^2 = 95%, $p < 0.001$ *The prevalence of hepatitis B was higher in men (18.91%) than in women (12.02%);* OR = 1.72, 95%CI 1.17 to 2.53, $p < 0.05$, I^2 = 0%, $p = 0.88$ *Overall prevalence of hepatitis C;* 5 studies, N = 6,638, prevalence = 7.21%, 95%CI 4.44 to 11.50, I^2 = 95%, $p < 0.001$ *The prevalence of hepatitis C was higher in men (9.16%) than in women (5.43%);* OR = 2.01, 95%CI 1.16 to 3.20, $p < 0.05$, I^2 = 55%, $p = 0.06$ Authors report no evidence of publication bias.	
Consistency	Mostly inconsistent
Precision	Imprecise

Directness	Direct

Dare LO, Bruand PE, Gerard D, Marin B, Lameyre V, Boumediene F, Preux PM

Associations of mental disorders and neurotropic parasitic diseases: a meta-analysis in developing and emerging countries

BMC public health 2019; 19: 1645

View review abstract online

Comparison	**Rates of toxoplasmosis or toxocariasis in people with schizophrenia vs. controls.** **Some samples included people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, direct, inconsistent, imprecise) finds an increased rate of toxoplasmosis or toxocariasis in people with schizophrenia.**
Toxoplasmosis or toxocariasis	
Significant medium-sized effect of increased rate of toxoplasmosis and/or toxocariasis in people with schizophrenia; 16 studies, N = 3,558, OR = 2.3, 95%CI 1.7 to 3.2, I^2 = 75%	
Consistency	Inconsistent
Precision	Imprecise
Directness	Direct

Hughes E, Bassi S, Gilbody S, Bland M, Martin F

Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness: a systematic review and meta-analysis

Lancet Psychiatry 2016; 3: 40-48

View review abstract online

Comparison	**Regional differences in the prevalence of HIV and hepatitis in people with a severe mental illness. The sample included schizophrenia, bipolar disorder and other psychoses.**
Summary of evidence	**Moderate to low quality evidence (unable to assess sample size, consistency or precision, direct) suggests prevalence rates of HIV and hepatitis in people with severe mental illnesses vary across regions; HIV = 1.5% in Asia, 1.9% in Europe, 2.7% in Central and South America, 6% in North America, and 19.2% in Africa. Hepatitis B = 2.2% in North America, 2.6% in Central and South America, 2.7% in Europe, and 9.7% in Asia. Hepatitis C = 3.0% in Central and South America, 3.1% in Oceania, 4.4% in Asia, 4.9% in Europe, and 17.4% in North America.** **Authors report these rates are higher than general population rates in regions with low overall prevalence rates, but similar in regions with high overall prevalence rates.**
HIV and hepatitis	
North America; HIV: 21 studies, prevalence = 6.0%, 95%CI 4.3 to 8.3 Hepatitis B: 2 studies, prevalence = 2.2%, 95%CI 0.5 to 9.9 Hepatitis C: 13 studies, prevalence = 17.4%, 95%CI 13.2 to 22.6 *Europe;* HIV: 5 studies, prevalence = 1.9%, 95%CI 0.8 to 4.8 Hepatitis B: 4 studies, prevalence = 2.7%, 95%CI 1.8 to 3.9 Hepatitis C: 6 studies, prevalence = 4.9%, 95%CI 3.0 to 7.9 *Oceania;* Hepatitis C: 1 study, prevalence = 3.1%, 95%CI 1.0 to 9.3 *Africa;* HIV: 8 studies, prevalence = 19.2%, 95%CI 14.4 to 25.2 *Asia;* HIV: 5 studies, prevalence = 1.5%, 95%CI 1.0 to 2.4 Hepatitis B: 10 studies, prevalence = 9.7%, 95%CI 0.6 to 15.3 Hepatitis C: 7 studies, prevalence = 4.4%, 95%CI 2.8 to 6.9 *Central and South America;* HIV: 5 studies, prevalence = 2.7%, 95%CI 0.8 to 8.2	

Hepatitis B: 3 studies, prevalence = 2.6%, 95%CI 1.0 to 6.1 Hepatitis C: 2 studies, prevalence = 3.0%, 95%CI 1.8 to 5.0 Authors report that the prevalence of HIV and hepatitis in people with serious mental illness was higher than in the general population in places with low prevalence of HIV and hepatitis, such as in the USA and Europe, but similar to the general population in regions with high prevalence of HIV and hepatitis (Africa for HIV and southeast Asia for hepatitis B virus and hepatitis C virus).	
Consistency	Unable to assess; no measure of consistency is reported.
Precision	Unable to assess; no measure of precision is reported.
Directness	Direct

Lluch E, Miller BJ

Rates of hepatitis B and C in patients with schizophrenia: A meta-analysis

General Hospital Psychiatry 2019; 61: 41-6

View review abstract online

Comparison	**Rates of hepatitis B and C in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, some inconsistency, imprecise direct) finds medium-sized increased rates of hepatitis B and C in people with schizophrenia.**
Toxoplasmosis or toxocariasis	
Significant medium-sized effects of increased rates of hepatitis B and C in people with schizophrenia; Hepatitis B: 4 studies, N not reported, OR = 2.36, 95%CI 1.61 to 3.47, $p < 0.001$, $I^2 = 0\%$ Prevalence in patients = 7% Hepatitis C: 5 studies, N = not reported, OR = 3.29, 95%CI 1.50 to 7.23, $p = 0.003$, $I^2 = 99\%$ Prevalence in patients = 6% Meta-regressions showed no moderating effects of sex, age, and geography.	
Consistency	Consistent for hepatitis B only.
Precision	Imprecise

Directness	Direct

Senn T, Carey M

HIV testing among individuals with severe mental illness: review, suggestions for research, and clinical implications

Psychological Medicine 2009; 39: 355-363

View review abstract online

Comparison	**Prevalence of HIV testing amongst people with a severe mental illness. The sample included schizophrenia, bipolar disorder and other psychoses.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests the lifetime prevalence of HIV testing in patients with an SMI averages around 57%.** **Note: authors reported that HIV interventions promoting testing may lead to an increase in testing levels.** **Authors also suggest that homelessness, engaging in risky behavior, and having greater social support may increase testing, while fear of the results, having misgivings about sensitivity or stigma, or believing risk of HIV is low may decrease testing.**

HIV testing rates

Prevalence of HIV testing in patients with severe mental illness.

Tested while hospitalised;

1 study (N = 655) found 9.5% of individuals with an SMI had been HIV tested while hospitalised

Tested in the past 3 months;

1 study (N = 5,890) found 38% of individuals with an SMI had been HIV tested

Tested in the past 6 months;

1 study (N = 300) found 17% of individuals with an SMI had been HIV tested

Tested in the past year;

3 studies (N = 2,104) found 17.6 to 47% of individuals with an SMI had been HIV tested

Tested over the lifetime; 13 studies (N = 3,520) found 11 to 89% of individuals with an SMI had been HIV tested *Individuals with an SMI compared to individuals without an SMI;* 1 study (N = 1,834) found 46.5% of individuals with an SMI vs. 31% without had been HIV tested
HIV testing predictors
Authors report the following possible predictors for increasing testing by individuals with an SMI; Homelessness, engaging in risky behaviour (drug use, high risk sexual behaviour), having greater social support, having a stronger therapeutic alliance with the primary clinician, receiving services in an urban environment (vs. suburban), using treatment services and knowing someone who had acquired or died from AIDS.
Authors report the following possible predictors for decreasing testing by individuals with an SMI; Believing risk of HIV is low, fear of the results, misgivings about provider sensitivity or stigma.
Authors report the following possible predictors for increasing return for test results; Higher education, not having a disability (other than mental illness), being tested previously, not having an STD, having fewer drug problems and having previously received an HIV test result.
Interventions to promote testing among individuals with an SMI
1 study developed the 'Screen, Test, Immunise, Reduce risk, and Refer' (STIRR) intervention which reported: At one mental health center, 136 out of 173 (79%) patients were tested At a second mental health center, 65 out of 99 (66%) patients with a dual diagnosis were tested. 1 study reported that 78% of patients in a state psychiatric hospital were tested for HIV after the initiation of a voluntary hepatitis and HIV screening program.

Consistency in results	Unable to assess
Precision in results	Unable to assess
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, HIV = human immunodeficiency virus, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SMI = severe mental illness, vs. = versus

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[8].

† 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. Standardised 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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[8].

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[9]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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.

‡ 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. I^2 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. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[8];

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

§ 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[10].

‖ 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.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Senn T, Carey M (2009): HIV testing among individuals with a severe mental illness: Review, suggestions for research, and clinical implications. *Psychological Medicine* 39: 355-63.
4. Hughes E, Bassi S, Gilbody S, Bland M, Martin F (2016): Prevalence of HIV, hepatitis B, and hepatitis C in people with severe mental illness: A systematic review and meta-analysis. *The Lancet Psychiatry* 3: 40-8.
5. Ayano G, Tulu M, Haile K, Assefa D, Habtamu Y, Araya G*, et al.* (2018): A systematic review and meta-analysis of gender difference in epidemiology of HIV, hepatitis B, and hepatitis C infections in people with severe mental illness. *Annals of General Psychiatry* 17.
6. Dare LO, Bruand PE, Gerard D, Marin B, Lameyre V, Boumediene F*, et al.* (2019): Associations of mental disorders and neurotropic parasitic diseases: a meta-analysis in developing and emerging countries. *BMC public health* 19: 1645.
7. Lluch E, Miller BJ (2019): Rates of hepatitis B and C in patients with schizophrenia: A meta-analysis. *General Hospital Psychiatry* 61: 41-6.
8. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
9. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
10. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*