TECHNICAL COMMENTARY

Duration of untreated psychosis and outcomes

Introduction

The duration of untreated psychosis (DUP) is generally determined as the time from the onset of psychotic symptoms to initiation of treatment or first clinical presentation, when diagnosis of a first episode of psychosis (FEP) may be made. FEP is distinct from diagnosis of a first episode of schizophrenia, which requires particular symptoms to be present for a defined period, whereas FEP can refer to a number of different psychotic disorders. It has been proposed that untreated psychosis may have an inherently "toxic" effect, contributing to psychological deterioration and possibly adverse neural processes with longer DUP being associated with poorer prognosis. DUP is also thought to be a predictor of the likelihood and extent of recovery in first-episode schizophrenia. Consequently, understanding the effects of DUP is particularly important because it is potentially modifiable and thereby altering prognosis.

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 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 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 matters 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 ten systematic reviews that met our inclusion criteria[3-12].

- Moderate to high quality evidence indicates longer DUP, particularly over 9 months, is associated with more positive, negative and general symptoms, more depression and anxiety, poorer social and overall

functioning, quality of life, and response to treatment. Moderate quality evidence also suggests less likelihood of remission. Effect sizes were all small to medium-sized.

- Moderate quality evidence suggests a large effect of increased homicide and a small effect of increased deliberate self-harm with longer duration of untreated psychosis.

- Moderate quality evidence suggests brain structural anomalies in people with first-episode psychosis are not consistently associated with length of DUP.

NeuRA | Duration of untreated psychosis and outcomes | August 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Page 2

Anderson KK, Rodrigues M, Mann K, Voineskos A, Mulsant BH, George TP, McKenzie KJ

Minimal evidence that untreated psychosis damages brain structures: A systematic review

Schizophrenia Research 2015; 162: 222-233

View review abstract online

Comparison	**DUP and brain structure changes.**
Summary of evidence	**Moderate quality evidence (large sample, appears inconsistent, unable to assess precision, direct) suggests brain structural anomalies are not consistently associated with DUP.**

Brain structure	

Only 9 of 48 studies (total N = 2,813) reported a statistically significant association between brain structure changes and DUP.

6% of 264 brain structures were found to have a statistically significant association with longer DUP. These were clustered in the parietal lobe (25% of examined structures), thalamus (17% of examined structures), basal ganglia (14% of examined structures), and the frontal lobe (13% of examined structures).

Consistency in results‡	No measure of consistency is reported; appears inconsistent.
Precision in results§	Unable to assess; no measure of precision is reported.
Directness of results‖	Direct

Boonstra N, Klaassen R, Sytema S, Marshall M, De Haan L, Wunderink L, Wiersma D

Duration of untreated psychosis and negative symptoms - A systematic review and meta-analysis of individual patient data

Schizophrenia Research 2012; 142: 12-19

View review abstract online

Comparison	**DUP and negative symptoms.**

NeuRA | Duration of untreated psychosis and outcomes | August 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Page 3

Summary of evidence	Moderate to high quality evidence (large sample, some inconsistency, precise, direct) indicates longer DUP, particularly over 9 months is associated with increased negative symptom severity.
Negative symptoms	
Significant association between longer DUP and increased negative symptoms;	
16 studies, N = 3,339	
1 to 2 years: Fisher's z = 0.180, 95%CI 0.086 to 0.274, I^2 = 75.9%	
5 to 8 years: Fisher's z = 0.202, 95%CI 0.137 to 0.267, I^2 = 27.3%	
Authors report that people with a DUP shorter than 9 months showed the greatest symptom improvement over time.	
Consistency in results	Consistent in the long-term only.
Precision in results	Precise
Directness of results	Direct

Bora E, Yalincetin B, Akdede BB, Alptekin K

Duration of untreated psychosis and neurocognition in first-episode psychosis: A meta-analysis

Schizophrenia Research 2018; 193: 3-10

View review abstract online

Comparison	DUP and neurocognition.
Summary of evidence	High quality evidence (large sample, consistent, precise, direct) indicates longer DUP is associated with reduced planning and problem solving ability in people with first-episode psychosis. There were no associations with global cognition, IQ, verbal memory, visual memory, working memory, sustained attention, fluency, executive functioning-speed, and processing speed.
Neurocognition	

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Page 4

A very small but significant association with reduced planning/problem-solving ability;

12 studies, N = 1,257, r = -0.09, 95%CI -0.14 to -0.03, p = 0.003, I^2 = 0%

There were no significant associations with global cognition, IQ, verbal memory, visual memory, working memory, sustained attention, fluency, executive functioning-speed, and processing speed.

Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Challis S, Nielssen O, Harris A, Large M

Systematic meta-analysis of the risk factors for deliberate self-harm before and after treatment for first-episode psychosis

Acta Psychiatrica Scandinavica 2013; 127: 442-454

View review abstract online

Comparison	DUP and suicide attempts or other deliberate self-harm.
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, precise, direct) suggests a small effect of increased risk of deliberate self-harm with longer duration of untreated psychosis.**

Deliberate self-harm (DSH)

A small, significant effect of increased risk of DSH with increased duration of untreated psychosis;

14 studies, N not reported, SMD = 0.20, 95%CI 0.05 to 0.35, p = 0.008, I^2 = 63.2%, p = 0.001

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

NeuRA | Duration of untreated psychosis and outcomes | August 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au | Page 5
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

---

Doyle R, Turner N, Fanning F, Brennan D, Renwick L, Lawlor E, Clarke M

First-Episode Psychosis and Disengagement From Treatment: A Systematic Review

Psychiatric Services 2014; 65(50): 603-611

View review abstract online

Comparison	DUP and engagement in treatment.
Summary of evidence	**Low quality evidence (no measured provided) is uncertain as to the associations between DUP and engagement in treatment.**

Engagement in treatment
10 studies indicated that approximately 30% of individuals with first-episode psychosis or schizophrenia disengage from services (range 20-40%).
Authors report that the variations in disengagement rates is due to the differences in study setting, type of service provided, and how each study measured disengagement.
The most consistent predictors of disengagement were; comorbid substance abuse/dependence and the involvement/support of family. Less consistent predictors were; greater symptom severity, duration of untreated psychosis, and reduced insight.

Consistency in results	Unable to formally assess, appears inconsistent.
Precision in results	Unable to assess
Directness of results	Direct

Farooq S, Large M, Nielssen O, Waheed W

The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: A systematic review and meta-analysis

Schizophrenia Research 2009; 109(1-3): 15-23

View review abstract online

Comparison	DUP and symptoms, disability and mortality at ~12 months post-treatment in low and middle income countries.

Summary of evidence	High quality evidence (large sample, precise, consistent, direct) indicates longer DUP is associated with more social disability by 12 months post-treatment.
	Moderate quality evidence (inconsistent) indicates longer DUP is also associated with poorer response to treatment by 12 months.
Symptoms	
A significant, small to medium-sized association between longer DUP and more symptoms; 5 studies, N = 446, r = -0.290, 95%CI -0.483 to -0.069, $p < 0.011$, Q = 25.2, I^2 = 84%	
Social disability	
A significant, small association between longer DUP and more disability; 4 studies, N = 1,030, r = 0.195, 95%CI 0.126 to 0.262, $p < 0.000$, Q = 1.245, I^2 = 0.00	
Mortality	
1 study found patients with a DUP > 1 year had 6.7 times the mortality of those with DUP < 1 year.	
Consistency in results	Consistent for disability, inconsistent for symptoms.
Precision in results	Precise for symptoms and disability.
Directness of results	Direct

Large M, Nielssen O

Evidence for a relationship between the duration of untreated psychosis and the proportion of psychotic homicides prior to treatment

Social Psychiatry and Psychiatric Epidemiology 2008; 43(1): 37-42

View review abstract online

Comparison	**DUP and homicide.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests a large association between increased mean DUP and the proportion of homicides in people with first-episode psychosis.**
Homicide	

NeuRA | Duration of untreated psychosis and outcomes | August 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Page 7

A large association was found between increased mean DUP and increased number of homicides;

13 studies, N = 1,361, R = 0.822, R^2 = 0.676, *p* = 0.003

No significant relationship was found between average Log^{10} median DUP and the proportion of homicides.

Previous treatment vs. contact with mental health services was used as a covariate.

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	Not applicable

Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T

Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review

[View review abstract online](#)

Comparison	**DUP and symptoms, functioning, quality of life, and remission.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, consistent, precise, direct) suggests longer DUP is associated with higher ratings of depression, anxiety, negative symptoms, positive symptoms, and lower ratings of overall functioning, social functioning and quality of life (small to medium-sized effects). Moderate quality evidence (imprecise) also suggests an association with less likelihood of remission.**

Symptoms

Significant, small to medium-sized associations between longer DUP and increased symptoms by 1 year post-treatment;

Total symptoms: N = 385, *r* = 0.282, 95%CI 0.191 to 0.368, *p* < 0.05

Depression and anxiety: N = 376, *r* = 0.194, 95%CI 0.094 to 0.291, *p* < 0.05

Negative symptoms: N = 779, *r* = 0.176, 95%CI 0.106 to 0.244, *p* < 0.05

Positive symptoms: N = 777, *r* = 0.283, 95%CI 0.216 to 0.347, *p* < 0.05

Significant, small association between longer DUP and increased positive, but not negative symptoms by 2 years post-treatment;

Positive symptoms: N = 164, r = 0.170, 95%CI 0.017 to 0.315, $p < 0.05$
Negative symptoms: N = 164, r = -0.110, 95%CI -0.259 to 0.044, $p > 0.05$
After controlling for pre-morbid adjustment, the association between DUP and outcomes remained significant. The relationship between DUP and positive symptoms was particularly robust.
Functioning and quality of life
Significant, small to medium-sized associations between longer DUP and poorer functioning and quality of life by 1 year post-treatment;
Overall functioning: N = 287, r = 0.277, 95%CI 0.165 to 0.382, $p < 0.05$
Social functioning: N = 191, r = 0.234, 95%CI 0.093 to 0.366, $p < 0.05$
Quality of life: N = 403, r = 0.251, 95%CI 0.157 to 0.340, $p < 0.05$
Significant, small to medium-sized associations between longer DUP and poorer overall functioning and quality of life, but not social functioning, by 2 years post-treatment;
Overall functioning: N = 68, r = 0.280, 95%CI 0.045 to 0.486, $p < 0.05$
Social functioning: N = 55, r = 0.190, 95%CI -0.079 to 0.433, $p > 0.05$
Quality of life: N = 164, r = 0.200, 95%CI 0.048 to 0.343, $p < 0.05$
After controlling for pre-morbid adjustment, the association between DUP and outcomes remained significant.
Remission
Significant, medium-sized effects of fewer remissions with longer DUP;
At 6 months: N = 266, OR = 3.55, 95%CI 2.03 to 6.18
At 12 months: N = 133, OR = 2.75, 95%CI 1.14 to 6.64
At 24 months: N = 206, OR = 2.72, 95%CI 1.20 to 6.17
At 269 months: N = 491, OR = 2.42, 95%CI 1.51 to 3.86
After controlling for pre-morbid adjustment, the association between DUP and outcomes remained significant.

Consistency in results	Authors state the results were reasonably consistent at 1 year.
Precision in results	Precise for symptoms, functioning and quality of life, imprecise for remission.
Directness of results	Direct

Penttila M, Jaaskelainen E, Hirvonen N, Isohanni M, Miettunen J

Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis

The British Journal of Psychiatry 2014; 205: 88-94

View review abstract online

Comparison	DUP and long-term outcomes.
Summary of evidence	**Moderate t high quality evidence (large samples, inconsistent, precise, direct) suggests small effects of longer DUP being associated with poorer long-term outcomes for symptoms, remission and social functioning. There were no associations with the number of hospital admissions, employment or quality of life.**

Symptoms and remission >2 years after first contact with treatment

Significant, small associations between longer DUP and poorer general symptomatic outcome, more severe positive and negative symptoms, and lesser likelihood of remission;

General symptomatic outcome: 15 studies, N = 1,878, r = -0.15, 95%CI -0.22 to -0.09, $p < 0.05$, I^2 = 38.9%, $p = 0.061$

Positive symptoms: 18 studies, r = -0.14, N = 2,079, %CI -0.22 to -0.07, $p < 0.05$, I^2 = 56.1%, $p = 0.002$

Negative symptoms: 18 studies, r = -0.13, N = 2,079, 95%CI -0.21 to -0.05, $p < 0.05$, I^2 = 66.1%, $p < 0.001$

Remission: 10 studies, N = 1,656, r = -0.14, 95%CI -0.23 to -0.06, $p < 0.05$, I^2 = 54.7%, $p = 0.019$

No association was found between DUP and the number of hospital admissions;

11 studies, r = -0.09, N = 1,123, 95%CI -0.22 to 0.04, $p > 0.05$, I^2 = 75.8%, $p < 0.001$

Meta-regression showed longer follow-up resulted in stronger associations between DUP and negative symptoms ($p = 0.035$), and hospital admissions ($p = 0.046$).

Higher national income level resulted in stronger correlation between DUP and general symptomatic outcome ($p = 0.008$) and positive symptoms ($p = 0.016$).

Sex distribution, age at onset, length of DUP, the proportion of participants with schizophrenia, withdrawal percentage and study design did not affect the correlation between DUP and outcomes.

Functioning, quality of life, employment >2 years after first contact with treatment

NeuRA | Duration of untreated psychosis and outcomes   August 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au   Page 10
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Significant, small association between longer DUP and poorer long-term global outcomes and social functioning;	
Global outcomes: 19 studies, N = 2,190, r = -0.17, 95%CI -0.26 to -0.07, $p < 0.05$, I^2 = 73.8%, $p < 0.001$	
Social functioning: 14 studies, N = 1,822, r = -0.18, 95%CI -0.27 to -0.09, $p < 0.05$, I^2 = 68.2%, $p < 0.0011$	
No association was found between DUP and employment or quality of life;	
Employment: 7 studies, N = 718, r = -0.05, 95%CI -0.16 to 0.06, $p > 0.05$, I^2 = 55.1%, p = 0.038	
Quality of life: 7 studies, N = 772, r = -0.10, 95%CI -0.22 to 0.01, $p > 0.05$, I^2 = 55.0%, p = 0.038	
Meta-regression revealed longer follow-up resulted in stronger associations between DUP and global outcome (p = 0.035).	

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Perkins DO, Gu H, Boteva K, Lieberman JA

Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis

American Journal of Psychiatry 2005; 162(10): 1785-804

View review abstract online

Comparison	**DUP and response to antipsychotic treatment.**
Summary of evidence	**Moderate to high quality evidence (large samples, unable to assess consistency, precise, direct) suggests an association between longer DUP and poorer response to treatment.**
Symptoms and functioning	

Duration of untreated psychosis and outcomes

Significant, small to medium-sized associations between longer DUP and poorer response to treatment; Global symptoms: 5 studies, N = 527, *r* = 0.29, 95%CI 0.20 to 0.36, *p* < 0.05 Positive symptoms: 13 studies, N = 1,359, *r* = 0.27, 95%CI 0.21 to 0.31, *p* < 0.05 Negative symptoms: 14 studies, N = 1,345, *r* = 0.23, 95%CI 0.17 to 0.27, *p* < 0.05 Functioning: 7 studies, N = 646, *r* = 0.21, 95%CI 0.13 to 0.28, *p* < 0.05	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, DUP = Duration of Untreated Psychosis, FEP = first-episode psychosis, GP = general practitioner, N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result (*p* < 0.05 generally regarded as significant), *r* = correlation coefficient, vs. = versus

NeuRA | Duration of untreated psychosis and outcomes | August 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

Page 12

Explanation of technical terms

*Bias has the potential to affect reviews of both RCT and 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[13].

---

† Different effect measures are reported by different reviews.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an 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 dependent 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.

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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[13].

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

NeuRA | Duration of untreated psychosis and outcomes | August 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia
Page 13

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, an 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. An 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[14]. 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.

---

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) which 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 substantial heterogeneity and 75% to 100%: considerable heterogeneity. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

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

---

§ 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, this criteria should be relaxed[15].

‖ 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 so is 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.

NeuRA | Duration of untreated psychosis and outcomes | August 2020

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au | Page 14
To donate, phone 1800 888 019 or visit www.neura.edu.au/donate/schizophrenia

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. Anderson KK, Rodrigues M, Mann K, Voineskos A, Mulsant BH, George TP*, et al.* (2015): Minimal evidence that untreated psychosis damages brain structures: A systematic review. *Schizophrenia Research* 162: 222-33.
4. Boonstra N, Klaassen R, Sytema S, Marshall M, De Haan L, Wunderink L*, et al.* (2012): Duration of untreated psychosis and negative symptoms - A systematic review and meta-analysis of individual patient data. *Schizophrenia Research* 142: 12-9.
5. Doyle R, Turner N, Fanning F, Brennan D, Renwick L, Lawlor E*, et al.* (2014): First-episode psychosis and disengagement from treatment: A systematic review. *Psychiatric Services* 65: 603-11.
6. Farooq S, Large M, Nielssen O, Waheed W (2009): The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: A systematic review and meta analysis. *Schizophrenia Research* 109: 15-23.
7. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T (2005): Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Archives of General Psychiatry* 62: 975-83.
8. Penttila M, Jaaskelainen E, Hirvonen N, Isohanni M, Miettunen J (2014): Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: Systematic review and meta-analysis. *British Journal of Psychiatry* 205: 88-94.
9. Perkins DO, Gu H, Boteva K, Lieberman JA (2005): Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *American Journal of Psychiatry* 162: 1785-804.
10. Large M, Nielssen O (2008): Evidence for a relationship between the duration of untreated psychosis and the proportion of psychotic homicides prior to treatment. *Social Psychiatry & Psychiatric Epidemiology* 43.
11. Bora E, Yalincetin B, Akdede BB, Alptekin K (2018): Duration of untreated psychosis and neurocognition in first-episode psychosis: A meta-analysis. *Schizophrenia Research* 193: 3-10.
12. Challis S, Nielssen O, Harris A, Large M (2013): Systematic meta-analysis of the risk factors for deliberate self-harm before and after treatment for first-episode psychosis. *Acta Psychiatrica Scandinavica* 127: 442-54.
13. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
14. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
15. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*.