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Treatment adherence

Introduction

Non-adherence to maintenance treatments, for example antipsychotic medication, is a widespread issue that plagues clinical management for schizophrenia. It reduces the success of the treatment regimen and the ability to achieve remission from illness, but it also increases the burden for psychotic relapse treatments, emergency admissions and hospitalisation. Identifying risk factors for non-adherence may help to increase treatment concordance. Greater adherence to treatment can contribute not only to more successful disease management and better quality of life, but also to improved attitudes towards treatment and medication, as well as increasing insight and confidence.

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. We have prioritised reviews with pooled data 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 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 13 reviews that met inclusion criteria[3-15].

- Moderate to high quality evidence found around 56% of people with schizophrenia were non-adherent to medication. Moderate

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quality evidence found the dropout rate for psychosocial treatments was around 13%.

- Factors associated with non-adherence include poor insight, increased psychopathology, negative attitude towards medication, previous treatment non-adherence, poor alliance with clinicians, low outpatient contact, inadequate discharge planning, being young, male, having low social functioning, having a history of substance abuse, having affective symptoms, long hospital stays, being married, having a longer duration of untreated psychosis, and having cognitive impairment.
- Factors associated with better treatment adherence include having previous psychiatric contacts, family support, good social functioning, living alone/being single, high education, good therapeutic alliance, facilities for follow up appointments, lower dosage frequency, and positive attitudes towards medication.
- Subjective methods including patient self-report, clinical provider report, significant other report, and chart review are more commonly used in studies as measures of treatment adherence than objective measures such as pill count, blood or urine analysis, electronic monitoring, and electronic refill records.
- Better medication adherence is associated with better clinical and service utilisation outcomes, and better economic outcomes. The cost of re-hospitalisation due to non-adherence ranged from US$1392 million to US$1826 million in 2005 alone.
- High quality evidence suggests no differences in antipsychotic adherence between people of African American and non-African American descent, and between people of Latino and non-Latino descent. Moderate quality evidence also suggests no differences between people of Asian, Maori, Pacific Islander, or Black British descent.
- Moderate to low quality evidence suggests no differences in rates of refusal of treatment and premature termination of treatment.

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Boswell KA, Cook CL, Burch SP, Eaddy MT, Cantrell R

Associating Medication Adherence With Improved Outcomes: A Systematic Literature Review

American Journal of Pharmaceutical Benefits 2012; 4(4): 97-108

View review abstract online

Comparison	**Relationships between medication adherence and outcomes.**
Summary of evidence	**Moderate quality evidence (unclear sample size, consistent, unable to assess precision, direct) suggests medication adherence is associated with better clinical and service utilization outcomes. Moderate to low quality evidence (inconsistent) suggests treatment adherence may also be associated with better economic outcomes.**
Medication adherence and outcomes	
11 studies, N not reported 100% reported significantly better clinical and service utilisation outcomes with medication adherence. 50% reported significantly better economic outcomes, 33.3% reported significantly worse economic outcomes and 16.7% reported no differences economic outcomes with medication adherence.	
Consistency in results‡	Consistent for clinical and service utilisation, inconsistent for economic outcomes.
Precision in results§	Unable to assess; no measure of precision is reported.
Directness of results‖	Direct

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

Treatment adherence

Comparison	**Factors associated with engagement in treatment after a first-episode of psychosis.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision, direct) suggests substance abuse or dependence, greater symptom severity, longer duration of untreated psychosis, and reduced insight resulted in less engagement in treatment, while involvement and support of family resulted in more 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 assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

Edgcomb JB, Zima B

Medication Adherence Among Children and Adolescents with Severe Mental Illness: A Systematic Review and Meta-Analysis

Journal of Child & Adolescent Psychopharmacology 2018; 28: 508-20

View review abstract online

Comparison	**Prevalence and factors associated with medication adherence in children and adolescents with a severe mental illness.** **The sample included psychotic disorders, bipolar disorder, depression, and mixed diagnoses.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly inconsistent, precise, direct) found factors associated with**

	medication non-adherence include greater illness severity, medication side effects, and having a comorbid substance use disorder or ADHD. Moderate quality evidence (imprecise) finds factors associated with medication adherence include having positive patient and family attitudes toward care, a positive clinician-patient relationship, adherence to psychotherapy, patient insight, and a comorbid medical illness.
Assessment methods	
28 studies, N = 180,870; 65.9% were medication adherent. *Medication adherence was associated with;* Positive patient attitudes toward care: 8 studies, N = 474, OR = 3.41, 95%CI 1.50 to 7.77, p = 0.001, I^2 = 78% Positive family attitudes toward care: 6 studies, N = 3884, OR = 2.82, 95%CI 1.79 to 4.45, p = 0.001, I^2 = 80% Positive clinician-patient relationship: 3 studies, N = 1,742, OR = 5.92, 95%CI 1.73 to 18.55, p = 0.002, I^2 = 54% Adherence to psychotherapy: 6 studies, N = 752, OR = 5.70, 95%CI 2.51 to 12.95, p < 0.001, I^2 = 83% Patient insight: 3 studies, N = 3,784, OR = 3.60, 95%CI 1.42 to 9.10, p = 0.003, I^2 = 88% Comorbid medical illness: 3 studies, N = 1,786, OR = 1.82, 95%CI 0.96 to 3.46, p = 0.033, I^2 = 33% *Medication non-adherence was associated with;* Illness severity: 11 studies, N = 2,911, OR = 0.44, 95%CI 0.32 to 0.62, p < 0.001, I^2 = 51% Medication side effects: 8 studies, N = 4,036, OR = 0.52, 95%CI 0.26 to 1.02, p = 0.029, I^2 = 76% Comorbid alcohol use: 4 studies, N = 3,889, OR = 0.82, 95%CI 0.70 to 0.96, p = 0.008, I^2 = 0% Comorbid substance use: 7 studies, N = 5,681, OR = 0.66, 95%CI 0.45 to 0.98, p = 0.020, I^2 = 40% Comorbid ADHD: 5 studies, N = 1,920, OR = 0.61, 95%CI 0.41 to 0.91, p = 0.008, I^2 = 18%	
Consistency in results	Mostly inconsistent
Precision in results	Imprecise for medication adherence, precise for medication non-adherence.
Directness of results	Direct

Treatment adherence

Lacro JP, Dunn LB, Dolder CR, Leckband SG and Jeste DV

Prevalence of and Risk Factors for Medication Nonadherence in Patients With Schizophrenia: A Comprehensive Review of Recent Literature

Journal of Clinical Psychiatry 2002; 63: 892-909

View review abstract online

Comparison	**Rates and risk factors of medication non-adherence**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests rates of medication non-adherence in people with schizophrenia may be around 40%.** **Factors influencing non-adherence include poor insight, negative attitude towards medication, previous non-adherence, poor alliance with clinicians, low outpatient contact, inadequate discharge planning**

Medication non-adherence

Any deviation from the prescribed medication regimen;

39 studies (N = 4,285) unweighted mean non-adherence rate (±SD) = 40.5% (±18.5%)

Subgroup analysis: studies where trained personnel measured adherence or where patients' self-reports on adherence were confirmed by family members, care providers, or clinicians;

10 studies (N = 939) unweighted mean non-adherence rate (±SD) = 39.1% (±11.4%)

Subgroup analysis: studies where adherence was determined as 'medications being taken as prescribed at least 75% of the time';

5 studies (N = unclear) unweighted mean non-adherence rate (±SD) = 47.3% (±7.4%)

Likely risk factors for non-adherence;

10 of 14 studies reported poor insight into the disorder

8 of 10 studies reported negative attitude towards medication

4 of 4 studies reported negative subjective response to medication

3 of 3 studies reported previous non-adherence

5 of 5 studies report poor alliance with therapist or clinician or less outpatient contact

2 of 2 studies report inadequate discharge planning or poor aftercare environment

Potential risk factors;

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5 of 9 studies reported a current or past history of substance abuse 3 of 5 studies reported a shorter duration of illness 4 of 8 studies reported more severe psychotic symptoms 3 of 7 studies reported presence of mood symptoms 2 of 4 studies reported higher antipsychotic dose 2 of 3 studies reported greater antipsychotic regimen complexity 3 of 5 studies reported use of first generation (vs. second generation) antipsychotics *Factors not likely to be associated with non-adherence;* Current inpatient status, higher education level, non-white ethnicity, younger age, male sex, marital status, neurocognitive impairment, antipsychotic side effects, unstable living arrangements, and poor family involvement.

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

Medic G, Higashi K, Littlewood K, Diez T, Granstrom O, Kahn RS

Dosing frequency and adherence in chronic psychiatric disease: systematic review and meta-analysis

Neuropsychiatric Disease and Treatment 2013; 9: 119-131

View review abstract online

Comparison	**Relationship between medication adherence and dosing frequency.**
Summary of evidence	**Moderate quality evidence (large overall sample, unable to assess consistency or precision, direct) suggests better medication adherence is associated with lower dosage frequency.**

Medication adherence and dosing frequency

Measured by

Medication event monitoring system (MEMS), medication possession ratio (MPR), medication adherence questionnaire (MAQ) or clinician rating scale (CRS)

Treatment adherence

1 study (N = 25) reported that patients with once-daily regimens had better adherence than twice-daily regimens (78.2% vs. 66.2%). 1 study (N = 49) reported that patients with once-daily regimens had better adherence than patients twice-daily regimens, who had better adherence than patients with thrice-daily regimens (62% vs. 26% vs. 22%). 1 study (N = 52) reported that patients with once-daily regimens had better adherence than patients twice-daily regimens, who had better adherence than patients with thrice-daily regimens, who had better adherence than patients with four-times daily regimens (87% vs. 81% vs. 77% vs. 39%). PANSS total score (β= -0.429, *p* = 0.001) and dosing complexity (β -0.246, *p* = 0.054) were significant predictors of adherence. 1 study (N = 32,612) reported significantly improved adherence in patients changing from more than once-daily dosage to once-daily dosage (change 0.045, *p* = 0.001). There was also significantly reduced adherence in patients changing from once-daily dosage to over once-daily dosage (β -0.105, *p* = 0.001). 1 study (N = 409) reported that the higher the daily dosing frequency, the better the adherence.	
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

Nose M, Barbui C, Tansella M

How often do patients with psychosis fail to adhere to treatment programmes? A systematic review

Psychological Medicine 2003; 33: 1149-1160

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Comparison	**Rates and risk factors of treatment non-adherence.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests rates of adherence in people with schizophrenia are lower in larger studies (~23%) than in smaller studies (~49%).** **Factors associated with non-adherence include increased psychopathology; lack of insight; being young; male; low social functioning; having a history of substance abuse; affective**

	symptoms; long hospital stays; being married; and having cognitive impairment. **Factors associated with higher adherence include having previous psychiatric contacts; family support; good social functioning; living alone/being single; high education; good therapeutic alliance; and facilities for follow up appointments.**
Treatment (medication or consultation) non-adherence	
30 schizophrenia studies, N = 5,790, weighted (for sample size) mean rate of treatment non-adherence = 25.04%, 95%CI 17.42 to 32.66. *Subgroup analyses for 89 studies of patients with any severe mental disorder showed significant differences in non-adherence rates between the following factors;* Studies with larger sample size reported lower adherence rates <50 patients = 48.75%, 95%CI 39.93 to 57.56 >150 patients = 22.82%, 95%CI 18.01 to 27.62 First-contact cases (46.92%, 95%CI = 38.70 to 55.13) provided higher non-adherence rates than studies of patients already receiving treatment (23.21%, 95%CI = 20.02 to 26.39). *No significant differences in non-adherence rates were reported between studies for the following factors;* Studies conducted in Europe compared with those conducted in the USA; studies assessing non-adherence to medication vs. appointments; studies assessing differing diagnoses (schizophrenia, psychosis, other severe mental disorders); length of follow up; inpatient vs. outpatient settings; or study design. *The following patients' characteristics were most consistently associated with higher adherence;* Insight; previous psychiatric contacts; family support; good social functioning; living alone/being single; high education; good therapeutic alliance; facilities for appointments. *The following patients' characteristics were most consistently associated with non-adherence;* A history of non-adherence; increased psychopathology; lack of insight; being young; male; low social functioning; a history of substance abuse; affective symptoms ; long hospital stay; being married; and cognitive impairment.	
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

Treatment adherence

Puyat JH, Daw JR, Cunningham CM, Law MR, Wong ST, Greyson DL, Morgan SG

Racial and ethnic disparities in the use of antipsychotic medication: a systematic review and meta-analysis

Social Psychiatry and Psychiatric Epidemiology 2013; 48: 1861-1872

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Comparison	**Differences in the use of antipsychotic medication between ethnic groups.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests Latinos are prescribed newer antipsychotics less often than older antipsychotics when compared to non-Latinos.** **Moderate quality evidence (inconsistent) suggests African Americans are also prescribed newer antipsychotics less often than older antipsychotics when compared to non-African Americans.** **High quality evidence suggests no differences in use between African Americans and non-African Americans and between Latinos and non-Latinos. Moderate quality evidence (inconsistent or imprecise) also suggests no differences for Asians, Maoris, Pacific Islanders or Black British.**

Newer vs. older antipsychotics

African Americans and Latinos had a small significant effect of lower odds of receiving newer antipsychotics than non-African Americans and non-Latinos;

African Americans vs. non-African Americans: 8 studies, N = 76,235, OR = 0.62, 95%CI 0.50 to 0.78, I^2 = 73.2%, $p < 0.0001$

Latinos vs. non-Latinos: 6 studies, N = 75,390, OR = 0.77, 95%CI 0.73 to 0.81, I^2 = 0%, $p = 0.579$

Use vs. non-use of antipsychotics

No significant differences between using and not using antipsychotics;

African Americans vs. non-African Americans: 4 studies, N = 40,245, OR = 1.01, 95%CI 0.99 to 1.02, $p > 0.05$, I^2 = 0%, $p = 0.573$

Latinos vs. non-Latinos: 2 studies, N = 28,503, OR = 0.98, 95%CI 0.86 to 1.13, $p > 0.05$, I^2 = 0%, $p = 0.513$

Asians vs. non-Asians: 2 studies, N = 4,821, OR = 1.10, 95%CI 0.88 to 1.36, $p > 0.05$, I^2 = 0%, $p =$

0.458 Maoris vs. non-Maoris: 2 studies, N = 4,821, OR = 0.78, 95%CI 0.53 to 1.13, $p > 0.05$, $I^2 = 98.4$ %, $p < 0.001$ Pacific Islanders vs. non-Pacific Islanders: 2 studies, N = 4,821, OR = 0.97, 95%CI 0.84 to 1.11, $p > 0.05$, $I^2 = 66.9$%, $p = 0.082$ Black British vs. non-Black British: 1 study, N = 1,694, OR = 1.16, 95%CI 0.88 to 1.53, $p > 0.05$, I^2 = N/A	
Consistency in results	Inconsistent for African Americans (newer vs. older comparison), Maoris (use vs. non-use comparison), and a trend for Pacific Islanders (use vs. non-use comparison).
Precision in results	Imprecise for Asians, Maoris and Black British (all use vs. non-use comparison).
Directness of results	Direct

Richardson M, McCabe R, Priebe S

Are attitudes towards medication adherence associated with medication adherence behaviours among patients with psychosis? A systematic review and meta-analysis

Social Psychiatry and Psychiatric Epidemiology 2013; 48: 649-657

View review abstract online

Comparison	**Attitudes towards medication adherence.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests positive attitudes towards medication increases adherence to medication.**
Relationship between attitude towards medication and medication adherence	
Small significant effect of an association between positive attitude towards medication and increased adherence; Pearson's correlation: 13 studies, N = 1,911, $r = 0.25$, 95%CI 0.18 to 0.32, $p < 0.05$, $I^2 = 51.90$%, $p < 0.05$ Spearman's correlation: 6 studies, N = 780, $r = 0.26$, 95%CIs 0.12 to 0.38, $p = 0.01$, $I^2 = 67.43$ %, $p < 0.05$	

Subgroup analysis indicated that the between-study heterogeneity was not due to study quality.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Semahegn A, Torpey K, Manu A, Assefa N, Tesfaye G, Ankomah A

Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: a systematic review and meta-analysis

Systematic reviews 2020; 9: 17

View review abstract online

Comparison	**Prevalence of medication non-adherence in people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) found around 56% of people with schizophrenia were non-adherent to medication.**
Prevalence	
Over half of patients with schizophrenia were non-adherent; 9 studies, N = 2,643, medication non-adherence was 56%, 95%CI 48% to 63%, I^2 = 100% Authors suggest individual patient's behaviours, lack of social support, clinical, treatment, illness-related and health system factors influenced non-adherence,	
Consistency in results	Inconsistent
Precision in results	Appears precise
Directness of results	Direct

Sun SX, Liu GG, Christensen DB, Fu AZ

Review and analysis of hospitalization costs associated with antipsychotic non-adherence in the treatment of schizophrenia in the United States

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

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

Economic outcomes

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

Swift JK, Greenberg RP, Tompkins KA, Parkin SR

Treatment refusal and premature termination in psychotherapy, pharmacotherapy, and their combination: A meta-analysis of head-to-head comparisons

Psychotherapy 2017; 54: 47-57

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Comparison	**Rates of refusal of treatment and premature termination of treatment with antipsychotics vs. antipsychotics plus psychotherapy.**

Treatment adherence

Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision, direct) suggests no differences in rates of refusal of treatment and premature termination of treatment.**
Refusal of treatment and premature termination of treatment	
Rates of treatment refusal did not differ between those prescribed antipsychotics or a combination of antipsychotics and psychosocial therapies; Refusal of treatment: 2 studies, N = not reported, OR = 0.63, 95%CI 0.14 to 2.84, $p > 0.05$ Premature termination: 7 studies, N = not reported, OR = 1.54, 95%CI 0.82 to 2.92, $p > 0.05$	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Imprecise
Directness of results	Direct

Velligan DI, Lam YF, Glahn DC, Barrett JA, Maples NJ, Ereshefsky L, Miller AL

Defining and Assessing Adherence to Oral Antipsychotics: A Review of the Literature

Schizophrenia Bulletin 2006; 32(4): 724-742

View review abstract online

Comparison	**Methods of assessing antipsychotic adherence.**
Summary of evidence	**Moderate quality evidence (large number of studies/samples, unable to assess consistency or precision, direct) suggests subjective methods including patient self-report, clinical provider report, significant other report, and chart review are more commonly used in studies than objective measures such as pill count, blood or urine analysis, electronic monitoring, and electronic refill records.**
Assessment methods	

Treatment adherence

Definitions varied widely from 'agreeing to take any medication' to 'taking at least 90% of medication as prescribed'. Subjective methods of assessing the level of adherence included patient self-report; clinical provider report; significant other report; and chart review. These were the only methods of assessment used in 77% of studies (124 of 161 studies). Objective measures of assessment included pill count; blood or urine analysis; electronic monitoring; and electronic refill records. These were used in less than 23% of studies (37 of 161 studies).	
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

Villeneuve K, Potvin S, Lesage A, Nicole L

Meta-analysis of rates of drop-out from psychosocial treatment among persons with schizophrenia spectrum disorder

Schizophrenia Research 2010; 121: 266-270

View review abstract online

Comparison	**Rates of withdrawal from trials of psychosocial treatments (not necessarily non-adherence).**
Summary of evidence	**Moderate quality evidence (large number of studies/samples, unable to assess consistency or precision, direct) suggests the overall dropout rate for psychosocial treatments is around 13%.** **Factors associated with higher drop-out rates included higher age, longer illness duration, longer treatment duration, and male sex.** **Factors associated with lower dropout rates included studies in journals with a higher impact factor, and studies of hospitalised patients vs. outpatient or mixed settings.**
Withdrawal rates	

Treatment adherence

74 studies, N = not reported, composite dropout rate was 13%, event rate = 0.129, 95%CI 0.106 to 0.156, *p* = 0.0001, Q = 337.100, *p* = 0.0001 *Subgroup analyses suggest higher drop-out rates were associated with;* Higher age: 64 studies, β = 0.019, 95%CI 0.001 to 0.036, *p* = 0.032, Q = 4.609 Longer illness duration: 47 studies, β = 0.039, 95%CI 0.020 to 0.057, *p* = 0.00004, Q = 16.707 Longer treatment duration: 73 studies, β = 0.003, 95%CI 0.0001 to 0.004, *p* = 0.035, Q = 4.428 Male sex: 58 studies, β = 0.677, 95%CI -0.002 to 1.357, *p* = 0.051, Q = 3.808 *Dropout rate was lower in:* Studies of inpatients: 18 studies, rate = 0.091, 95%CI 0.058 to 0.142, *p* = 0.0001, Q = 3.152 vs. outpatients: 45 studies, rate = 0.134, 95%CI 0.104 to 0.171, *p* = 0.0001, Q = 3.152, or mixed settings: 11 studies, rate = 0.158, 95%CI 0.100 to 0.240, *p* = 0.0001, Q = 3.152 Lower in journals with a higher impact factor: 70 studies, β = -0.033, 95%CI -0.060 to 0.004, *p* = 0.024, Q = 5.115 Severity of illness and treatment modality (individual, group, multi-modal) did not influence the results.

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

Explanation of acronyms

CI = Confidence Interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size), 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), Q = statistic for the test of heterogeneity, *r* = correlation coefficient, vs. = versus

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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[16].

† 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[16].

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[17]. 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.

‡ 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[16];

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

§ 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[18].

‖ 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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