



REVIEW ARTICLE

Non-adherence to pharmacological treatment in schizophrenia and schizophrenia spectrum disorders – An updated systematic literature review



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Abstract

Background and objectives: The primary treatment for schizophrenia and schizophrenia-spectrum disorders is antipsychotic medication. One of the many public health challenges in mental illness, is to identify contributing factors to non-adherence to pharmacological treatment. The objective of this study was to perform an updated systematic review of risk factors for non-adherence to pharmacological treatment in schizophrenia in a European and American context.

Methods: The study was a systematic literature review of studies that included at least two measurements of pharmacological adherence in adult schizophrenic patients. This was done to validate the measures of adherence adequately which is rarely done in previous adherence research. It was conducted using PRISMA guidelines surveying Pubmed and PsycINFO.

Results: The definition of non-adherence varies greatly in eligible studies and the methodological approach to investigation of non-adherence is inconsistent. Thirteen studies fit the inclusion criteria and demonstrated several risk factors statistically influencing non-adherence rates. The most frequent risk factors identified for non-adherence were poor insight into or lack of awareness of illness, alcohol or drug abuse and unspecified younger age.

Conclusions: The findings in this systematic literature review are consistent with previous reviews on non-adherence and schizophrenia. It stresses the methodological challenges in psychiatric adherence research and establishes the need for more systematic and rigorous study design and methods within this field.

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Introduction

Mental illness affects all ages, ethnic, racial, socioeconomic and cultural groups.¹ No part of the world is exempted from these diseases and the burden of mental illness can therefore be considered a global public health problem.²

Schizophrenia is a major group of mental disorders characterized by psychosis. The causes are multifactorial and still largely unknown. The primary treatment for schizophrenia and schizophrenia-spectrum disorders is pharmacological and the most widely applied medications are second generation antipsychotics (SGA).³ SGA are administered orally or as long acting injection therapy (LAI), that were developed especially to improve adherence.⁴ Maintenance therapy with LAI has been shown to reduce relapse with relative and absolute risk reductions of 30% and 10% respectively⁵ and have been associated with 50–65% reduction in re-hospitalization.⁶

Side-effects of pharmacological treatment are common and can significantly influence patient's quality of life. The older first generation antipsychotics (FGA) can cause extrapyramidal symptoms, dry mouth and sedation as well as rare, but serious, side effects such as neuroleptic malignant syndrome and tardive dyskinesia. SGA have a different side effect profile linked to metabolic and cardiovascular complications often resulting in sexual dysfunction and reproductive complications, disruption in normal hormone production, weight gain, diabetes as well as cognitive deficits.^{7–9} The specific substance Clozapine, which is widely considered the golden standard of treatment of schizophrenia, also have an increased risk of possibly fatal agranulocytosis compared to other SGA.^{5,10,11}

One of the many challenges in treatment of mental illness is to identify contributing factors to non-adherence to pharmacological treatment as non-adherence is a known predictor for relapse and re-hospitalization.^{12,13} Patients who are non-adherent are 70% more likely to be hospitalized compared to patients with partial adherence, who are 30% more likely to be hospitalized than adherent patients.¹² The economic cost of patients who have relapse of illness are three times higher than stable patients and relapse leads to increased morbidity, mortality and decreased quality of life.^{12–14}

Within adherence research, both subjective and objective measures of adherence are applied. Objective measures are derived from clinical measurements such as blood and urine samples and are generally considered to be reliable but also expensive and intrusive for patients. Subjective measures are the most frequently applied measurement in adherence research with approximately 75% of current literature using information derived from patient, family or clinician.¹⁵ Both types of measurement have limitations when applied in clinical studies and methodology of current adherence research is heterogeneous.

This systematic literature review provides an updated assessment on factors associated with non-adherence. Furthermore it aims to evaluate the rate of non-adherence as well as expose and address potential methodological limitations within adherence-research.

Material and methods

Search strategy

This study was a systematic review conducted according to the PRISMA Statement for transparent reporting of systematic reviews.¹⁶ PubMed/Medline and PsycINFO was searched for a combination of the following terms: antipsychotic, neuroleptic, adherence, non-adherence, nonadherence, non adherence, compliance, non-compliance, noncompliance, non compliance, schizophrenia, risk factor, risk factors predictor, predictors. The search was restricted to articles published from 1 January 1990–31 December 2014.

Study selection

English language articles that were randomized clinical trials or observational studies were included if they assessed quantitative risk factors for non-adherence to psychopharmacological treatment in adults (age 18–65) with validated schizophrenia or schizophrenia-spectrum disorders (defined by ICD9/10 or DMS-IV/V). Adherence must be assessed by a minimum of two measurements and the study-population must represent the working age general population in the developed world, thereby excluding subpopulations such as veterans, adolescents and the elderly as well as studies from the developing world.

Titles and abstracts were screened and full-text articles were retrieved if they appeared relevant or if there was some ambiguity as to whether the article was relevant. References in all included articles were reviewed and included in the systematic review if they meet the inclusion criteria.

Data extraction and quality assessment

From each of the included studies the following characteristics were extracted:

Study-specific: Country of origin, study design, study period, population size as well as age, sex and ethnicity of included patients.

Treatment-specific: Type of antipsychotic treatment (FGA/SGA), medication administration regime (Oral/LAI) and setting (Inpatient/Outpatient) were extracted if available.

Adherence-specific: Rate of adherence and type of measure (subjective/objective and dichotomous/categorical) as well as reported risk factors for non-adherence, divided into patient-related, mental illness-related, medication-related and environmental-related risk factors for non-adherence.

The quality of each included study was critically appraised using The STROBE Statement checklist for cross-sectional, cohort and case/control studies,¹⁷ and The Quality Assessment Tool for Observational Cohort and cross-sectional studies developed by the National Institute of Health (NIH).¹⁸

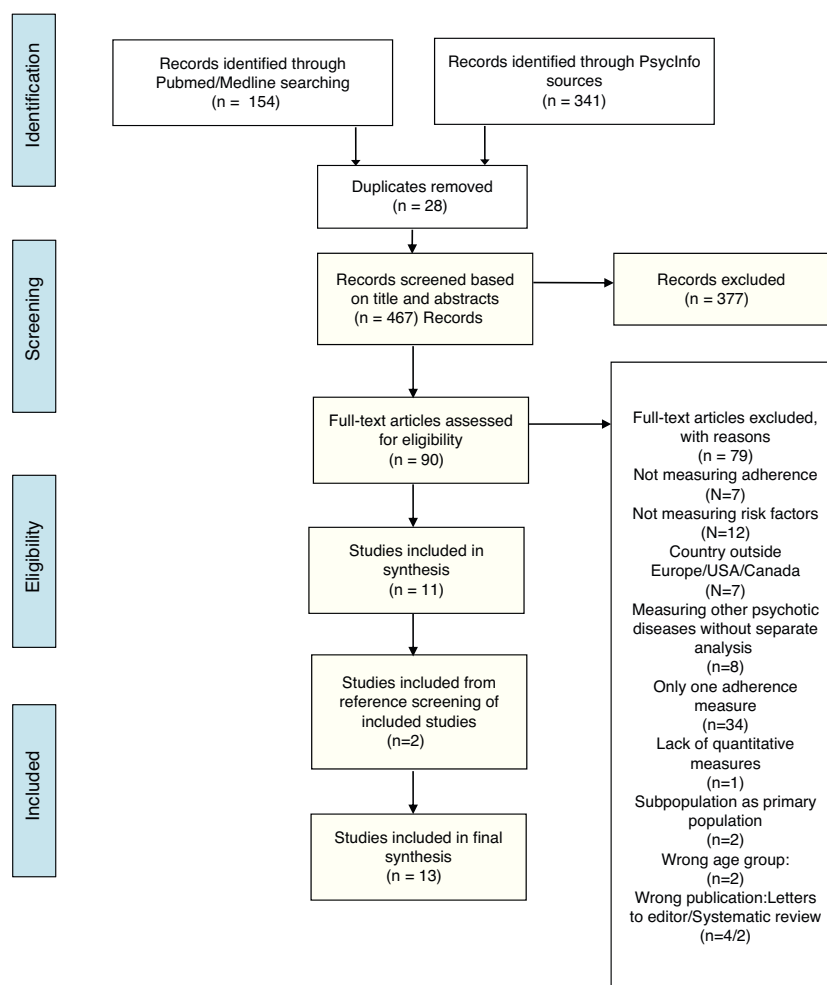


Figure 1 PRISMA 2009 Flow Diagram.

Ethics in publishing

The manuscript does not contain clinical studies or patient data.

Results

Thirteen studies were included in this review. The PRISMA flowchart provides an overview of the selection process (Fig. 1). Six studies were cross-sectional studies and seven were cohort studies (four prospective and three retrospective) (Table 1). Study period was 1–5 years. The population size in each study ranged from 78 to 28,238 participants (Table 2). The mean age was 23.6–45.2 years and participants were predominantly male, comprising 46.8–94% of the population. Data on ethnicity was not available in all studies.^{19–22} The type of antipsychotic treatment was reported in five studies^{21,23–26} with SGA being treatment in 46.6–85% of cases. FGAs were prescribed in 9.7–53.5% of cases and a combination was prescribed in 11.4–14.8% of cases. Medication regime was not reported in four studies.^{20,23,27,28} All studies investigated an outpatient population and six studies investigated both an outpatient

and inpatient population.^{20–22,25,28,29} Three studies described their sample as first-episode psychosis.^{20,22,28}

Adherence measures

Classification of non-adherence was heterogenic and made it impossible to provide an overall combined non-adherence rate (Table 3). The non-adherence rates across studies were within a range of 11.0–71.9%. Ten studies reports non-adherence dichotomously as adherence or non-adherence^{19,21,22,25–31} and three studies report non-adherence categorically as full-adherence, partially adherence/inadequate adherence or non-adherence.^{20,23,24} The instruments applied for measuring adherence are heterogeneous and subjective measures of adherence was applied in all studies but two,^{21,25} where 10 studies used patient-reporting,^{19,22–24,26–31} three studies used family-reporting^{19,22,29} and six studies used clinician reporting.^{19,20,22,26,28,31} Objective measures of adherence were applied in all but four studies. Two studies applied prescription cards,^{22,30} three studies applied medical records review,^{20,27,30} one study applied blood samples (serum concentration),²³ two studies applied MPR, medication persistence, consistency and maximum continuous

Table 1 Author, year of publication, country of origin and study design.

Author	Year	Country of origin	Design	Duration
Agerwal, M.	1998	United Kingdom	Retrospective cohort	12 months
Ascher-Svanum, H.	2006	USA	Prospective cohort	3 years
Coldham, E.	2002	Canada	Prospective cohort	12 months
Hudson, T.J.	2004	USA	Cross-sectional	
Jónsdóttir, H.	2012	Norway	Cross-sectional	
Kikkert, M.J.	2008	Holland (London, Verona, Leipzig, Amsterdam) ^a	Cross-sectional	
Kozuki, Y.	2003	USA	Cross-sectional	
Lang, K.	2010	USA	Retrospective cohort	12 months
Lang, K.	2013	USA	Retrospective cohort	12 months
Meier, J.	2010	Germany (London, Amsterdam, Italy) ^a	Cross-sectional	
Nageotte, C.	1997	USA	Cross-sectional	
Quach, P.L.	2009	Denmark	Prospective cohort	2 years
Robinson, D.G.	2002	USA	Prospective cohort	5 years (until relapse then 100 days after)

^a Indicates that data from the countries in brackets have been included.

gap calculations,^{21,25} and one study applied systematic examination of case notes.²² All significant risk factors for non-adherence are reported in Table 4.

Patient-related factors

All 13 studies investigated patient-related factors. Age between 20–29 and age <35 as well as younger age (unspecified) was found to be a significant factor for non-adherence in four studies.^{19–22} One study investigated age groups where being in the age group <45 compared to age group >45 was a risk factor.²⁵ All studies included age as a potential risk factor.

Being non-white, being married vs. being single and showing hostility/excitement and feeling victimized was found to be a significant risk factor in one study.³⁰ One study showed that an educational level of below or equivalent to high school level was a significant factor.²⁷ Lower education level (unspecified) was found to be a factor in one study when measuring time to discontinuation of treatment at the time of first relapse.²⁸ Four studies did not investigate ethnicity.^{19,20,22,28} All except one²² reported marital status. Hostility/excitement, feeling victimized or stigmatized was investigated in only two studies.^{27,30}

Four studies showed an association between non-adherence and alcohol abuse^{20,23,27,30} and four studies showed illicit drug use/substance abuse to be associated with non-adherence.^{20,23,27,30} One additional study found that having a substance abuse diagnosis was a factor for non-adherence²⁵ and one study showed an associated between harmful use of or dependency of psychoactive drugs, alcohol and tobacco.²² Three studies did not investigate any factors related to substance abuse.^{26,31,28}

One study found an association between non-adherence and prior non-adherence,³⁰ which only two studies investigated.^{20,30} Another study showed that poor premorbid cognitive function was a significant risk factor,²⁸ which was investigated by four studies.^{20,23,27,28}

Lack of insight of illness was a factor in five studies^{19,22,23,29,31} which were investigated in nine out of 13 studies. One study showed lack of awareness of mental disorder was a significant factor for non-adherence as well as lack of awareness of medication effect.²²

Both higher and lower Global Assessment of Function (GAF) scores were associated with a higher risk of being non-adherent. Two out of four studies applied this instrument.^{22,31} One study showed poorer premorbid functioning was associated with non-adherence as well.²⁰ Premorbid functioning differs from premorbid cognitive ability, as it investigates general function and not only cognitive abilities.

One study showed no significant factors in any of the risk factor groups although claiming Drug Attitude Inventory (DAI) was significant. There was however no statistical evidence to support this interpretation.²⁶

Mental illness-related factors

Seven studies investigated mental illness-related factors.^{19–21,25,27,28,30} Several studies showed that co-existing mental illnesses were factors for non-adherence. Two studies showed that depressive symptoms were factors for non-adherence^{28,30} and depression or anxiety was found to be significant factors in one study.³⁰ Another study measured the use of antidepressants, anxiety medication and mood stabilizer use as being a risk factor.²⁵ These factors are not medication-related in the terms applied in this review as they are considered treatment for another concomitant

Table 2 Subjects' demographics and patient-related characteristics.

Author	Population size	Age (mean $\pm$ SD)	Sex (male%)	Ethnicity	Diagnostic system	Generation of antipsychotics	Medication regime reported	Setting
Agerwal, M. 1998	78	Non-adherent: 39.2 $\pm$ 11.5 Adherent: 33.2 $\pm$ 9.6	68%	NA	ICD-10	NA	Oral LAIs	NA
Ascher-Svanum, H. 2006	1579	Non-adherent: 41.6 $\pm$ 11.2 Adherent: 42.44 $\pm$ 11.3	59.9%	White 58.1% Other 41.9%	NA	NA	Oral: NA LAIs: 17.06% Combination: NA	Outpatients
Coldham, E. 2002	186	23.6 $\pm$ 7.7	66%	NA	DSM-IV	NA	NA	Outpatients First-episode
Hudson, T.J. 2004	153	45.2 $\pm$ NA	94%	White 22%	ICD-9	NA	NA	Outpatients
Jonsdóttir, H. 2012	154	33.2 $\pm$ 9.3	54%	White 79.2%	DSM-IV	First gen 9.7% Second gen 85% Unknown 5.3%	NA	Outpatients
Kikkert, M.J. 2008	329	41.3 $\pm$ 1.6	56%	White 77%	ICD-10	NA	Oral LAIs	Outpatients
Kozuki, Y. 2003	132	39.8 $\pm$ 12.5	64%	White 41.6% Black 30.6% Hispanic 7.5% Other 18.7%	DSM-IV	First gen 53.5% Second gen 46.6%	Oral	Outpatients

Table 2 (Continued)

Author	Population size	Age (mean $\pm$ SD)	Sex (male%)	Ethnicity	Diagnostic system	Generation of antipsychotics	Medication regime reported	Setting
Lang, K. 2010	12.032	43.2 $\pm$ 13.0	48%	White 27% Black 25% Hispanic 36% Unknown 1%	ICD-9	First gen 16% Second gen 70% Combined 14%	Oral LAIs	Inpatients Outpatients
Lang, K. 2013	28.238	Medicaid: 42.6 $\pm$ 14.1 Commercial: 47.9 $\pm$ 17.1	46.8%	NA	ICD-9	First gen 18.6% Second gen 70% Combination 11.4%	Oral: 79.9% LAIs: 20.1%	Inpatients Outpatients
Meier, J. 2010	409	41.5 $\pm$ 11.5	59.9%	White 76%	ICD-10	First gen 26.7% Second gen 58.5% Combination 14.8%	Oral: 73.9% LAIs 17.1% Combination 9.0%	Outpatients
Nageotte, C. 1997	202	34.7 $\pm$ 8.8	68%	White 21% Black 79%	Chart Diagnosis ^a	NA	Oral: 78% LAIs 22%	Inpatients Outpatients
Quach, PL. 2009	547	26.7 $\pm$ 6.4	57.5%	NA	ICD-10	NA	Oral: NA LAIs > 5%	Inpatients Outpatients First-episode
Robinson, DG. 2009	118	25.0 $\pm$ 6.5	53%	White 40% Black 38% Hispanic 12% Other 10%	RDC	NA	NA	Inpatients Outpatients First-episode

Sample size, age and distribution of sex reported at start of study. Age reported for the entire sample if available. Generation of antipsychotics and type of treatment reported with distributions if available

NA: not available, ICD-9/10: International Classification of Disease, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, RDC: Research Diagnostic Criteria.

^a No further definition available.

Table 3 Definitions of adherence and adherence measures.

Authors	Adherence definition	Measures	Non-adherence rate
Agerwal, M. 1998	Dichotomous Non-adherence: Patient report of not taking medication, only taking it while supply, family or general practitioner claiming the patient had not been taking medication regularly or discontinued taking medication on the disappearance of perceived symptoms Adherence: If deemed adherent by all of the above	Patient-reported Family-reported Clinician-reported: Assessed over previous 12 months by method used by Lin et al. (1979)	38.5% ^a
Ascher-Svanum, H. 2006	Dichotomous Adherence: Medical possession rate >80% during 1 year and reporting adherence in 2 consecutive assessments Non-adherence: All other reports	Patient-reported: 5 point rating scale (SCAP-HQ) Medical records review Prescription cards: Systematically abstracted every 6 months	18.8%
Coldham, E. 2002	Categorical Non-adherence: Dropped out before 1 year and/or took medication erratically or not at all Inadequate adherence: Took medication irregularly by skipping doses but not longer than a few weeks at a time during 1-year period Good adherence: Rarely or never missed a dosage	Clinician-reported: 3 point scale adopted from Hayward et al. (1995) Medical records review: By primary rater and compared to case managers adherence rating	Non-adherence 39.3% Inadequate adherence 19.9%
Hudson, T.J. 2004	Dichotomous Adherence: Rating of 1 or 2 (Never missed medication or missed a couple of times) Non-adherence: Rating of 3–5 (Missed several times but took at least half, stopped taking medication altogether) Non-adherence: if research assistants reviewed medical records for all inpatient and outpatient encounters and found that patient had not taken antipsychotic medication prior to encounter	Patient-reported: 5-point scale, 30 days prior to interview. Medical records review: With instrument by the corresponding author	Inpatients: 94% Outpatients: 55%
Jónsdóttir, H. 2012	Categorical Full adherence: 100% reported adherence and serum ratio within reference range or higher Partial adherence: 95–12% reported adherence and serum ratio lower than recommended Non-adherence: 0% reported adherence and no detectable drugs	Patient-reported: Likert scale 0–100% Blood samples (serum concentration)	Non-adherence: 11% ^a Partial adherence: 33.8% ^a
Kikkert, M.J. 2008	Dichotomous Non-adherence was defines as being non-adherent in at least two of the applied measures	Patient-reported: MAQ by Morisky et al. (1986) Clinician-reported: CRS 7-point scale. Drug Attitude Inventory: 10 yes/no statements reflecting patients' experiences, attitudes and beliefs about medication	18.3%

Table 3 (Continued)

Authors	Adherence definition	Measures	Non-adherence rate
Kozuki, Y. 2003	Categorical An algorithm including multiple adherence measures determined rates of non-adherence to psychotropic medication for the 3 weeks prior to hospitalization	Patient-reported: Via the Rating of Medication Influences (ROMI) Questionnaire Medical records review	Complete non-adherence: 56.1% Partial non-adherence: 18.2%
Lang, K. 2010	Dichotomous Non-adherence: MPR < 0.8 Adherence: MPR ≥ 0.8	MPR (several calculations) Medication persistence Consistency Maximum continuous gap	34%
Lang, K. 2013	Dichotomous Non-adherence: MPR < 0.8 Adherence: MPR ≥ 0.8	MPR (several calculations) Medication persistence Consistency Maximum continues gap	39%
Meier, J. 2010	Dichotomous Non-adherence: MAQ < 4 or CRS < 5 Adherence: MAQ ≥ 4 or CRS ≥ 5	Patient-reported: MAQ (available for 396 patients) Clinician-reported: CRS 7 point scale (available for 377 patients)	Based on MAQ: 52.8% Based on CRS: 23.6%
Nageotte, C. 1997	Dichotomous All medication or occasionally missed = adherent. Less than or equal to pen half of medication = non-adherent. Disagreement between family and subject = non-adherence	Patient-reported Family-reported: By Miklowitz et al. (1986)	47%
Quach, PL. 2009	Dichotomous Scores calculated from the following six categories: 0 = prescribed but not started 1 = prescribed but discontinued 2 = unregulated medicated 3 = medicated as prescribed 8 = medication not prescribed 9 = missing Scores indicating good adherence with medication or poor adherence with medication	Patient-reported Clinician-reported (Information from psychiatrist) Systematic examination of case notes Prescription cards	First year: 51% Second year: 44%
Robinson, DG. 2002	Dichotomous Medication discontinuation/non-adherence: failure to take medication for 1 week of longer	Patient-reported Family-reported Clinician-reported (information from psychiatrist)	26%

For prospective cohorts, adherence rates are reported at one-year follow-up. Further rates at different points of follow-up are reported if available

^a Calculated non-adherence rates from available information were possible.

mental illness. The presence of other psychoses was also significantly associated with non-adherence in one study.²¹ Only two studies did not report investigating co-existing mental illnesses or related factors.^{29,31} Age of onset when between 20 and 30 years of age where more likely to be non-adherent in one study¹⁹ but was only investigated by three studies in total. Earlier onset of illness was also found to be a factor in one study.²⁰ One study found that episodic duration of illness was a factor for non-adherence.¹⁹ Six studies did not report investigating factors associated with course of illness.^{21–25,31}

Higher symptom severity according to Positive and Negative Syndrome Scale (PANSS) total score was associated with non-adherence in one study,²⁷ although five studies used PANSS.

Medication-related factors

Measures of side effects were included in ten studies^{19,20,22–24,26–30} of which one study showed an association with the lack of side effects and non-adherence.¹⁹

Table 4 Risk factors for non-adherence.

Author	Patients-related risk factors	Mental Illness-related risk factors	Medication-related risk factors	Environment-related risk factors
Agerwal, M. 1998	- Between 20–29 years of age (<i>p</i> -value 0.03) - Lack of insight into illness (<i>p</i> -value 0.03)	- Episodic duration of illness (<i>p</i> -value <0.001) - Earlier age at onset of illness (<i>p</i> -value <0.001)	- Lack of side effects (<i>p</i> -value 0.04)	- Key relative is employed (<i>p</i> -value 0.02)
Acher-Svanum, H. 2006	- Non-white (<i>p</i> -value 0.043) - Married (vs. single) (<i>p</i> -value 0.004) - Hostility/excitement (<i>p</i> -value 0.007) - Alcohol use (<i>p</i> -value <0.001) - Illicit drug use (<i>p</i> -value <0.001) - Violent behavior (<i>p</i> -value 0.005) - Feeling victimized (<i>p</i> -value <0.001) - Prior non-adherence (<i>p</i> -value <0.001)	- Depressive symptoms (<i>p</i> -value <0.001) - Depression/anxiety (<i>p</i> -value <0.001)	- Extra-pyramidal symptoms (<i>p</i> -value 0.016) - Subjective adverse effect (<i>p</i> -value <0.001) - Subjective medication-related cognitive impairment (<i>p</i> -value <0.001)	- Arrested/jailed (<i>p</i> -value <0.001) - Prior psychiatric hospitalization (<i>p</i> -value 0.011)
Coldham, E. 2002	- Younger age ^a (<i>p</i> -value 0.015) - Poorer insight into illness (<i>p</i> -value 0.02) - Cannabis (<i>p</i> -value 0.04) - Alcohol use (<i>p</i> -value 0.02) - Poorer premorbid functioning (<i>p</i> -value 0.006)	- Earlier onset of illness (<i>p</i> -value 0.002)		
Hudson, T.J. 2004	- Education (below or equivalent to high school level) (<i>p</i> -value 0.02) - Alcohol/drug abuse (<i>p</i> -value 0.01) Barriers = >2 ^b (<i>p</i> -value 0.05)	- PANS ^d total score (symptomer) (<i>p</i> -value 0.05)		
Jónsdóttir, H. 2012	- Reduced insight (<i>p</i> -value 0.013) - Substance and alcohol abuse (<i>p</i> -value 0.001)			
Kikkert, M.J. 2008	- Lower GAF ^c score (<i>p</i> -value 0.005) - Reduced illness insight (<i>p</i> -value 0.005)			
Kozuki Y. 2003				- Homelessness (<i>p</i> -value <0.001)

Table 4 (Continued)

Author	Patients-related risk factors	Mental Illness-related risk factors	Medication-related risk factors	Environment-related risk factors
Lang, K. 2010 ^e	- Substance abuse diagnosis (CI95% 1.39–1.71) - Age <45 compared to >45 (CI95% (1.20–1.47)	- Mood stabilizer use (CI95% 1.06–2.90) - Antidepressant use (CI95% 1.32–1.96) - Anxiety medication use (CI95% 1.15–1.63)	- New-start user (CI95% 3.03–3.88) - LAIs 1. generation use only, when compared to 1. generation oral (CI95% 1.05–1.59)	
Lang, K. 2013	- Younger age <35% (<i>p</i> -value 0.001) - Substance abuse (<i>p</i> -value 0.001)	- Other psychosis (<i>p</i> -value 0.001)	- New-start user (<i>p</i> -value <0.001) - Baseline anxiolytic use (<i>p</i> -value 0.03)	
Meier, J. 2010				
Nageotte, C. 1997	- Lack of illness insight (<i>p</i> -value <0.05)			- Inpatient status (<i>p</i> -value <0.01) - No care in the last three months (<i>p</i> -value <0.05)
Quach, PL. 2009	- Lack of insight into illness (<i>p</i> -value 0.001) - Lack of awareness to mental disorder (<i>p</i> -value 0.001) - Comorbidity harm or dependence syndrome (<i>p</i> -value 0.01) - Young age (<i>p</i> -value 0.008) - High GAF ^c function at 1 year follow up (<i>p</i> -value 0.03) - Less aware of the medication effect and consequences of mental disorder (<i>p</i> -value 0.001)		- Negative attitudes toward medication (<i>p</i> -value 0.0001)	- No upbringing by both parents (<i>p</i> -value 0.01) - No key relative to interview at entry (<i>p</i> -value 0.03)
Robinson, DG. 2002	- At 1. relapse ^f : Poor cognitive function (<i>p</i> -value 0.01) - Lower education level (<i>p</i> -value <0.05)	- At 1. relapse ^f : Depressive symptoms (<i>p</i> -value <0.05)	- At 1. relapse ^f : Parkinson-like side effects (neurological side effects) (<i>p</i> -value <0.01)	- At 1. relapse ^f : Poorer parental social class (<i>p</i> -value <0.01)

^a No further definition reported in original article.

^b Barriers are not allocated to any specific risk factor group because they contain measures that vary in risk factor association. <2 barriers indicate that if patients have more than two barriers, they are more likely to be non-adherent.

^c Global Assessment of Functioning.

^d The Positive and Negative Syndrome Scale.

^e No *p*-values available.

^f At 1. Relapse indicates the risk factors measured at the time the patient relapse for the first time during the study, although some of the participants are follow for a longer time period.

One study showed neurological side effects were associated with non-adherence.²⁸

Differences in administering of antipsychotics were not a primary outcome measure in most studies, but one study found an association between the use of FGA as LAI and

non-adherence when comparing FGA administered orally.²⁵ Five studies investigated type of medication^{21,23–26} and two reported dosage changes over time.^{26,31} The use of anticholinergic drugs was found to be a risk factor in one study²¹ and being a new-start user of antipsychotic therapy was also

found to be a risk factor in two another studies.^{21,25} Six studies investigated attitudes toward medication^{19,22,24,26,29,31} but only one study found a significant association between a negative attitude toward medication and the risk of being non-adherent.²² Four studies investigated awareness of medication effect^{19,24,26,29} and one study investigated lack of trust in provider.²⁷ None of these found significant results linked to non-adherence.

Environmental-related factors

One study investigated being arrested/jailed as a factor and which proved to be a significant factor for being non-adherent.³⁰ Another study supported this claim by showing inpatient status as being a factor for non-adherence, which might be explained by compulsory hospitalization.²⁹ Only three studies investigated patient status as a potential factor. Homelessness was investigated by one study and proved to be a factor for non-adherence,²⁴ but eight studies investigated living circumstances in general.^{19,20,22,24,26,27,29,31} No care received in the last three months was also a significant factor investigated by one study.²⁹

One study showed an association between not having a key relative connected to the study when conducting the entry interview as well as not having been brought up by both parents during childhood.²²

One study found that when a key relative was employed, the patient seemed more likely to be non-adherent to pharmacological treatment.¹⁹ Investigating different aspects of social support was only done in five studies^{19,20,22,27,29} and without consistency in type of social support, varying from family knowledge of disease to unspecified social support. One study found that poorer parental social class was also a significant factor for non-adherence.²⁸ Families socioeconomic status was only investigated in this study.

One study examined barriers toward adherence to pharmacological treatment.²⁷ The authors predefined several possible barriers (stigma, adverse drugs reactions, memory problems, lack of social support, afraid of medication, denial of illness, lack of trust in provider, difficulty with regime and "other" barriers such as homelessness or substance abuse). In the analysis, it was concluded that patients who had more than two barrier present were significantly more likely to be non-adherent to treatment.²⁷

Quality appraisal

According to STROBE and the NIH tool for quality assessment nine studies were deemed to be of fair quality.^{19–21,23,24,26,27,29,31} Two studies were deemed to be of poor quality, and susceptible to selection bias due to lack of information on population sample and participation rate of eligible participants as well as not explaining how to address bias in general.^{22,28} Two studies were of good quality with reporting of almost all items in both quality appraisal tools.^{25,30} Across the studies, the item mostly lacking sufficient reporting, was power calculations to argue sufficient power for the statistical analysis. Reporting of statistical analysis were also lacking especially with regards to reporting of missing data, loss to follow-up and performing sensitivity analysis.

Discussion

This systematic review found several risk factors for non-adherence to pharmacological when assessing peer-reviewed literature in two supplementary databases Pubmed and PsycINFO and identified a non-adherence rates across studies within the range of 11.0–71.9%.

Previous published reviews report an average rate of medication adherence of 40–60%.^{32,33} Some studies indicate that adherence rates decline with a rate of 75–90% within 1–2 years from discharge.^{34,35} However, non-adherence is without a clear definition as some publications consider a patient taking medication 75–80% of the time to be an acceptable level of adherence.^{36–38} Developing and implementing interventions to support patient adherence have been reported to be difficult due to this lack of a standard definition.³⁹

Patient-related factors

Ethnicity (being non-white), marital status, lower level of education and younger age were significant factors in the included articles but are not consistent throughout the literature^{40–42} and were only investigated in a few studies in this review. Eight studies found any substance abuse (alcohol and/or drugs) was associated with pharmacological non-adherence. This association is well established in current available literature.^{32,33,40,43,44} It is however problematic, that studies do not share a common definition of alcohol and/or substance abuse and many studies rely on self-reported abuse, which are unvalidated and may result in underestimation.

Poor cognitive function is likely to have an effect on the ability to be adherent to a pharmacological regime. A bimodal effect of cognitive function to non-adherence is a distinct possibility with one study reporting that poor cognitive function was associated with non-adherence to pharmacological.²⁸ This risk factor was not identified in the other reviews^{32,40} but other studies report conflicting data with regards to cognitive impairment and non-adherence.^{45,46} Some studies even demonstrate that executive function and memory impairment are predictors for adherence.^{46,47} There is also discrepancy between GAF-scores effect on adherence with one study demonstrating low GAF-score being associated with non-adherence and another associating high GAF-scores with non-adherence.^{22,31} It cannot be excluded that the study by Kikkert et al, which is a cross-sectional study, simply demonstrates a lower level of functioning due to nonadherence. Seven out of 13 studies found significant results linking poor insight or lack of awareness of illness as a factor for non-adherence. Essentially they all come to the conclusion that lack of insight/awareness can result in lack of understanding for the need for treatment, as consequences of illness are poorly perceived. Patient-related factors have shown an inconsistent pattern of association with non-adherence.^{32,41}

Mental illness-related factors

The course of illness has been identified as having an effect on adherence and earlier age at onset of illness was found to

be a risk factor for non-adherence. This could be due to the fact that patients are in general younger (demonstrated as a possible risk factor for non-adherence earlier in this review) or that earlier onset of illness is possibly associated with a more severe course of illness. During longer lasting illness, the need for antipsychotic medication might be conceived to be less or patients might find it hard to continue prolonged and possible life-long antipsychotic treatment in the absence of self-perceived symptoms. Episodic duration of illness was also found to be a risk factor for non-adherence in another study. It might seem contradictory that almost all courses of illness seem to be associated with non-adherence, but it emphasizes the need for establishing psychopharmacological treatment early in the course of illness and maintaining increased focus on treatment when being very prolonged or when only episodic symptoms are present.

Symptom severity measured by PANSS total score was found to be a factor in one study although several studies applied it and used it for differential outcome measures. There were inconsistencies with regards to symptoms severity being a factor for non-adherence in other systematic reviews related to this topic.³² Psychiatric comorbidity defined as having a diagnosis of depression or anxiety were significant factors for non-adherence in three studies. Contributing factors from psychiatric comorbidity can influence level of functioning or contribute with other symptoms, which makes it difficult to remain adherent. Comparing with a recently published review, the association between psychiatric comorbidity and non-adherence was only partially established.³² A possible explanation could be that symptoms of psychiatric comorbidity could be under-diagnosed as the main focus is on the schizophrenia diagnosis. Additional use of psychopharmacology such as mood stabilizers, antidepressants and anxiety medication was found to be a risk factor for non-adherence in one study. However this can be a confounder, being in reality an expression of the presence of psychiatric comorbidities, which may themselves contribute to non-adherence. The use of several types of medication can also be an expression of a more comprehensive medication regime, which can have implications for adherence as complexity increases. In conclusion, symptom severity seems to be highly associated with non-adherence, resulting in lower adherence as symptoms increase.⁴⁸

Medication-related factors

One study found negative attitudes toward antipsychotic medication to be a risk factor for non-adherence. In the review by Sendt et al. it was found that patients whose family demonstrated a more positive attitude toward medication were more likely to be adherent.⁴⁰ The study by Lacro et al. also showed that negative attitudes or subjective response to medication was associated with non-adherence.³² One study found that at first relapse of patients, Parkinson-like-side-effects (neurological side-effects) were found to be associated with non-adherence.²⁸ In the review by Sendt et al. three studies found a relationship between fewer experienced side effects and better adherence.⁴⁰ In conclusion, when considering medication-related risk factors of non-adherence, a complex medication regime is associated with non-adherence, whereas side

effects experienced do not show a clear effect on non-adherence.^{28,32,44,49} Polypharmacy is not recommended as first-line treatment for schizophrenia and there is limited evidence of the effect of concurrent use of multiple antipsychotic medications although it is common in clinical practice.⁵⁰

Environmental-related factors

This review found several risk factors for non-adherence associated with patients social environment. Having a key relative employed was associated with a risk of being non-adherent in one study.¹⁹ Availability of a key relative might be lacking if no relative was present at study entry, which was also found to be a risk factor in one study as well as lack of upbringing by both parents.²² Poorer parental social class was also found to be a risk factor.²⁸ Those findings might indicate lack of social support and a lack of a stable home environment. Psychical environment was also found to be a potential risk factor. Having been arrested/jailed was found to be associated with a risk of being non-adherent to pharmacological treatment³⁰ as was prior psychiatric hospitalizations. Having been arrested/jailed or psychiatrically hospitalized could be due to a more severe course of illness, which would explain the findings. Being homeless was found in one study to be associated with non-adherence although it is not a factor comprehensively investigated in the studies included in this review.²⁴ One study found an association between non-adherence and lack of psychiatric care in the last three-months.²⁹ This risk factor stresses the importance of a support system and continuous outpatient care to maintain adherence. Prior psychiatric hospitalization were another risk factor which both can be associated to the environment of a psychiatric hospital as well as being severely ill.³⁰ Two studies investigated this factor.^{30,31}

Measurements

Objective measures of non-adherence provide a momentary expression of current behavior, depending on the dosages regimen and drug metabolism.⁵¹ A momentary expression of a lifelong illness limits the accuracy of the measurement in a longitudinal assessment. These variations may result in misclassification of adherence, especially if applying a dichotomous definition of adherence. As argued by Sendt et al. a shift from a dichotomous definition to a view that consider adherence and non-adherence are two ends of the spectrum, would be much more useful in research, but are yet to be established as the standard in adherence-research.^{38,40}

The review by Jónsdóttir et al., with a 11% non-adherence rate, had a very rigorous definition of non-adherence: patient self-reported to be 0% adherent and with no detectable drugs in the blood. Partial adherence was defined when the patient reported being adherent between 12% and 95% and with a serum ratio lower than recommended.²³ This providing a large partially adherent group compared to the deviation in other studies. Hudson et al. had divided their non-adherence rate in an inpatient and outpatient group. Whereas the inpatient group where 95% non-adherent the outpatient group 55% non-adherent.²⁷

Counting pills and the Medication Event Monitoring System (MEMS) are methods frequently applied in attempt to measure adherence. When using MEMS, manipulation by patients is quite easily done, thereby questioning the accuracy of this method.^{52,53} Monitoring pharmacy records is also widely applied as an objective measure but does not confirm ingestion of the medication retrieved at the pharmacy.¹⁵

The studies included in this review are no exception from the extensive use of subjective measures in adherence research with 11 out of 13 studies applying subjective measures in forms of structured interviews or questionnaires. The two studies that did not apply these types of subjective measures were register-based studies.^{21,25} Lack of validation of subjective instruments is a well-known problem.³¹ In general, overestimation of adherence levels as well as liability to recall- and reporting bias by patients and family as well as underdetection of non-adherence by clinicians is potential problems with subjective measurements.^{54–56} No measurement is therefore considered exhaustive and multiple measures, as applied in this review, are advised to more accurately reflect adherence level or status. By defining criteria that only included articles with two adherence measures, this review is conservative in its inclusion and therefore may exclude studies with otherwise thorough research methodology. This also explains the discrepancies however minute from previously performed systematic reviews on this subject. If considering risk factors as independent variables and adherence as the dependent variable the heterogeneity of instruments used to measure these variables pose a problem in establishing correlation and possible causation. The direct comparison between different instruments evaluating the same domain is not appropriate, although it is common, therefore a combined non-adherence rate could not be calculated in this review. Due to a low number of suitable articles none were excluded due to applying un-validated questionnaires when assessing adherence.

Strengths and limitations

The generalizability of the findings in this review, is impaired due to the diversity in measuring and evaluating adherence as described previously. Also the focus of this review was to include studies on the general schizophrenic population without including studies that focus solely on sub-groups such as the elderly or veterans. When examining the actual study population, the results found in this systematic review are primarily based on a young to middle-aged white male schizophrenic population with the majority of studies originating from the USA.

Two databases were applied in the effort to include as many relevant articles as possible, which broadened the scope of articles for review. To identify potential studies for inclusion after this review was performed, a supplementary search was conducted using the same criteria and the search-period 01/01/2015 until 18/08 2016. This supplementary search yielded no further eligible articles.

The quality appraisal was done using two different tools to ensure a thorough evaluation of the articles included in this systematic review. Only minor differences in the appraisals of the included studies were identified. The lack of consistency in applied measurements, definition of

adherence and misrepresentation of risk factors stresses the importance of strengthening the methodological framework within adherence research. More research is needed within the field of adherence in psychiatric research to improve methodology and to get a more clear understanding of the mechanisms contributing to non-adherence.

Conclusion

In conclusion this review identifies several risk factors for non-adherence whereas some of the most frequently identified are younger age, substance abuse and lack of insight into own illness. It is although important to notice that there are many other factors to consider when investigating non-adherence in a schizophrenic population. Many factors have a direct or indirect effect on other factors, which is why it is recommended to address the risk factors from a broader perspective. Due to heterogeneity in the methodological framework in the included studies future adherence research should focus on establishing a consensus concerning the definition of adherence. This updated systematic review provides an overview of current literature, but further studies concerned with testing and implementing support initiatives for patients with schizophrenia is urgent to improve adherence in this patient population.

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Conflict of interest

None.

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