CNS Drugs (2020) 34:579–598
https://doi.org/10.1007/s40263-020-00713-9

SYSTEMATIC REVIEW

Adherence to Oral Antipsychotics Measured by Electronic Adherence Monitoring in Schizophrenia: A Systematic Review and Meta-analysis

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Published online: 26 March 2020

Abstract

Background Poor adherence to oral antipsychotics is common in patients with schizophrenia; nonetheless, there has been no systematic review or meta-analysis on medication adherence measured by electronic adherence monitoring (EAM), considered by many as the 'gold standard' assessment.

Methods We systematically searched MEDLINE and Embase to identify studies investigating adherence to oral antipsychotics using EAM in patients with schizophrenia spectrum disorder. There were no exclusion criteria. We looked at the methodology in each study and defined which type of adherence was used in the study. Data on medication adherence, definition of satisfactory adherence (i.e., the threshold set in terms of the percentage of times medication was taken as prescribed), and factors associated with adherence were extracted for the included studies. Further, data on the rates of medication adherence were quantitatively synthesized.

Results A total of 19 studies involving 2184 patients were included. EAM-measured medication adherence was classified into three outcome types: taking adherence, regimen adherence, and timing adherence. The meta-analysis yielded oral antipsychotic adherence rates (defined as a continuous variable) of 71.1% for taking adherence [from seven studies, $n=256$, 95% confidence interval (CI) 58.0–84.1], 70.0% for regimen adherence (from five studies, $n=174$, 95% CI = 63.6–76.4), and 64.9% for timing adherence (from four studies, $n=212$, 95% CI 53.2–76.6), respectively. The proportions of patients with oral antipsychotic adherence, when defined as a dichotomous variable, ranged from 50 to 78.3% for the 70% threshold for satisfactory adherence, 29.8–75.7% for the 75% threshold, and 47.8–75.7% for the 80% threshold. Factors associated with poor medication adherence were greater symptom severity, more frequent dosing regimen, poorer insight, and more negative drug attitude.

Conclusions Oral antipsychotic adherence rates in schizophrenia, defined as a continuous variable and measured by EAM, were in the range of 70%, lower than the 80% threshold used widely to define satisfactory adherence.

1 Introduction

Treatment with antipsychotic medications is necessary in both the acute and maintenance phases of schizophrenia to improve symptoms and prevent relapse [1–3]. However, in schizophrenia, poor adherence to oral antipsychotics (e.g., defined as taking medications as prescribed 75% of the time or less) is common, with reported rates in the range of 50% [4, 5], and it is associated with an increased risk of relapse, re-hospitalization, and suicide [6]. Factors related to poor medication adherence include lack of insight into illness, substance abuse, negative attitude to medication, cognitive impairment, and poor therapeutic alliance [7–9].

Medication adherence is evaluated by various measures such as self-report, patient rating scales (e.g., Drug Attitude Inventory (DAI) [10], Brief Adherence Rating Scale (BARS)

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Key Points

This is the first systematic review and meta-analysis of medication adherence, as measured by electronic adherence monitoring (EAM) (considered the gold standard for assessment of adherence) in schizophrenia.

EAM-measured medication adherence was classified into taking adherence, regimen adherence, and timing adherence: the meta-analysis yielded oral antipsychotic adherence rates (defined as a continuous variable) of 71.1%, 70.0%, and 64.9%, respectively.

Thresholds of 70%, 75%, and 80% were used across studies to define satisfactory medication adherence: the proportions of patients with oral antipsychotic adherence (defined as a dichotomous variable) ranged from 50% to 78.3%, 29.8% to 75.7%, and 47.8% to 75.7%, respectively.

Oral antipsychotic adherence rates in schizophrenia, defined as a continuous variable and measured by EAM, were in the range of 70%, lower than the 80% threshold used widely to define satisfactory adherence.

[11]), clinician/caregiver rating scales (e.g., Brief Evaluation of Medication Influences and Beliefs (BEMIB) [12]), pill count, blood drug concentrations, and electronic monitoring. While patients' or clinicians' ratings are the most commonly used, these often overestimate medication adherence [13]. Notably, an expert consensus guideline identified electronic monitoring, pill count, and plasma drug levels as reliable assessments [14]. Pill counts can be complicated in tracking dispensed medication, while therapeutic drug monitoring (TDM) struggles with precise thresholds for individual antipsychotics and inter- as well as intra-individual variability [15]. Among the different options for monitoring medication adherence, electronic adherence monitoring (EAM) such as the Medication Event Monitoring System (MEMS®) is considered the gold standard [16]. This consists of a medication bottle cap with a microprocessor that records the occurrence and time of each bottle opening.

There have been a number of investigations evaluating medication adherence in schizophrenia using EAM [17–19]. However, there are substantial differences between studies in how medication adherence is calculated, in addition to how satisfactory medication adherence is defined. Moreover, to our knowledge there has been no meta-analysis to summarize EAM-measured adherence to oral antipsychotics in schizophrenia. In light of this, we conducted a systematic review and meta-analysis to (1) summarize the methodology of EAM studies, (2) identify factors related to EAM-measured medication adherence, and (3) estimate overall EAM-measured adherence to oral antipsychotics in schizophrenia.

2 Methods

2.1 Literature Search and Study Selection

Two authors (H.Y. and S.K.) independently conducted a systematic literature search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20]. MEDLINE (1946–present) and Embase (1947–present) were searched using the following keywords (schizophreni* OR schizoaffective OR psychosis OR antipsychotic* OR neuroleptic*) AND ((electronic* AND monitor*) OR MEMS OR medication event monitoring system), with a limitation of English language (first search: August 5, 2018; last search: March 20, 2019). Studies that met the following eligibility criteria were selected: (1) investigating adherence to oral antipsychotics; (2) using EAM; and (3) including patients with schizophrenia spectrum disorders (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder, and delusional disorder). There were no exclusion criteria. Study selection was performed as follows: first, records were screened according to title and abstract, at which point the full text of articles was assessed for eligibility. Any disagreements in study selection were resolved by discussion with the senior corresponding author (H.T.).

2.2 Data Extraction

Two authors (H.Y. and S.K.) independently extracted the methodology from selected studies, including the definition of satisfactory medication adherence as well as the following clinical outcome data: (1) oral antipsychotic adherence rates when defined as a continuous variable; (2) adherence rates as per dichotomous variable definition; and (3) factors associated with medication adherence/non-adherence. We looked at the methodology in each study and defined which type of adherence was used in the study. Any disagreements in data extraction were resolved by discussion with the senior corresponding author (H.T.). It should be noted that for a randomized controlled trial (RCT) comparing medication adherence between an intervention group (i.e., using EAM with an alarm function) and a treatment-as-usual (TAU) group (i.e., using EAM without the alarm function) [21], we only included the TAU group, given the possibility that the alarm function inflated medication adherence.

2.3 Data Analysis

We performed a meta-analysis of rates of adherence to oral antipsychotics as a continuous variable from studies if the data were provided. Pooled estimates of mean rates of EAM-measured adherence to oral antipsychotics with two-sided 95% confidence intervals (CIs) were calculated using a random-effects model [22] by Comprehensive Meta-Analysis Version 2.0. The random-effects model was chosen because underlying true effects were assumed to vary between studies. Study heterogeneity was quantified using the I^2 statistic, with an I^2 value $\geq 50\%$ indicating significant heterogeneity. Funnel plots were visually inspected to assess the likelihood of overt publication bias [23].

3 Results

3.1 Characteristics of Included Studies

A total of 19 studies, involving 2184 patients and detailed in 26 articles [11, 13, 17–19, 21, 24–43] met eligibility criteria and were included in the systematic review (Fig. 1). Tables 1 and 2 summarize study characteristics and information on antipsychotics. The studies were published between 2004 and 2018, with study duration ranging from 1.5 to 12 months. Two types of EAM were used in the studies; one was a bottle cap type such as MEMS® ($N=16$) [11, 13, 17–19, 24, 25, 27–32, 34–43] and the other was a pill container type such as DoPill® with or without an alarm function ($N=2$ [26, 33] or $N=1$ [21], respectively). The former embeds a microprocessor that records occurrence and time of each bottle opening in the bottle cap. The latter is an electronic dispenser with 28 compartments that can contain multiple pills and often has sensors that record the time of opening, but also visual and sound alarms that alert the user when it is time to take medications. Only two studies [24, 43] were conducted in a blind fashion, where medication adherence was measured without disclosure to participants. Most participants were diagnosed with schizophrenia or schizoaffective disorder, and only one study [41] recruited patients with first-episode schizophrenia. Second-generation antipsychotics (SGAs) were administered more frequently than first-generation antipsychotics (FGAs) in all studies; antipsychotic details were not reported in five studies [13, 33, 35, 36, 43], and daily dose was reported in only one study [42]. Patients receiving clozapine and long-acting injectable antipsychotics (LAIs) were excluded in two [24, 32] and seven studies [17, 21, 24, 25, 29, 30, 32, 36, 43], respectively, while information regarding dosing regimen was provided in eight studies [13, 19, 24, 27–29, 32, 37–39].

3.2 Medication Adherence

Electronic adherence monitoring-measured medication adherence can be classified in three dimensions: taking adherence, regimen adherence, and timing adherence [44]. Collectively, they represent three levels of adherence. The most liberal, taking adherence, was defined as the number of bottle cap openings divided by the number of prescribed doses during the monitoring period. At the next level, regimen adherence was defined as the percentage of days that the correct number of doses was taken, a more stringent definition. Timing adherence, the most stringent definition, was defined as the percentage of doses taken within an assigned time window. The majority of included studies did not clarify whether adherence data represented the primary or secondary outcome.

Table 3 addresses the methods of evaluating medication adherence. There were two strategies; the first assesses medication adherence as a continuous variable ($N=14$) [11, 13, 21, 24–29, 31, 32, 34–40]. Figure 2 summarizes the results of the meta-analysis for oral antipsychotic adherence rates when defined as a continuous variable. The combined rates of taking adherence, regimen adherence, and timing adherence were 71.1% ($N=7$ [11, 26, 32, 34, 36, 37, 39], $n=256$, 95% CI 58.0–84.1, $I^2=94\%$), 70.0% ($N=5$ [13, 24, 34, 36, 37], $n=174$, 95% CI 63.6–76.4, $I^2=59\%$), and 64.9% ($N=4$ [25, 27, 34, 37], $n=212$, 95% CI 53.2–76.6, $I^2=95\%$), respectively. We performed a sensitivity analysis excluding one study [26] using the container type of EAM; the combined rate for taking adherence was 71.8% ($N=6$ [11, 32, 34, 36, 37, 39], $n=230$, 95% CI 57.2–86.3). Also, we performed a sensitivity analysis excluding one study [32] with an outlying result; the combined rate for taking adherence was 77.0% ($N=6$ [11, 26, 34, 36, 37, 39], $n=207$, 95% CI 67.3–86.8). All funnel plots were symmetrical, indicating no overt publication bias with regard to the outcomes. The second strategy is to treat medication adherence as a dichotomous variable and calculate proportion of patients with satisfactory medication adherence ($N=13$) [11,13, 17–19, 24–27, 29–31, 33–36, 39, 42, 43], defined using an arbitrary threshold. For example, it has been suggested by an expert consensus guideline that satisfactory adherence is defined as a patient taking $\geq 80\%$ of prescribed medications [14]. Amongst the 13 studies addressing this issue, we identified three thresholds of dichotomous medication adherence, above which medication adherence had been defined as satisfactory: 70%, 75%, and 80% were used in five [11, 13, 26, 31, 33, 39], four [18, 19, 36, 43], and six studies [17, 24, 25, 27, 29, 30, 39, 42], respectively. The proportions of patients with satisfactory oral antipsychotic adherence, defined as a dichotomous variable, ranged from 50 to 78.3% for the 70% threshold, 29.8–75.7% for the 75% threshold, and 47.8–75.7% for the 80% threshold of satisfactory adherence.

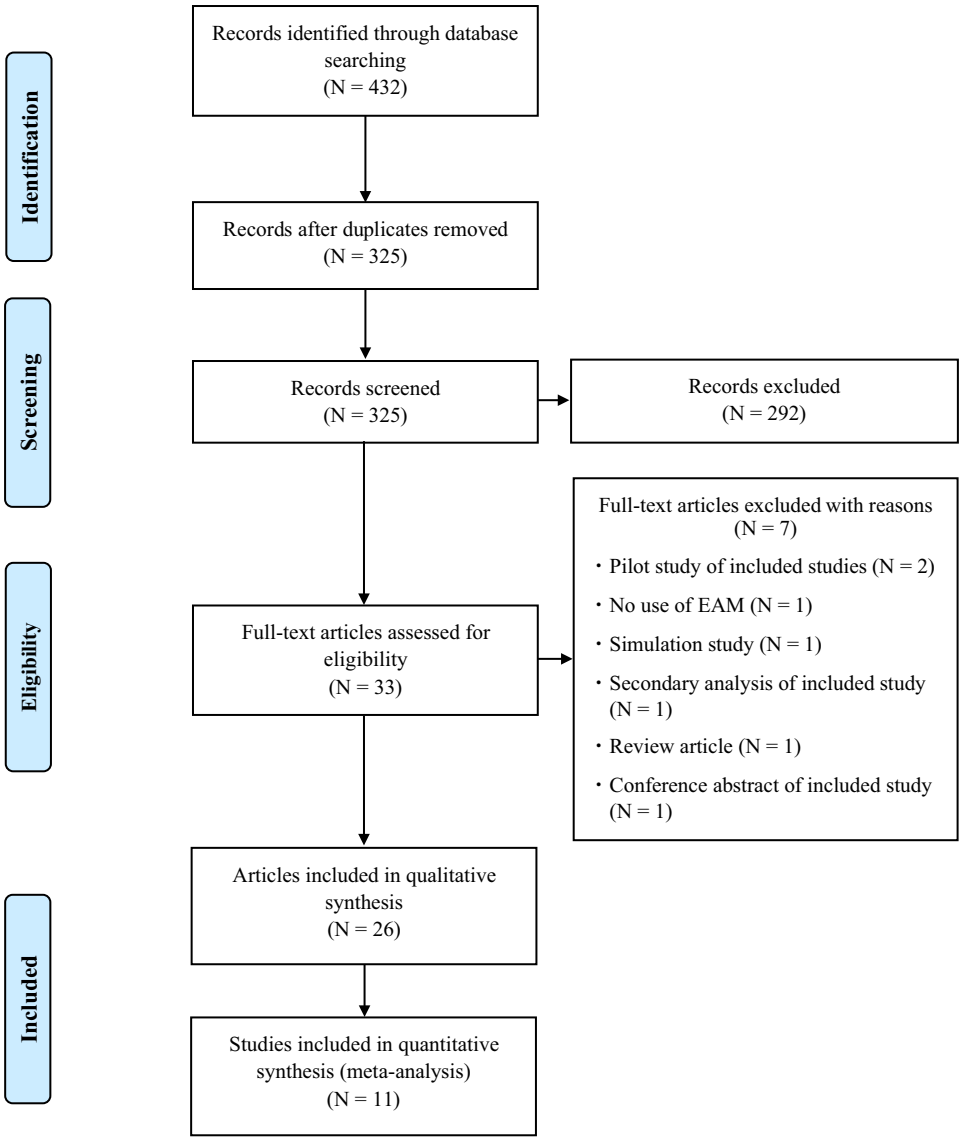


Fig. 1 PRISMA flow diagram. *EAM* electronic adherence monitoring, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Medication adherence measures other than EAM included pill count ($N=9$) [18, 21, 24, 25, 29, 34, 35, 41, 42], TDM ($N=5$) [30, 34, 35, 41, 42], and patient- or clinician-rating scales [e.g., BARS, BEMIB, DAI, Visual Analogue Scale (VAS)] ($N=11$) [11, 13, 17, 18, 24–26, 29, 31, 34, 36, 41, 42]. Five studies examined the relationship between medication adherence measures: pill count, BARS, and self-report were associated with EAM in three studies [24, 30, 42], one study [11], and one study [34], respectively.

In terms of factors related to poor medication adherence, greater symptom severity, more frequent dosing regimen, poorer insight, and negative attitude to medication were identified in six [11, 19, 24, 25, 40, 41], three [24, 32, 37], two [18, 19], and two [17, 25] studies, respectively.

4 Discussion

To our knowledge, this is the first systematic review and meta-analysis of medication adherence as measured by EAM (considered the gold standard for assessment of adherence) in schizophrenia. The main findings are (1) rates of EAM-measured adherence to oral antipsychotics, when defined as a continuous variable, approximated 70%; (2) thresholds of 70%, 75%, and 80% were used across studies to define satisfactory medication adherence; and (3) factors associated with poor medication adherence included greater symptom severity, more frequent dosing regimen, poor insight, and negative attitude toward medication.

The current meta-analysis revealed that the rates of EAM-measured adherence to oral antipsychotics in schizophrenia,

Table 1 Description of included studies

Study	Study duration, months	Patient awareness[a]	EAM type	Total n[b] (n[c])	Diagnosis, n (%)	Male, n (%)	Mean age, years	Mean education year	Mean illness duration, years
Diaz et al. (2004) [32]	3	Yes	Bottle cap type	49 (50) [Note: 1 in quetiapine group was excluded]	SCZ, 21 (43) SCA, 28 (57)	37 (74)	34.1	NR	NR
Byerly et al. (2005) [13]	3	Yes	Bottle cap type	25 (25)	SCZ, 18 (72) SCA, 7 (28)	18 (72)	39.2	NR	NR
Kozuki et al. (2005) [34]	3	NR	Bottle cap type	23 (23) [note: 45 EAM units. All participants received VFT]	SCZ, 16 (69.6) SCA, 2 (8.7) Mood disorders with psychotic features, 5 (21.7)	14 (60.9)	42.5	NR	NR
Kozuki and Schepp (2006) [35]	3	NR	Bottle cap type	14 (30) [note: 15 of 30 participants received VFT and 1 lost]	SCZ, 16 (53.3) SCA, 7 (23.3) Mood disorders with psychotic features, 7 (23.3)	17 (56.7)	46.5	NR	NR
(a) Nakonezny and Byerly (2006) [38] (b) Byerly et al. (2007) [31] (c) Byerly et al. (2008) [11] (d) Nakonezny et al. (2008) [40]	6	Yes	Bottle cap type	(a) (b) (c) (d) 61 (61)	(a) (b) (c) (d) SCZ, 35 (57.4) SCA, 26 (42.6)	(a) (b) (c) (d) 30 (49.2)	(a) (b) (c) (d) 44.3	(a) NR (b) NR (c) (d) NR [note: less than a high school education, $n=24$ (39.3%); at least a high school education, $n=37$ (60.7%)]	(a) NR (b) 21.2 (c) 20.9 (d) NR
Remington et al. (2007) [24]	1	No	Bottle cap type	52 (52)	SCZ, 35 (67.3) SCA, 17 (32.7)	26 (50)	36.0	13.2	13.2
Velligan et al. (2007) [42]	3	NR	Bottle cap type	52 (52)	SCZ, 52 (100)	27 (52)	42.4	NR	NR
(a) Acosta et al. (2009) [19] (b) Acosta et al. (2013) [27] (c) Acosta et al. (2014) [28]	3	Yes	Bottle cap type	(a) 74; 60 in oral group, 14 in oral + LAI group (97; 23 in LAI group) (b) 74 (74; 62 in oral group, 12 in oral + LAI group) (c) 57 (57; 47 in oral group, 10 in oral + LAI group)	(a) SCZ, 97 (100) (b) SCZ, 74 (100) (c) SCZ, 47 (100)	(a) 70 (72.2) (b) 51 (68.9) (c) 29 (61.7)	(a) 42.4 (b) 41.5 (c) 42.5	(a) (b) (c) NR [note: primary or below, $n=79$ (81.4%)]	(a) (b) (c) 16.8
Guevremont et al. (2010) [33]	1.5	NR	Pill container type with alarm	20 (20)	SCZ, 20 (100)	NR	NR	NR	NR

Table 1 (continued)

Study	Study duration, months	Patient awareness[a]	EAM type	Total n^b (n^c)	Diagnosis, *n* (%)	Male, *n* (%)	Mean age, years	Mean education year	Mean illness duration, years
Gutierrez-Casares et al. (2010) [18]	3	Yes	Bottle cap type	≤1360 (1848)	SCZ, 1360 (100)	1201 (65)	NR [note: < 20, 2%; 21–30, 24%; 31–40, 33%; 41–50, 24%; 51–60, 12%; > 60, 5%]	NR [note: tertiary or further, 5%]	13.1
Zhao et al. (2010) [43]	6	No	Bottle cap type	50 (50)	SCZ or SCA, 50 (100)	NR	NR	NR	NR
Lee et al. (2011) [36]	2	NR	Bottle cap type	10 (10)	SCZ or SCA, 10 (100)	5 (50)	33.1	12.8	8.5
Yang et al. (2012) [25]	2	NR	Bottle cap type	51 (51)	SCZ, 51 (100)	22 (43.1)	39.0	12.2	10.1
(a) Brain et al. (2013) [17] (b) Brain et al. (2014) [29] (c) Brain et al. (2014) [30]	12	Yes	Bottle cap type	(a) 112 (112) (b) 111 (111) (c) 117 (131)	(a) SCZ, 75 (67.0); delusional disorder, 10 (8.9); psychotic disorder NOS, 27 (24.1) (b) SCZ, 76 (68.4); delusional disorder, 9 (8.1); psychotic disorder NOS, 26 (23.4) (c) SCZ, 91 (69.5); delusional disorder, 10 (7.6); psychotic disorder NOS, 30 (22.9)	(a) 69 (61.6) (b) 70 (63.1) (c) 83 (63.4)	(a) 45.9 (b) 45.8 (c) 46	(a) NR (note: > 12 years, *n* = 64) (b) NR (note: > 12 years, *n* = 63) (c) NR (note: > 12 years, *n* = 71)	(a) (b) (c) 19.5
Nakonezny et al. (2013) [39]	6	Yes	Bottle cap type	23 (23)	SCZ, 9 (39.1) SCA, 14 (60.9)	11 (47.8)	46	NR [note: less than a high school education, *n* = 4 (17.4%); at least a high school education, *n* = 19 (82.6%)]	21.2
Stip et al. (2013) [26]	1.5	NR	Pill container type with alarm	26 (26)	SCZ, 18 or 19 (71)	16 (61.5)	38	12	11
Velligan et al. (2013) [21]	9	Yes	Pill container type	47 (47)	SCZ or SCA, 47 (100)	25 (52.8)	42	12.4	NR

Table 1 (continued)

Study	Study duration, months	Patient awareness[a]	EAM type	Total n^b (n^c)	Diagnosis, *n* (%)	Male, *n* (%)	Mean age, years	Mean education year	Mean illness duration, years
Subotnik et al. (2014) [41]	12	NR	Bottle cap type	66 (66)	SCZ, 41 or 42 (63) SCA, 7 (11) Schizophreniform disorder, 16 or 17 (25) Psychotic disorder NOS, 1 (1)	42 (69.7)	22.6	13.2	10.2 months[d]
Misdrahi et al. (2018) [37]	6	Yes	Bottle cap type	64 (68)	SCZ, 47 (69.1) SCA, 21 (30.9)	45 (66.2)	38.9	NR [note: primary or lower, $n = 36$ (52.9%)]	12.7

EAM electronic adherence monitoring, *LAI* long-acting injection, *NOS* not otherwise specified, *NR* not reported, *SCA* schizoaffective disorder, *SCZ* schizophrenia, *VFT* visual feedback therapy

[a]Disclosure of being monitored by EAM to participants

[b]Participants monitored by EAM

[c]All participants

[d]All patients had first-episode schizophrenia

defined as a continuous variable, were in the range of 70%. More specifically, the combined rates were 71.1%, 70.0%, and 64.9% for taking adherence, regimen adherence, and timing adherence, respectively, which notably diminishes as the stringency of definition increases. For comparison purposes, a meta-analysis evaluating EAM-measured medication adherence in chronic cardiovascular diseases reported ranges of 80.1–93.1% for taking adherence, 65.4–84.9% for regimen adherence, and 57.1–76.3% for timing adherence [44]. Further to this point, an observational study examining EAM-measured medication adherence in depressive disorders reported a mean of 68.5% for taking adherence [45]. It remains, however, that there are few studies measuring medication adherence with EAM in psychiatric disorders other than schizophrenia. Summarizing, medication adherence in schizophrenia may align with other psychiatric disorders such as depression, but together may be poorer than has been established in medical illnesses such as chronic cardiovascular disease. We would add that the paucity of EAM studies across psychiatry prevents clear conclusions regarding medication adherence in schizophrenia versus other diagnoses.

Notably, oral antipsychotic adherence rates in schizophrenia, defined as a continuous variable and measured by EAM, were in the range of 70%, lower than the 80% threshold recommended by expert consensus and used widely to define satisfactory adherence. Therefore, the results of the current meta-analysis indicate wide-spread non-adherence to oral antipsychotics even using the most liberal classification of adherence, taking adherence. Further, adherence in the global population of antipsychotic-taking patients may be even lower, as the current meta-analysis would have excluded a considerable proportion of patients already identified as non-adherent and receiving LAIs. In addition, EAM may actually be associated with increased medication adherence as participants may be aware adherence is being monitored, as was the case in 17 of the 19 studies included in our meta-analysis. However, one of the remaining two studies [24, 43] where EAM was not disclosed reported the mean rate of medication adherence as 66.1%, which calls into question this hypothesis [24]. This said, it would be valuable to use EAM in clinical practice if it is proven that patient awareness of monitoring improves adherence. It is also possible that the antipsychotic type may influence results; of note, SGAs were used more than FGAs in all included studies. Some studies reported that patients receiving SGAs demonstrated greater medication adherence and/or a more positive attitude toward medications than those receiving FGAs [46–48], while other studies did not [38, 49]. Because of inconclusive evidence, the relationship between the type of antipsychotics and medication adherence remains controversial.

Table 2 Antipsychotics monitored by EAM

Study	Total n^a (n^b)	Antipsychotic type, *n* (%) [mean ± SD dose, mg/day]	Antipsychotic dosing regimen, *n* (%)	Inclusion of LAI	Inclusion of clozapine
Diaz et al. (2004) [32]	49 (50) [Note: 1 in quetiapine group was excluded]	FGAs, 17 (34) [NR] Olanzapine, 18 (36) [NR] Quetiapine, 1 (2) [NR] Risperidone, 14 (28) [NR]	Once daily, 17 (34.7) Twice daily, 30 (61.2) Three times a day, 2 (4.1)	Excluded	Excluded
Byerly et al. (2005) [13]	25 (25)	NR	Once daily, 22 (88) Twice daily, 3 (12)	NR	NR
Kozuki et al. (2005) [34]	23 (23) [note: 45 EAM units. All participants received VFT]	Clozapine, NR (NR) [NR] Haloperidol, NR (NR) [NR] Olanzapine, NR (NR) [NR] Quetiapine, NR (NR) [NR] Risperidone, NR (NR) [NR] Ziprasidone, NR (NR) [NR]	NR	NR	Included
Kozuki and Schepp (2006) [35]	14 (30) [note: 15 of 30 participants received VFT and 1 lost]	NR	NR	NR	NR
(a) Nakonezny and Byerly (2006) [38] (b) Byerly et al. (2007) [31] (c) Byerly et al. (2008) [11] (d) Nakonezny et al. (2008) [40]	(a) (b) (c) (d) 61 (61)	(a) (c) (d) FGAs, 25 (41.0) [NR] SGAs, 36 (59.0) [NR] (b) NR [Note: FGAs (fluphenazine, 1; haloperidol, 7; loxapine, 2; molindone, 1; perphenazine, 9; thiothixene, 3; trifluoperazine, 2), SGAs (aripiprazole, 1; clozapine, 3; olanzapine, 13; quetiapine, 13; risperidone, 4; ziprasidone, 2)]	(a) Once daily, 47 (77.0) Twice daily, 11 (18.0) Three times a day, 2 (3.3) Routine plus as needed, 1 (1.6) (b) (c) (d) NR	(a) (b) (c) (d) NR	Included
Remington et al. (2007) [24]	52 (52)	FGAs, 16 (31) [NR] SGAs, 36 (69) [NR]	Once daily, 39 (75.0) Twice daily, 12 (23.1) Three times a day, 1 (1.9)	Excluded	Excluded
Velligan et al. (2007) [42]	52 (52)	Haloperidol, 2 (4) [11.67 ± 7.64] Olanzapine, 20 (38) [17.75 ± 10.35] Risperidone, 30 (58) [3.95 ± 2.44]	NR	NR	Patients receiving only haloperidol, olanzapine, or risperidone were included.

Table 2 (continued)

Study	Total n^a (n^b)	Antipsychotic type, *n* (%) [mean ± SD dose, mg/day]	Antipsychotic dosing regimen, *n* (%)	Inclusion of LAI	Inclusion of clozapine
(a) Acosta et al. (2009) [19] (b) Acosta et al. (2013) [27] (c) Acosta et al. (2014) [28]	(a) 74; 60 in oral group, 14 in oral + LAI group (97; 23 in LAI group) (b) 74 (74; 62 in oral group, 12 in oral + LAI group) (c) 57 (57; 47 in oral group, 10 in oral + LAI group)	(a) (b) (c) FGAs, 4 (5.4) [NR] SGAs, 70 (94.6) [NR]	(a) (b) (c) Once daily, 46 (62.2) Twice daily or three times a day, 28 (37.8)	(a) Adherence with LAIs was considered as a dose administered within 3 days of the scheduled dose. [Note: In patients with LAIs ($n=37$), mean adherence rate was 97.7 ± 9.8 (%, mean ± SD). Patients receiving only LAIs ($n=23$) were considered as non-adherence in terms of calculating rate of good adherence] (b) Patients receiving only LAIs were excluded (c) Adherence to LAIs was defined as correct administration of at least 80% of prescribed injections. Administration was considered correct if it took place within 3 days before or after the scheduled date. For the patients with oral plus injectable treatment, adherence was calculated through the mean of both adherence rates	NR
Guevremont et al. (2010) [33]	20 (20)	NR	NR	NR	NR
Gutierrez-Casares et al. (2010) [18]	≤1360 (1848)	FGAs, 286 (15.5) [NR] SGAs, 1074 (58.1) [NR]	NR	Adherence with LAIs was considered as a dose administered within 3 days of the scheduled dose. Patients with adherence rates > 80% were considered as showing good compliance with treatment	NR
Zhao et al. (2010) [43]	50 (50)	NR	NR	Excluded	NR
Lee et al. (2011) [36]	10 (10)	NR	NR	Excluded	NR

Table 2 (continued)

Study	Total n^a (n^b)	Antipsychotic type, *n* (%) [mean ± SD dose, mg/day]	Antipsychotic dosing regimen, *n* (%)	Inclusion of LAI	Inclusion of clozapine
Yang et al. (2012) [25]	51 (51)	Amisulpride, 11 (21.6) [NR] Aripiprazole, 5 (9.8) [NR] Olanzapine, 7 (13.7) [NR] Quetiapine, 7 (13.7) [NR] Risperidone, 17 (33.4) [NR] Ziprasidone, 4 (7.8) [NR]	NR	Excluded	NR
(a) Brain et al. (2013) [17] (b) Brain et al. (2014) [29] (c) Brain et al. (2014) [30]	(a) 112 (112) (b) 111 (111) (c) 117 (131)	(a) Aripiprazole, 24 (21.4) [NR] Clozapine, 21 (18.8) [NR] Flupentixol, 7 (6.3) [NR] Haloperidol, 6 (5.4) [NR] Olanzapine, 24 (21.4) [NR] Paliperidone, 12 (10.7) [NR] Perphenazine, 1 (0.9) [NR] Quetiapine, 16 (14.3) [NR] Risperidone, 17 (15.2) [NR] Sertindole, 1 (0.9) [NR] Ziprasidone, 5 (4.5) [NR] Zuclopenthixol, 5 (4.5) [NR] (b) FGAs, 15 (13.5) [NR] (c) Aripiprazole, 26 (19.8) [NR] Clozapine, 24 (18.3) [NR] Flupentixol, 7 (5.3) [NR] Haloperidol, 6 (4.6) [NR] Olanzapine, 25 (19.1) [NR] Paliperidone, 13 (9.9) [NR] Perphenazine, 1 (0.8) [NR] Quetiapine, 16 (12.2) [NR] Risperidone, 17 (13.0) [NR] Sertindole, 1 (0.8) [NR] Ziprasidone, 5 (3.8) [NR] Zuclopenthixol, 5 (3.8) [NR]	(a) NR (b) NR (c) Once daily, 91 (76) Twice daily, 26 (22) Three times a day, 2 (2)	(a) (b) (c) Excluded	Included
Nakonezny et al. (2013) [39]	23 (23)	FGAs, 5 (21.7) [NR] SGAs, 18 (78.3) [NR]	Once daily, 16 (69.6) Twice daily, 6 (26.1) Three times a day, 1 (4.3)	NR	NR

Table 2 (continued)

Study	Total n^a (n^b)	Antipsychotic type, *n* (%) [mean ± SD dose, mg/day]	Antipsychotic dosing regimen, *n* (%)	Inclusion of LAI	Inclusion of clozapine
Stip et al. (2013) [26]	26 (26)	Clozapine, 7 (NR) [NR] Haloperidol, 2 (NR) [NR] Olanzapine, 7 (NR) [NR] Paliperidone, 1 (NR) [NR] Perphenazine, 2 (NR) [NR] Polypharmacy, 6 (NR) [NR] Quetiapine, 4 (NR) [NR] Risperidone, 2 (NR) [NR] Ziprasidone, 3 (NR) [NR] Zuclopenthixol, 1 (NR) [NR]	NR	NR	Included
Velligan et al. (2013) [21]	47 (47)	Olanzapine, 16 (34.5) [NR] Others, 11 (24.1) [NR] Risperidone, 20 (41.4) [NR]	NR	Excluded	NR
Subotnik et al. (2014) [41]	66 (66)	Risperidone, NR (NR) [NR]	NR	NR	Patients receiving only risperidone were included.
Misdrahi et al. (2018) [37]	64 (68)	FGAs, 2 (2.9) [NR] SGAs, 66 (97.1) [NR]	Once daily, 42 (65.6) Twice daily, 20 (31.2) Three times a day, 1 (1.6) More than three times a day, 1 (1.6).	Patients receiving only LAIs were excluded.	NR

EAM electronic adherence monitoring, *FGA* first-generation antipsychotic, *LAI* long-acting injectable antipsychotic, *NR* not reported, *SD* standard deviation, *SGA* second-generation antipsychotic, *VFT* visual feedback therapy

[a]Participants monitored by EAM

[b]All participants

Table 3 Medication adherence outcomes

Study	Total n^a (n^b)	Other adherence measurements	Adherence outcomes					
			Adherence rate, mean ± SD, %	Method of calculating adherence by EAM	Definition of satisfactory adherence	Rate of satisfactory adherence, *n* (%)	Factors associated with satisfactory adherence	Association between adherence measures
Diaz et al. (2004) [32]	49 (50) [Note: 1 in quetiapine group was excluded]	NR	37.5 ± 36.0 in primary analysis 47.0 ± 38.3 in secondary analysis	Taking	NR	NR	Dose frequency and male gender in MVA	NR
Byerly et al. (2005) [13]	25 (25)	Clinician assessment (CRS)	78.2 ± 18.1	Regimen	≥ 70% by EAM and ≥ 5 on CRS	13 (52)	NR	NR
Kozuki et al. (2005) [34]	23 (23) [note: 45 EAM units. All participants received VFT]	Pill count Plasma drug concentrations Patient assessment	83.3 ± 23.3 for taking adherence 74.9 ± 25.2 for regimen adherence 64.2 ± 28.7 for timing adherence 74.7 ± NR by self-report	Taking, Regimen, Timing	NR	NR	NR	EAM self-report
Kozuki and Schepp (2006) [35]	14 (30) [note: 15 of 30 participants received VFT and 1 lost]	Pill count Plasma drug concentrations	88.5 at 2 weeks 82.3 at 4 weeks 75.9 at 8 weeks 68.4 at 12 weeks	Taking	NR	NR	NR	NR
(a) Nakonezny and Byerly (2006) [38] (b) Byerly et al. (2007) [31] (c) Byerly et al. (2008) [11] (d) Nakonezny et al. (2008) [40]	(a) (b) (c) (d) 61 (61)	(a) NR (b) Clinician assessment (VAS) Patient assessment (VAS) (c) Patient assessment (BARS) (d) NR	(a) 64.35 ± 24.75 (FGA), 69.17 ± 24.18 (SGA) (b) 67 ± NR (c) 66.8 ± 23.1 (d) 67.2 ± 26.3	(a) (c) (d) Taking (b) Regimen	(a) NR (b) ≥ 70% by EAM (c) ≥ 70% by EAM (d) NR	(a) NR (b) 35 (57.4) (c) 35 (57.4) (d) NR	(a) NR (b) Lower education (c) (d) Higher total PANSS scores	(a) NR (b) Both patients and prescribers grossly overestimated medication adherence (c) EAM-BARS (d) NR
Remington et al. (2007) [24]	52 (52)	Pill counts Clinician assessment Patient assessment (self report and DAI)	66.1 ± 31.0	Regimen	> 80% by EAM	25 (48)	Higher PANSS total scores and increased dosing complexity	The only significant correlation existed between EAM and pill count

Table 3 (continued)

Study	Total n^a (n^b)	Other adherence measurements	Adherence outcomes					
			Adherence rate, mean ± SD, %	Method of calculating adherence by EAM	Definition of satisfactory adherence	Rate of satisfactory adherence, *n* (%)	Factors associated with satisfactory adherence	Association between adherence measures
Velligan et al. (2007) [42]	52 (52)	Pill count Plasma drug concentrations Clinician assessment (VAS) Patient assessment (VAS)	NR	Taking	≥ 80% by EAM	33 (63)	NR	Pill count EAM, clinician assessment
(a) Acosta et al. (2009) [19] (b) Acosta et al. (2013) [27] (c) Acosta et al. (2014) [28]	(a) 74; 60 in oral group, 14 in oral + LAI group (97; 23 in LAI group) (b) 74 (74; 62 in oral group, 12 in oral + LAI group) (c) 57 (57; 47 in oral group, 10 in oral + LAI group)	NR	(a) NR (b) 58.8 ± 3.0 for timing adherence (c) 96.7 ± 4.3 in oral group, 96.0 ± 5.2 in oral + LAI group	(a) Regimen (b) Regimen, Timing (c) Regimen	(a) ≥ 75% by EAM (b) ≥ 80% by EAM (c) Full (100%), non-full (100 > adherence ≥ 80%) by EAM	(a) 56 (75.7) (b) 56 (75.7) [note: 26 (35) in restrictive definition] (c) 13 (27.7) for full	(a) Higher scores on the Amador Insight Scale and higher scores in the PANSS items of conceptual disorganization in MVA (b) NR (c) Higher scores in the PANSS items of delusions and guilt feelings in UVA (trend in MVA)	NR
Guevremont et al. (2010) [33]	20 (20)	NR	NR	Taking	≥ 70% by EAM	10 (50)	NR	NR
Gutierrez-Casares et al. (2010) [18]	≤ 1360 (1848)	Pill count Patient assessment (MARS and DAI)	NR	Taking	> 75% by EAM	≤ 405 (29.8)	Poorer insight on VAS, high toxic habits (alcohol intake, cigarette smoking, and cannabis and cocaine use), low familial support, and treatment with oral antipsychotics in UVA	NR
Zhao et al. (2010) [43]	50 (50)	NR	NR	NR	≥ 75% by EAM	32 (64)	Longer average time gap	NR

Table 3 (continued)

Study	Total n^a (n^b)	Other adherence measurements	Adherence outcomes					
			Adherence rate, mean ± SD, %	Method of calculating adherence by EAM	Definition of satisfactory adherence	Rate of satisfactory adherence, *n* (%)	Factors associated with satisfactory adherence	Association between adherence measures
Lee et al. (2011) [36]	10 (10)	Clinician assessment (BEMIB)	71.8 ± 30.5 for taking adherence 55.9 ± 31.3 for regimen adherence	Taking, Regimen	> 75% by EAM	NR	NR	NR
Yang et al. (2012) [25]	51 (51)	Pill count Clinician assessment (CRS) Patient assessment (DAI-10)	80.5 ± 20.9	Timing	> 80% by EAM	30 (58.8)	Higher scores on PANSS and lower scores on DAI total score in MVA	NR
(a) Brain et al. (2013) [17] (b) Brain et al. (2014) [29] (c) Brain et al. (2014) [30]	(a) 112 (112) (b) 111 (111) (c) 117 (131)	(a) Patient assessment (DAI-10) (b) Pill count Clinician assessment Care giver assessment Patient assessment (DAI-10) (c) Plasma drug concentrations	(a) (b) NR (c) 84 ± NR	(a) (b) (c) Regimen	(a) (b) (c) > 80% by EAM	(a) (b) (c) 81 (73.0)	(a) Lower scores on DAI-10, higher scores on PANSS positive subscale, higher scores on PANSS item G12, higher scores on UKU-SERS-Pat, and lower scores on PSP in UVA Lower scores on DAI-10 and PSP in MVA (b) Lower scores on DISC subscale (overcoming stigma) in UVA (c) NR	(a) NR (b) NR (c) EAM – pill count
Nakonezny et al. (2013) [39]	23 (23)	NR	78.2 ± 18.6	Taking	≥ 70% by EAM ≥ 80% by EAM ≥ 90% by EAM	18 (78.3) for ≥ 70% 11 (47.8) for ≥ 80% 0 (0) for ≥ 90%	NR	NR
Stip et al. (2013) [26]	26 (26)	Patient assessment (BARS)	66.6 ± 35.1	Taking	≥ 70% by EAM	14 (53.8)	NR	NR
Velligan et al. (2013) [21]	47 (47)	Pill count	72 ± NR	Timing	NR	NR	In-person and electronic interventions	NR

Table 3 (continued)

Study	Total n^a (n^b)	Other adherence measurements	Adherence outcomes					
			Adherence rate, mean ± SD, %	Method of calculating adherence by EAM	Definition of satisfactory adherence	Rate of satisfactory adherence, *n* (%)	Factors associated with satisfactory adherence	Association between adherence measures
Subotnik et al. (2014) [41]	66 (66)	Pill count Plasma drug concentrations Clinician assessment Patient assessment	NR	NR	NR	NR	Higher scores on SAPS and SANS	NR
Misdrahi et al. (2018) [37]	64 (68)	NR	91.9 ± 26.0 for taking adherence 66.5 ± 27.4 for regimen adherence 56.1 ± 31.8 for timing adherence	Taking, Regimen, Timing	NR	NR	Dose frequency	NR

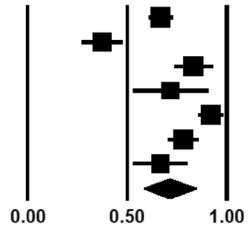
BARS Brief Adherence Rating Scale, *BEMIB* Brief Evaluation of Medication Influences and Beliefs, *CRS* Clinician Rating Scale, *DAI* Drug Attitude Inventory, *DISC* Discrimination and Stigma Scale, *EAM* electronic adherence monitoring, *FGA* first-generation antipsychotic, *LAI* long-acting injectable, *MARS* Medication Adherence Rating Scale, *MVA* multivariate analysis, *NR* not reported, *PANSS* Positive and Negative Syndrome Scale, *PSP* Personal and Social Performance scale, *SANS* Scale for the Assessment of Negative Symptoms, *SAPS* Scale for the Assessment of Positive Symptoms, *SD* standard deviation, *SGA* second-generation antipsychotic, *UKU-SERS* UKU Side Effect Rating Scale, *UVA* univariate analysis, *VAS* Visual Analog Scale, *VFT* visual feedback therapy

[a]Participants monitored by EAM

[b]All participants

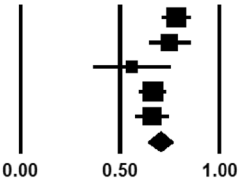
A : Taking adherence[a]

Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Byerly 2008 [11]	0.668	0.030	0.001	0.610	0.726	22.585	0.000
Diaz 2004 [32]	0.375	0.051	0.003	0.274	0.476	7.292	0.000
Kozuki 2005 [34]	0.833	0.049	0.002	0.738	0.928	17.146	0.000
Lee 2011 [36]	0.718	0.096	0.009	0.529	0.907	7.444	0.000
Misdrahi 2018 [37]	0.919	0.033	0.001	0.855	0.983	28.277	0.000
Nakonezny 2013 [39]	0.782	0.039	0.002	0.706	0.858	20.163	0.000
Stip 2013 [26]	0.666	0.069	0.005	0.531	0.801	9.675	0.000
	0.711	0.067	0.004	0.580	0.841	10.680	0.000



B : Regimen adherence[b]

Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Byerly 2005 [13]	0.782	0.036	0.001	0.711	0.853	21.602	0.000
Kozuki 2005 [34]	0.749	0.053	0.003	0.646	0.852	14.254	0.000
Lee 2011 [36]	0.559	0.099	0.010	0.365	0.753	5.648	0.000
Misdrahi 2018 [37]	0.665	0.034	0.001	0.598	0.732	19.416	0.000
Remington 2007 [24]	0.661	0.043	0.002	0.577	0.745	15.376	0.000
	0.700	0.033	0.001	0.636	0.764	21.409	0.000



C : Timing adherence[c]

Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Acosta 2013 [27]	0.588	0.003	0.000	0.581	0.595	168.606	0.000
Kozuki 2005 [34]	0.642	0.060	0.004	0.525	0.759	10.728	0.000
Misdrahi 2018 [37]	0.561	0.040	0.002	0.483	0.639	14.113	0.000
Yang 2012 [25]	0.805	0.029	0.001	0.748	0.862	27.506	0.000
	0.649	0.060	0.004	0.532	0.766	10.884	0.000

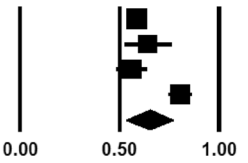


Fig. 2 Forest plots of the rates of adherence to antipsychotics. **A** Taking adherence[a]. **B** Regimen adherence[b]. **C** Timing adherence[c]. *CI* confidence interval. [a]Number of bottle cap openings divided by the prescribed number of doses. [b]Percentage of days with the appropriate number of doses taken. [c]Percentage of doses taken within assigned intervals

The studies included in this systematic review used one of three cut-off points, 70%, 75%, and 80%, above which medication adherence was defined as satisfactory. The threshold of 70% was derived from research demonstrating that adherence to antipsychotics below 70% is associated with a greater risk of hospitalization in schizophrenia [50]. The threshold of 80% is recommended by an expert consensus survey on medication adherence in schizophrenia [14], and was used most frequently in the included studies. Given that both continuous and dichotomous medication adherence data provide useful information, we suggest that both be reported. In doing so, we can explore how adherence rates, when defined as a continuous variable, correspond to figures where adherence is defined as a dichotomous variable, and vice versa.

The current systematic review identified that poor oral antipsychotic adherence, as measured by EAM in schizophrenia, was associated with poorer insight into illness, greater illness severity, and greater complexity of dosing regimen, which aligns with the previous literature, which includes various adherence measures. A systematic review found that the main risk factors for medication non-adherence in schizophrenia were younger age, substance abuse, poor insight, cognitive impairments, low level of education, minority ethnicity, poor therapeutic alliance, experience of barriers to care, high intensity of delusional symptoms and

suspiciousness, and low socioeconomic status [5]. In addition to these factors, an expert consensus survey on medication adherence in schizophrenia listed treatment-associated factors such as fear of side effect, lack of efficacy, and complexity of treatment regimen [14]. Certainly, simplifying dosing regimens may enhance medication adherence; for example, a meta-analysis of RCTs revealed that a once-daily dosing regimen was associated with better medication adherence than twice-daily dosing in chronic cardiovascular disease [51]. Similarly, another meta-analysis indicated a consistent trend of better medication adherence with less frequent dosing regimens in chronic psychiatric disorders [52]. Indeed, at least some studies included in the current systematic review showed that dosing frequency was a better predictor of medication adherence than antipsychotic type [24, 32, 37]. To our knowledge, though, no RCTs have been conducted to examine if simplifying dosing regimens improves medication adherence in psychiatric disorders.

It should be noted that EAM is not without its own limitations; for example, because confirmation that the bottle was opened does not guarantee that the medication was taken, EAM may overestimate medication adherence. On the other hand, in the case where a patient moves medications from EAM to a pill case, EAM can also underestimate the medication adherence. Nonetheless, EAM provides important and useful information that can shed light on the type of gaps that may be occurring [16]. In addition, a systematic review reported that self-report, self-rating/clinician rating, and pill count overestimated medication adherence by 17%, 6%, and 8%, respectively, compared to EAM [53]. As noted in Sect. 1, plasma concentrations of antipsychotics also offer only indirect information regarding actual adherence, and are subject to marked intra-, as well as inter-individual, variability [29]. Accordingly, at present, EAM remains the gold standard in measuring medication adherence. This may, of course, change as the field advances; for example, novel methods, such as the Proteus Digital Health®, that can capture medication adherence more directly are now accessible as options. This particular system consists of ingestible sensors and a wearable sensor patch, which can provide confirmation that the medication was ingested [54, 55]. As of yet, though, there are not enough data available to closely evaluate this system [56]. In addition, systems of this sort call into play ethical issues related to autonomy, confidentiality, and privacy that are yet to be resolved [57, 58].

The present findings need to be interpreted in the context of several limitations. First, only studies published in English were included in the current systematic review, so there may be additional studies relevant to the topic. Second, the time course of medication adherence is another important topic, and is not addressed in this study. Third, a small number of studies were included in the meta-analysis to estimate overall EAM-measured adherence to antipsychotics. Moreover, significant study heterogeneity was identified for all three outcomes. Fourth, results of the current meta-analysis may not be representative of the global population; for example, a considerable proportion of patients already identified as non-adherent and receiving LAIs were excluded. Fifth, the findings may not be applied to specific patient populations such as first-episode and treatment-resistant schizophrenia; to this point, in the present investigation, only one study [41] and none exclusively included these specific populations, respectively. In line with this, the findings cannot expand to clozapine as no studies investigating adherence to clozapine with EAM were identified in the literature search. While clozapine is associated with a higher rate of treatment continuation than other antipsychotics [59], it is surprising that only one study addressed clozapine adherence, using medication possession ratio (MPR) and reporting a range of 66–75% [60]. Similarly, there have been no studies focusing on adherence to concomitant oral antipsychotics separately in patients receiving LAIs with EAM, whereas there have been a few investigating adherence to oral antipsychotics and LAIs together [18, 28].

5 Conclusions

Oral antipsychotic adherence rates in schizophrenia, when defined as a continuous variable and measured by EAM, were in the range of 70%, lower than the 80% threshold used widely to define satisfactory adherence. There remain important questions that require further investigation, e.g., what constitutes a threshold that impacts response and negative outcomes (e.g., relapse, hospitalization, and suicide), what is the impact of patterns of nonadherence, and what are the possible differences in nonadherence as a function of antipsychotic type. EAM continues to provide benefits in addressing such questions.

Compliance with Ethical Standards

Funding None.

Conflict of interest Dr. Yaegashi has received speaker's fees from Eisai, Meiji Seika Pharma, Janssen, Otsuka, Pfizer, and Sumitomo Dainippon Pharma. Dr. Kirino has received speaker's fees from Novartis Pharma. Dr. Remington has received research support from the Canadian Institutes of Health Research (CIHR), HLS Therapeutics, Novartis Canada, and Research Hospital Fund–Canada Foundation for Innovation (RHF-CFI); conference support from Neurocrine Biosciences for data presentation; and advisory board support from HLS Therapeutics. Dr. Misawa has received speaker's fees from Eli Lilly, Janssen, Novartis Pharma, Otsuka, Pfizer, and Sumitomo Dainippon Pharma. Dr. Takeuchi has received fellowship grants from Astellas Foundation for Research on Metabolic Disorders, the Canadian Institutes of Health Research (CIHR), Centre for Addiction and Mental Health (CAMH) Foundation, and the Japanese Society of Clinical Neuropsychopharmacology; speaker's fees from Meiji Seika Pharma, Mochida, Otsuka,

Sumitomo Dainippon Pharma, and Yoshitomiyakuhin; and manuscript fees from Sumitomo Dainippon Pharma.

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