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Weighing the Evidence for Harm from Long-term Treatment with Antipsychotic Medications, A Systematic Review

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Abstract

Research findings supporting the use of antipsychotic medication for acute treatment of schizophrenia are relatively consistent and undisputed. However, the rationale for recommending long-term antipsychotic medication treatment - the current standard of care treatment strategy-- is unclear. A controversial hypothesis proposed recently suggests people with schizophrenia who are exposed to long-term treatment with antipsychotic medications have worse outcomes than people with schizophrenia who are not exposed to these medications. We tested whether a systematic appraisal of published literature would produce data consistent with this hypothesis. We reviewed the published literature to identify studies of patients with psychotic disorders who were followed for at least two years that compared outcomes in patients who received antipsychotic medication during the follow-up with patients who did not receive antipsychotic medication at follow-up. We included all English language articles published through 2013 in this review. Our process for selecting studies and documenting study findings included a consensus decision of two members of the research team. We found the published data to be inadequate to test this hypothesis. By extension, these data were also inadequate to conclusively evaluate whether long-term antipsychotic medication treatment results in better outcomes on average. We conclude that careful re-appraisal of existing data is useful to ensure standard of care treatment strategies are indeed evidence-based. In the case of long-term use of antipsychotic medications, new data may be

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AUTHOR CONTRIBUTION

All 6 authors contributed to the design, data collection and analysis, and writing of the paper

needed to establish a sufficient evidence base to understand its benefit/risk balance for patients with schizophrenia.

CONTEXT

Standardized clinical treatment guidelines recommend that patients with schizophrenia be managed with antipsychotic medications both in the acute phase and in the longer term maintenance and recovery phases (American Psychiatric Association, 2006; Kreyenbuhl, Buchanan, Dickerson, & Dixon, 2010). The origins of this approach can be traced to 1954, when the U.S. Food and Drug Administration first approved chlorpromazine for the treatment of schizophrenia (Lopez-Munoz et al., 2005). Marketed as Thorazine in the U.S., chlorpromazine was credited for relieving numerous institutionalized patients with schizophrenia of positive symptoms and for facilitating their return to community living, resulting in its quick acceptance by the medical community and widespread use (Krieg, 2001). Considerable data have been collected over decades that fairly consistently demonstrate that patients with schizophrenia who are treated with antipsychotic medications experience greater improvements in positive symptoms in the short run than those who are not (Leucht et al., 2012, 2013).

Despite the relatively undisputed research supporting the use of antipsychotic medication for acute treatment of schizophrenia, the rationale for recommending long-term treatment is less clear. Antipsychotic medications, even the newest of the second generation drugs, are known to cause serious and sometimes irreversible neurologic and metabolic side effects (Lieberman, 2004). These risks typically increase over time (Caroff, Hurford, Lybrand, & Cambell, 2011), making some patients and physicians cautious about high dose and longer duration regimens. Antipsychotic medications do not improve negative symptoms, which cause great distress and disability. Some patients with schizophrenia improve over time without any pharmacologic intervention (Torgalsbøen, 2012). For these reasons and others, patients' antipsychotic medication use patterns are irregular, often including repeated periods of non-use both due to side effects and illness characteristics. It is not surprising that longitudinal studies evaluating the benefits of long-term antipsychotic medication are difficult to conduct and interpret. Several recent reviews and commentaries question the adequacy of the evidence base on which current recommendations for long term use antipsychotic medication are based (Harrow & Jobe, 2013; McGorry, Alvarez-Jimenez, & Killackey, 2013).

Recently, Robert Whitaker advanced a troubling interpretation of the evidence base for long-term use of antipsychotic medication. He reviewed a number of epidemiological and clinical studies and concluded that antipsychotic medications are an iatrogenic cause of chronicity of schizophrenia, and that these medications may lead to the deterioration of patients' health and wellbeing over time (Whitaker, 2010). His explanation rested on the notion that antipsychotic medication may induce a hypersensitivity to dopamine (Whitaker, 2004).

We were concerned by Whitaker's findings and wondered whether a systematic appraisal of published literature would produce the same results. Therefore, we conducted a systematic literature review to test the hypothesis that long-term treatment with antipsychotic

medications is less beneficial than no antipsychotic medication treatment for patients with schizophrenia. We attempted to review all published English language literature through 2013, and included all studies that followed patients with psychotic disorders for at least two years and compared outcomes in patients who received antipsychotic medication during the follow-up with patients not receiving antipsychotic medication at follow-up.

EVIDENCE REVIEW

Study Inclusion Criteria

To test this hypothesis, we attempted to identify all empirical research published through 2013 that met three inclusion criteria. First, studies must report on long-term outcomes of patients with psychotic disorders. Long-term outcome was defined as any clinical or social outcome that was measured over at least two-years of follow-up (Zubin, 1956). We included studies reporting on re-hospitalization, negative symptoms, positive symptoms, or social functioning, and on patients who were diagnosed with schizophrenia, schizoaffective disorder, schizophrenia spectrum disorders, or, more generally, psychosis. These diagnoses could be either clinical diagnoses or based on research criteria.

Second, studies must permit a comparison of patients who were exposed to antipsychotic medications with patients who were not exposed to medications over the two-year follow-up period. The exposed group must include patients who, at the start of the follow-up period, were assigned to take antipsychotic medications in a trial or were prescribed antipsychotic medications in an observational study, and this status continued during the two years of follow-up or until the patient stabilized. The unexposed group must include patients who, at the start of the follow-up period, were assigned to not take maintenance antipsychotic medications in a trial or were not prescribed maintenance antipsychotic medications in an observational study during the follow-up period.

Finally, the study must have been published in English.

Study Identification

Studies were identified initially from three sources: MEDLINE, PUBMED, and an online university library catalog that includes books and other published resources (Columbia University Libraries Information Online, CLIO). We developed a two-step screening process for identifying eligible articles that included a preliminary search and review to identify studies that were likely to meet the above criteria and then a second more stringent review to confirm eligibility. The final eligibility decisions were discussed in meetings of the research team. We describe this process below.

Two members of the research team (GC, NS) conducted independent searches, one using MEDLINE and one using PUBMED. Studies were identified using a combination of two of the following three categories of subject headings and text words: (1) ‘psychotic disorders’ or ‘mental disorders’ or ‘schizophrenia’ (2) ‘follow-up study’ or ‘cohort study’ or ‘prospective study’ or ‘randomized controlled trial’; and (3) ‘neuroleptic medication’ or ‘antipsychotic medication’. Reviewers eliminated studies identified in the initial searches if, based on explicit information in the abstracts, they could determine that any of the three

inclusion criteria (above) were not met. If information about any criterion was unclear for any study, the study was included in the initial list. A total of 239 abstracts were identified from one or both searches. While commentaries and review articles were not eligible for inclusion, we maintained a list of these articles for later reference.

Each identified study was assigned to one of the six members of the research team. Members read and reviewed assigned articles using a standard form to verify that articles met the study inclusion criteria. The full article review confirmed that 38 unique studies from the 239 abstracts satisfied the three eligibility criteria. We identified additional studies by reviewing the reference lists from the eligible studies and the commentaries and review articles that were identified in this initial review and two new eligible studies were identified.

To identify books for review, we used CLIO. We reviewed books to ensure that we did not overlook empirical studies that met our three inclusion criteria in the MEDLINE and PUBMED searches. One member of the research team (SS) identified books and book chapters reporting on long-term outcome comparisons of antipsychotic medication treatment versus no treatment in people with psychosis. Search terms included: ‘schizophrenia’ AND ‘medication’ AND ‘long-term’. A total of 11 chapters in three books were identified that reported on studies not previously included in the MEDLINE and PUBMED searches. These chapters were reviewed using the same criteria and standard form as used for studies identified from MEDLINE and PUBMED. None were eligible after this review. In total, 40 studies were identified from the first step of our screening process.

In the second step of our screening process, each of the 40 reports preliminarily deemed eligible were re-reviewed by a second member of the research team to ensure outcome measures and comparison groups met our criteria. A checklist of outcome and exposure criteria was developed so the eligibility determination could be objectively made. Twenty-one studies that did not have appropriate exposure data to clearly define the comparison groups were eliminated, and one natural history report that only reported on mortality rates was eliminated. In total 18 reports were deemed eligible by the research team (Bockoven & Solomon, 1975; Boonstra, Burger, Grobbee, & Kahn, 2011; Carpenter, Heinrichs, & Hanlon, 1987; Crow, MacMillan, Johnson, & Johnstone, 1986; Engelhardt, Rosen, Freedman, & Margolis, 1967; Harrow, Jobe, & Faull, 2012; Hogarty, Goldberg, Schooler, & Ulrich, 1974; May, Tuma, Dixon, Thiele, & Kraude, 1981; McWalter, Mercer, Sutherland, & Watt, 1961; Moilanen et al., 2013; Mosher & Menn, 1978; Nishikawa, Tsuda, Tanaka, Koga, & Uchida, 1982; Odegard, 1964; Pietzcker et al., 1993; Pritchard, 1967; Rappaport, Hopkins, Hall, Belleza, & Silverman, 1978; Tiihonen, 2006; Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013).

Data Collection

Two members of the research team independently reviewed each of the 18 eligible reports and recorded information on the target population, the study design, the study findings and study quality. For the target population, we collected data on: year(s) of data collection; country where the study was conducted; the specific criteria for defining the target population including study inclusion and exclusion criteria, whether study sample was

limited to patients experiencing their first psychotic episode, patient psychiatric diagnoses, and whether study subjects were followed only in treatment setting(s) versus post-discharge in community setting. For the study design, we collected data on the sample size, the specific design (experimental versus observational), length of planned and actual follow-up, criteria for designating/measuring exposure groups, and outcome measures. We recorded both the main and additional study findings. For study quality, we evaluated the following criteria: comparability of exposure groups at baseline, confounding by indication, loss to follow-up, sample size concerns, and quality of exposure measures. The independent reviews were compared and if there were discrepancies, the two reviewers discussed the discrepancies until a consensus was obtained.

Data Analysis

We first summarized the data collected for the 18 studies. Then, we summarized the study findings to preliminarily test the study hypothesis that long-term treatment with antipsychotic medications causes harm to patients with schizophrenia. Finally, we attempted to identify factors, including those related to the study population, the study design, and the study quality, which could explain discrepancies in findings across studies.

FINDINGS

Description of Studies

Table 1 presents a description of each study including the study population and the study design, as well as our findings of whether the study data are consistent with the hypothesis that long-term treatment with antipsychotic medications causes harm to patients and the major violations of internal validity that influence the study quality. As we will describe, the studies were heterogeneous in study population, study design, and quality.

Of the 18 published reports, four were included in Whitaker's original evaluation. (Bockoven & Solomon, 1975; May et al., 1981; Rappaport et al., 1978; Mosher & Menn, 1978) Whitaker referred to six additional studies that we did not include because they were review articles, did not report separate data on the exposure groups, or were ecological studies in which no individual-level data was reported.

Study Population: Data for the 18 published reports were based on studies conducted between 1947 and 2010. Eight of the studies were based on patient populations in the United States, two in each of England, Finland, and the Netherlands, and one in each of Germany, Japan, Norway, and Scotland. The sample sizes ranged from 20 to more than 13,000 patients. Most of the studies focused on schizophrenia: 11 studies enrolled only patients with a diagnosis of schizophrenia; five studies enrolled patients with a broader range of diagnoses, including schizoaffective disorder, schizophreniform disorder, and schizophrenia spectrum disorder; and two enrolled patients with any psychotic disorder. Only two of the studies included mainly first admission patients and the rest included chronic patients (see table 1).

The study population characteristics regarding age, chronicity of illness and diagnosis, length of treatment, treatment setting, and symptom history varied widely. All studies were

initiated in some type of treatment setting and most enrolled consecutive admissions to an inpatient or outpatient psychiatric treatment setting (data not shown).

Study Design: Seven of the studies were observational (four pre-post studies comparing patients treated before antipsychotic medications were available with patients treated after these medications became available and three observational cohort studies) and eleven were conducted in the context of a randomized trial. Exposure groups were defined in three main ways across both experimental and observational designs: (1) Exposed group included patients recruited during the period when antipsychotic medication was widely used to treat psychosis and unexposed group included patients recruited before this widespread use (four studies, labeled “Treated during AP Era versus Treated before AP Era” in table 1); (2) Exposed group includes patients assigned or prescribed continuous antipsychotic medication treatment and unexposed group includes patients assigned or prescribed antipsychotic medications until stabilized and then taken off medication unless/until relapse (four studies, labeled “Consistent AP treatment/Intermittent AP treatment or Reduce dose/discontinue AP treatment” in table 1); and (3) Exposed group includes patients assigned or prescribed to receive antipsychotic medications and unexposed group includes patients assigned or prescribed to receive no antipsychotic medications (or a placebo), but length of time off medications was either not fully monitored or only monitored for a portion of the two-year follow-up period (ten studies, labeled “AP vs. No AP” or “AP vs. Placebo” in table 1). Irrespective of design, none of the studies had complete data on compliance with assigned or prescribed treatment. Only one study had a group of people with a documented history of never receiving antipsychotic medication (Rappaport et al., 1978). The actual follow-up time ranged from 2 to 20 years (see table 1), but follow-up rates varied a great deal over the studies (data not shown).

No outcome measure category was used consistently across all 18 studies. Ten studies reported on services outcomes only (whether or not patients were discharged from the hospital, whether or not people were readmitted to the hospital, number of hospital readmissions, and duration of hospitalization); eight studies reported on symptoms and functioning, either using standardized scales or clinician judgment; and two studies reported on summary measures that included a combination of services and symptom/functioning information. One study reported mortality. (Note several studies reported more than one outcome measure.)

Study Findings and Study Quality: Data from eight of 18 studies were not consistent with the hypothesis that patients with long-term exposure to antipsychotic medications have worse outcomes than patients with no exposure to antipsychotic medications. Data from three studies were consistent with the hypothesis and, in seven studies, data from some but not all of the outcomes that were measured were consistent with the hypothesis. (See table 1) No study characteristic (e.g., target population or follow-up time) could account consistently for the observed variation in findings.

More importantly, we were unable to draw firm conclusions regarding our study hypothesis from these studies due to ubiquitous study design flaws that introduce significant non-comparability between exposure groups. Table 1 lists these flaws, which include non-

comparability of exposure groups at baseline, confounding by indication, loss to follow-up, sample size concerns, and quality of exposure measures: The most common and significant sources of non-comparability were confounding by indication and non-comparable groups at baseline. Non-comparability was potentially present as well in imprecisely defined exposure categories.

Confounding by indication was a concern in all of the observational cohort studies, and in the randomized trials that compared some form of intermittent antipsychotic medication treatment with ongoing maintenance treatment. Patients with more severe and treatment-resistant symptoms are more likely to be prescribed maintenance antipsychotic medications both initially at hospital discharge and for longer periods and more consistently over the follow-up than patients exhibiting less severe symptoms or whose symptoms stabilized more rapidly. It is therefore impossible to determine if observed differences in outcomes were caused by differences in exposure to antipsychotic medications or were due to differences in severity or type of illness.

Non-comparability at baseline between the exposed and non-exposed groups was particularly pervasive in studies that compared outcomes collected during different historical periods. It is likely that factors influencing patient outcomes, such as diagnostic practices and institutionalization policies, changed over time. These factors, which could not be controlled in analysis, could confound any observed differences between the study groups.

Due to losses to follow-up and non-compliance with initially assigned/prescribed antipsychotic medication treatment, there were virtually no observational cohorts or randomized trials that compared groups of patients who were either exposed or not exposed to antipsychotic medication for the full follow-up period. The reasons for losses and non-compliance were not recorded in the majority of these studies, but both could be due to factors that indicate either recovery or worsening of their condition. This residual confounding may have biased the observed study results. Although the potential for residual confounding is present in all studies, the pervasiveness of this problem in the studies included in this review and our inability to predict the likely direction of the effect of the bias potential in these studies clearly undermines their validity.

CONCLUSIONS AND RELEVANCE

In this systematic review of the published literature, we addressed a hypothesis recently proposed by Robert Whitaker: People with schizophrenia exposed to long-term treatment with antipsychotic medications have worse outcomes than they would have had if they were not exposed to these medications. Whitaker argued that antipsychotic medications commonly prescribed to treat a range of mental illnesses can cause chronicity of this illness, and lead to social and clinical deterioration of patients (Whitaker, 2004, 2010). The results of the studies reviewed here are widely heterogeneous and the designs do not allow us to draw firm conclusions about Whitaker's hypothesis. Most importantly, there were no studies with patients who were documented to be taking antipsychotic medication continuously for two years, making it impossible to assess outcomes that are independently associated with long-term use.

Although it was not the purpose of our review, we note that our data also failed to determine whether long-term antipsychotic medication treatment results in greater benefits than harm on average when assigned or prescribed to patients with schizophrenia. It is clear, given the heterogeneity of findings across studies, that long-term antipsychotic medication treatment is not needed for *some* patients with schizophrenia who improve without such treatment. This mirrors recent observations by researchers and commentators who have argued that the evidence supporting recommendations for long-term continuous treatment with antipsychotic medication for all people with schizophrenia is lacking (Harrow & Jobe, 2013; Insel, n.d.) and that reducing exposure to antipsychotic medication may promote long-term health and functional status in some (McGorry et al., 2013). Unfortunately, there are insufficient data in the literature reviewed here to guide physicians and patients as to how to predict which patients will exhibit this response profile over the long term.

How is it that 60 years of research fails to produce evidence affirming the widespread clinical practice of maintenance antipsychotic treatment, or, alternatively fails to yield data that can refute claims of dire harms associated with this treatment approach? It is likely partly due to the rapidity with which the clinical community adopted this treatment strategy (Healy, 1997). For many years, this treatment approach has been so pervasive and clinicians' belief in the need for long-term use of antipsychotic medications strong (Lehmann, 1966) that it has been impossible to design a sound observational study to address the question of efficacy or harm because comparable groups of exposed and unexposed individuals could not be found. Furthermore, the presumed lack of equipoise about the benefit of long-term antipsychotic maintenance treatment has made it unethical to randomize patients such that they might be denied antipsychotic medications in a trial setting.

One strategy that researchers have used to overcome this problem is the medication withdrawal design. In this study design, at the time of hospital discharge when symptoms have been stabilized, patients are randomized either to maintenance antipsychotic medication treatment or to some form of reduced antipsychotic medication treatment, such as intermittent medication treatment, medication discontinuation, or a reduction in medication dose. Some designs include a provision that patients in the reduced antipsychotic medication treatment groups who relapse are given antipsychotic medications again until they stabilize. This strategy has been the center of much controversy that focuses on the ethicality of denying patients with psychosis maintenance antipsychotic medication, although prominent researchers have presented solid defenses (Applebaum, 1996; Carpenter, Schooler, & Kane, 1997; Carpenter, 1997; Kirkby, 2005; Lehmann, 1966). Unfortunately, it still is not ideally suited to address the study question set forth in the current paper. First, it omits patients who were never stabilized on antipsychotic medication, limiting the generalizability of the results. More importantly, it cannot distinguish between the effects of antipsychotic medication withdrawal from the effects of non-medication, and does not allow long-term follow-up of relapsed patient outcomes when they are not taking antipsychotic medication.

Nonetheless, this study design does inform us whether treatment strategies that reduce or minimize duration or dose of antipsychotic medication result in better outcomes for patients. A large review of studies using this or similar approaches showed that those who continue

taking medication after their initial treatment are less likely to relapse than those who are withdrawn from medication (Gilbert, Harris, McAdams, & Jeste, 1995). However these data are only relevant to questions around short-term antipsychotic medication use since the mean follow-up time of these studies was only 9.7 months. A more recent review found similar results (Leucht et al., 2012) but, again, the conclusions were based on studies with no more than two years of follow-up. This review noted that studies with more than one year of follow-up seem to show diminishing effectiveness of antipsychotic medications over time, although it was noted that this might be due to features of the study designs. We hope to find results from longer-term follow-up of these studies published in the coming years.

We would be remiss not to acknowledge the importance of the volumes of published data other than the epidemiological studies reviewed here that have greatly advanced our understanding of schizophrenia and treatment approaches. Recent examples include clinical treatment trials (J.A. Lieberman & Stroup, 2011) and imaging studies (e.g., Moncrieff & Leo, 2010). While not directly addressing this study's hypothesis, they provide an important context that influences how research on the impact of long-term antipsychotic medication treatment is evaluated and interpreted. In general, reappraisal of research thought to support long-held beliefs in the context of the current broader evidence-base is critical. Our systematic review found that the evidence-base is insufficient to adequately address questions about the potential harm and benefits of long-term antipsychotic medication use for people with schizophrenia given current scientific knowledge. Despite decades of research in this area, it seems new data may be needed to fully address these questions. To do this, researchers will have to find solutions for the numerous challenges to conducting rigorous and ethical longitudinal research in this area (McGlashan, 2006).

In the meantime, it is incumbent upon practitioners to accurately communicate to patients the uncertainty of evidence regarding the long-term use of antipsychotics in treatment of psychosis. Patrick McGorry and colleagues noted in 2001, that while “advising patients to remain on medication for a period of 2-5 years post recovery may be fully justifiable from a clinical point of view as an opinion... there are a number of problems with this viewpoint from an evidence-based medicine standpoint.” As the results of our review demonstrate, this statement remains true nearly 15 years later. Beyond appropriate risk benefit communication centered around empirical findings, it is also important to integrate and promote the recovery model where possible (Frese et al., 2001). Within a recovery framework (Jacobson, 2001), practitioners can promote patient autonomy and shared decision-making in the treatment process. These two principles complement empirical assessments of treatment risks versus benefits (Frese et al., 2001).

Our study has several limitations that should be noted. First, despite the fact that the selection of articles for this study followed a rigorous protocol, it is possible that eligible studies were missed that may have changed our conclusions. For example, our restriction to English language articles may have prevented our reviewing important findings that were published in other languages. Along the same lines, we were unable to determine a number of study design characteristics for several of the studies, including, at times, the precise duration of antipsychotic medication exposures. This made our determination of eligibility for several studies much more difficult than we anticipated. In the end, we found so few

studies that met our strict inclusion criteria that we included studies that did not have clearly defined exposure groups or a comparison group of patients that were not exposed to antipsychotic medications for two years. Second, because the number of eligible studies was small, we were unable to adequately explore factors that might be associated with discrepancies in study findings. It is possible that one or more consistent factors exist that we were unable to uncover in this analysis. Further data from these studies were insufficient to even preliminarily explore many potential reasons for inconsistencies such as differences across patients with schizophrenia that may make some more or less likely to respond to antipsychotic medications. Despite these limitations, we believe this study makes a meaningful contribution to the current debates about the potential for antipsychotic medication to harm patients with schizophrenia over the long term.

Conclusion

Our study did not support the hypothesis that long-term treatment with antipsychotic medication causes harm. This conclusion is based on the lack of available data to adequately test our research question. For this same reason, our study also could not conclusively evaluate whether long-term antipsychotic medication treatment results in better outcomes on average. We believe the pervasive acceptance of this treatment modality has hindered rigorous scientific inquiry that is necessary to ensure evidence-based psychiatric care is being offered. These findings mirror the recent commentaries that question the accepted clinical approaches, and indicate a need for both rigorous re-appraisal of existing data and new research approaches to evaluate this question.

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Table 1

Description of 18 long term (2-year) follow-up studies of patients with psychotic disorders comparing patients exposed to antipsychotic medications with those not exposed to antipsychotic medications

First author (year published)	Year(s)	Country	Exposed group[1]	Unexposed group[1]	Diagnoses included in study	Follow-up time	Sample size	All first admission (yes/no)	Outcomes measured[2]	Findings consistent with study hypothesis?	Main sources of bias[3]
Bockoven (1975)	1947-1972	United States	Treated during AP era	Treated before AP era	SZ (mainly)	6 years	200	no	Discharge, readmission, duration of hospitalization	mixed	Groups not comparable at baseline
Odegard (1964)	1948-1959	Norway	Treated during AP era	Treated before AP era	psychosis	5 years	13,312	yes	Discharge, readmission, mortality	no	Groups not comparable at baseline
McWalter (1961)	1949-1957	Scotland	Treated during AP era	Treated before AP era	SZ	3 years	349	no	Discharge, readmission, number readmissions, duration of hospitalization	yes	Groups not comparable at baseline
Pritchard (1967)	1952-1957	England	Treated during AP era	Treated before AP era	SZ	3 years	100	no	Readmission, duration of hospitalization	no	Groups not comparable at baseline
Moilanen (2011)	1966-2000	Finland	AP	No AP	SSD	8.5 years	70	no	Readmission	mixed	Exposure not well defined; confounding by indication
Harrow (2012)	1975-1983	United States	AP	No AP	SZ/SA	20 years	70	no	Recovery (defined by readmission) and symptom and functioning scales	mixed	Confounding by indication
Tiihonen (2006)	1995-2001	Finland	AP	No AP	SZ/SA	11 years	2,230	yes	Readmission, mortality	no	Confounding by indication
Engelhardt (1967)	1958-1961	United States	AP	Placebo	SZ	4 years	446	no	Readmission	mixed	Loss to follow-up

First author (year published)	Year(s)	Country	Exposed group[1]	Unexposed group[1]	Diagnoses included in study	Follow-up time	Sample size	All first admission (yes/no)	Outcomes measured[2]	Findings consistent with study hypothesis?	Main sources of bias[3]
May (1981)	1959 - 1962	United States	AP[5]	No AP[5]	SZ	2-5 years	228	yes	Symptom/ functioning scales, readmission, duration of hospitalization	no	Exposure not well defined
Rappaport (1978)	(Est) 1966 - 1978	United States	AP	No AP	SZ	3 years	80	yes (mainly)	Readmission, symptom and functioning scales	yes	Exposure not well defined
Hogarty (1974)	(Est) 1970	United States	AP	Placebo	SZ	2 years	374	no	Relapse (defined as clinical deterioration), time to relapse	mixed	Exposure not well defined
Mosher (1978)	(Est) 1976	United States	AP[4] (attends facility that treats with AP)	No AP[4] (attends facility that does not treat with AP)	SZ	2 years	79	no	Duration of hospitalization, number of readmissions, symptom and functioning scales	mixed	Exposure not well defined
Nishikawa (1982)	(Est) 1979	Japan	AP	Placebo	SZ	3 years	55	no	Number of symptom free days, remission/ relapse (defined by symptom scales)	no	Small sample size
Carpenter (1987)	(Est) 1979	United States	Consistent AP treatment	Intermittent AP treatment	SZ/SA	2 years	41	no	Readmission, symptom and functioning scales	no	Small sample size; loss to follow-up
Crow (1986)	1979-1982	England	AP	Placebo	SZ	2 years	120	yes	Relapse (defined by readmission and clinical rating)	no	Exposure not well defined; loss to follow-up

First author (year published)	Year(s)	Country	Exposed group[1]	Unexposed group[1]	Diagnoses included in study	Follow-up time	Sample size	All first admission (yes/no)	Outcomes measured[2]	Findings consistent with study hypothesis?	Main sources of bias[3]
Pietzcker (1993)	1983-1987	Germany	Consistent AP treatment	Intermittent AP treatment	SZ	2 years	364	no	Readmission, relapse (defined by clinician), symptom and functioning scales	mixed	Loss to follow-up
Wunderlink (2013)	2001-2010	The Netherlands	Consistent AP treatment	Reduce dose /discontinue AP treatment	Psychosis	7 years	103	yes	Recovery, remission, and relapse (all defined by symptom and functioning scales)	yes	Exposure not well defined
Boonstra (2011)	2002-2007	The Netherlands	Consistent AP treatment	Discontinue AP treatment	SZ, SZF, SA	2 years	20	yes	Relapse (defined by readmissions and symptom scales)	no	Exposure not well defined, small sample size; loss to follow-up

Dates of data collection estimated in some studies, indicated by (Est). AP=antipsychotic medication. SZ= schizophrenia, SA= schizoaffective disorder, SZF= schizophreniform disorder, SSD= schizophrenia spectrum disorder

[1]Studies were categorized has having one of three main types of exposed groups: Patients treated during the “AP medication era;” patients treated with or assigned to receive AP medications; patients treated with or assigned to receive AP medication throughout the treatment period. Studies were categorized has having one of three main types of unexposed groups: Patient treated before the AP medication era;” patients treated with or to assigned to be treated with something other than AP medications; patients assigned to discontinue AP medication at some point during the treatment period.

[2]The main study outcome measures are listed in the table

[3]The five types of study design issues explored include comparability of exposure groups at baseline, confounding by indication, loss to follow-up, sample size concerns, and quality of exposure measures

[4]In the Mosher, et al (1978) study the “no AP” group was considered the experimental (exposed) treatment group and the “AP” group was the control (unexposed) group.

[5]In the May, et al (2001) study, the “no AP” group included patients with psychotherapy only and the “AP” group included people with only medications and with medications in addition to psychotherapy. These comparisons were presented in the context of a randomized study with five arms that included the three listed above plus milieu and electroconvulsive therapy.