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Association of Aripiprazole With the Risk for Psychiatric Hospitalization, Self-harm, or Suicide

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IMPORTANCE Some reports have raised concerns regarding a potential psychiatric worsening associated with first-time use of aripiprazole in patients already treated with other antipsychotic medications. Whether aripiprazole use, particularly in the long term, increases the risk for serious psychiatric events is unclear.

OBJECTIVE To assess whether switching to or adding aripiprazole is associated with serious psychiatric treatment failure compared with switching to or adding another antipsychotic drug in patients previously exposed to antipsychotic medications.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study was conducted from January 1, 2005, to March 31, 2015. Data were obtained from the United Kingdom Clinical Practice Research Datalink, one of the world's largest computerized databases linked to the Hospital Episodes Statistics repository and the Office for National Statistics (ONS) mortality database. Within a base cohort of new users of antipsychotic drugs, patients switching or adding aripiprazole (n = 1643) were propensity matched 1:1 to patients switching to or adding another antipsychotic medication (n = 1643). All patients were followed up until psychiatric treatment failure, for 365 days (1 year) after cohort entry, until death from any cause other than suicide, until end of registration or linkage with the databases, or end of the study period (March 31, 2016).

MAIN OUTCOMES AND MEASURES Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% CIs of serious events of psychiatric treatment failure (psychiatric hospitalizations, self-harm, or suicide) associated with switching to or adding aripiprazole compared with other antipsychotic drugs. In addition to propensity score matching, all models were adjusted for age, number of psychiatric hospitalizations or self-harm events in the 6 months before cohort entry, number of different antipsychotic drugs before cohort entry, and quintiles of the Index of Multiple Deprivation.

RESULTS The study cohort included 1643 patients (949 [57.8%] were women with a mean [SD] age of 42.1 [16.8] years) starting aripiprazole use; they were matched 1:1 to 1643 patients (871 [53.0%] were women with a mean [SD] age of 42.4 [17.1] years) starting use of another antipsychotic drug. During 2692 person-years of follow-up, 391 incident serious psychiatric treatment failures occurred, with a crude incidence rate of 14.52 (95% CI, 13.16-16.04) per 100 person-years. First-time use of aripiprazole was not associated with an increased rate of psychiatric treatment failure (HR, 0.87; 95% CI, 0.71-1.06), psychiatric hospitalizations (HR, 0.85; 95% CI, 0.69-1.06), or self-harm or suicide (HR, 0.96; 95% CI, 0.68-1.36) compared with starting use of another antipsychotic drug. Results were consistent across several sensitivity analyses.

CONCLUSIONS AND RELEVANCE Initiating aripiprazole use, compared with another antipsychotic medication, after a previous antipsychotic exposure did not appear to be associated with psychiatric hospitalization, self-harm, or suicide; these findings warrant replication in large observational studies.

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Aripiprazole, an antipsychotic drug marketed in 2005 in the United Kingdom, has an effectiveness comparable to that of other first-line antipsychotic medications, but its pharmacodynamic properties and adverse effects profile differ.[1] Aripiprazole has been favored because of its reduced metabolic adverse effects, compared with some other antipsychotic drugs,[2] but some concerns have emerged that its use is associated with a potential psychiatric worsening. Several cases of abrupt psychotic worsening have been reported in patients who started taking aripiprazole after being treated with other antipsychotic drugs.[3-8] In particular, the risk seems greater in patients in a clinically vulnerable state, a condition named dopamine supersensitivity psychosis.[9,10] The proposed pharmacologic mechanism underlying the development of dopamine supersensitivity psychosis is the up-regulation of the D_2 dopamine receptor, caused by long-term and high-dose treatment with antipsychotic medications.[11,12] Consequently, introducing a D_2 dopamine receptor partial agonist such as aripiprazole after previous exposure to an antipsychotic drug could theoretically induce psychiatric exacerbations.[13]

A recent meta-analysis of clinical trials in the schizophrenia spectrum did not find evidence that switching to or adding aripiprazole to treatment was associated with psychotic worsening, compared with any other antipsychotic drug.[14] However, in the clinical trials used in this meta-analysis, misclassification of some adverse events was possible because the clinical distinction between psychotic worsening reports and lack of efficacy had not been defined.[15,16] To date, only 1 small cohort study has evaluated the risk for serious psychiatric worsening, such as psychiatric hospitalization, comparing those who switched to aripiprazole and those who switched to other antipsychotic medications; the study found no increased risk from aripiprazole use during a maximum follow-up of 6 months.[17] Therefore, there is a need to further examine, in a larger cohort and with longer follow-up, the risk for psychiatric worsening in patients who are taking a D_2 dopamine receptor partial agonist, such as aripiprazole, for the first time after a previous exposure to other antipsychotic drugs.[18]

The objective of this population-based cohort study was to assess whether initiation of aripiprazole is associated with an increased risk of psychiatric treatment failure, defined as a hospitalization for a psychiatric event, self-harm, or suicide, compared with the initiation of another antipsychotic drug, among patients previously exposed to antipsychotic medications.

Key Points

Question Are patients who switch to or add aripiprazole at an increased risk for psychiatric hospitalization, self-harm, or suicide, compared with switching to or adding another antipsychotic drug?

Findings In this population-based cohort study of 1643 patients who were starting aripiprazole use, compared with matched patients starting use of another antipsychotic medication, aripiprazole was not associated with an increased risk of hospitalization, self-harm, or suicide.

Meaning Switching to or adding aripiprazole may be associated with psychiatric worsening in some patients, but the findings suggest that these exacerbations do not lead to serious psychiatric treatment failure; these findings warrant replication in large observational studies.

Methods

The study protocol was approved by the Independent Scientific Advisory Committee of the United Kingdom Clinical Practice Research Datalink (CPRD) and by the Research Ethics Committee of the Jewish General Hospital (Montreal, Quebec, Canada). These committees waived the need for patient informed consent because the data used in this study were deidentified.

Data Source

This study obtained data from the CPRD, which was linked to the Hospital Episode Statistics (HES) repository and the Office for National Statistics (ONS) mortality database. The CPRD is one of the world's largest computerized databases of anonymized primary care medical records, containing the data of more than 15 million patients enrolled with more than 700 general practices in the United Kingdom.[19] The CPRD uses the Read classification system to define medical diagnoses,[20] and it records demographic data, lifestyle factors, and prescriptions based on the British National Formulary. Numerous studies have shown the validity and high quality of these recorded data.[21-23]

The HES repository contains all inpatient and day-case admission information, including primary and secondary diagnoses recorded using the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes and related hospital-based procedures. The HES repository is available for primary care practices that have consented to linkages, which represent approximately 50% to 55% of the CPRD. The ONS mortality database includes dates and causes of death recorded using *ICD-10* codes.

Study Population

Base Cohort

We assembled a cohort of all patients in the CPRD who were at least 13 years of age and initiating use of an oral antipsychotic drug (eMethods 1 in the Supplement) between January 1, 2005, and March 31, 2015. To form a base cohort of new users of antipsychotic drugs (incident users), all patients were required to have at least 1 year of medical history in the CPRD without any (oral or long-acting) antipsychotic prescriptions before their first oral antipsychotic prescription. Patients initially treated with aripiprazole and patients with advanced schizophrenia (defined as those who used clozapine or who received 2 or more antipsychotic prescriptions on the day of cohort entry) were excluded. To limit the base cohort to patients with psychiatric diseases, we also excluded patients with Parkinson disease or Alzheimer disease before cohort entry.

Study Cohort

From the base cohort, we identified a study cohort of all patients who received a prescription for aripiprazole or another oral antipsychotic drug (either as a switch from or add-on to a previous antipsychotic medication) on or after January 1, 2005

(the year that aripiprazole was licensed in the United Kingdom). Using a prevalent new-user design,[24] we matched 1:1 each patient starting aripiprazole use to a patient starting another antipsychotic drug on the basis of calendar year of cohort entry (within 5 years), time since first antipsychotic prescription (within 6 months), psychiatric disease history (schizophrenia, bipolar disorder, depression, other psychiatric diseases, or unknown), age (in categories), and time-conditional propensity score. We used conditional logistic regression to estimate the propensity score of exposure to aripiprazole compared with exposure to other oral antipsychotic medications, conditional on baseline covariates (eMethods 2 in the Supplement). Cohort entry was defined as the issue date of aripiprazole or another oral antipsychotic prescription for the matched patient.

Patients were followed up until psychiatric treatment failure, 365 days (1 year) after cohort entry, death from any cause other than suicide, end of registration with the CPRD-enrolled general practice, end of HES linkage, or end of the study period (March 31, 2016), whichever occurred first. Patients with a first prescription of clozapine during follow-up were censored on the date of this first prescription.

Exposure

Exposure to oral aripiprazole and other oral antipsychotic drugs (first and second generation) was defined according to issued prescriptions (eMethods 1 in the Supplement). Following the intent-to-treat approach, we considered all patients to be exposed to the antipsychotic medication at study cohort entry until the end of follow-up (maximum of 1 year), irrespective of whether they discontinued treatment or switched to another antipsychotic drug (eMethods 3 in the Supplement).

In a sensitivity analysis, the use of antipsychotic medications during follow-up was modeled as a time-varying variable. From the date the first prescription was issued at study cohort entry, patients were considered continuously exposed if the duration of 1 prescription overlapped with the date of the next prescription issue for the same medication. We allowed a grace period of 30 days in the event of 2 nonoverlapping successive prescriptions to account for residual effects and delays between prescription refills. Following an as-treated definition of exposure, we censored patients at the time of treatment discontinuation or switch during follow-up.

Outcomes

The primary outcome was the first psychiatric treatment failure, a composite of hospitalization for a psychiatric event, self-harm, or suicide. We identified psychiatric admissions by the *ICD-10* codes in the primary diagnosis position in the HES repository (eMethods 4 in the Supplement). Suicide was identified using the ONS mortality database, and self-harm was identified by the hospitalization for self-harm information in any diagnosis position in the HES repository, as defined in a previous CPRD study.[25,26]

Statistical Analysis

Descriptive statistics were used to compare the baseline characteristics between patients starting aripiprazole use and patients starting other antipsychotic drugs. Crude incidence rates of psychiatric treatment failure were estimated on the basis of a Poisson distribution by counting events and person-time of follow-up.

For the primary objective, we constructed Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% CIs for psychiatric treatment failure associated with use of aripiprazole compared with use of other antipsychotic medications. An intent-to-treat approach was used to define exposure, based on the issue of antipsychotic prescription at cohort entry. We used robust SEs to account for the correlation induced by the matching process.[27] In addition to matching on the basis of calendar year of cohort entry, time since first antipsychotic prescription, psychiatric disease history, age, and propensity score, we adjusted all models for age, number of previous psychiatric admissions or self-harm events in the 6 months before cohort entry, number of different antipsychotic drugs used before cohort entry, and quintiles of the Index of Multiple Deprivation as a proxy for socioeconomic status (eMethods 5 in the Supplement).

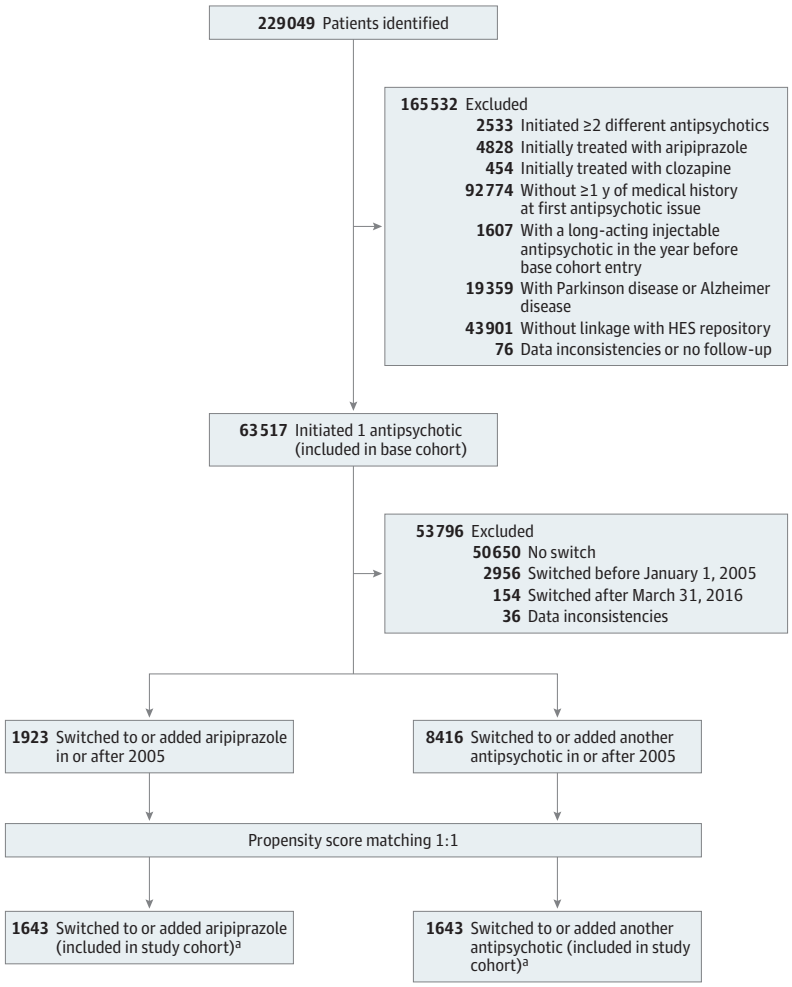
Secondary Analyses

We performed several secondary analyses. To take into account the burden of antipsychotic exposure history, we repeated the primary analysis stratified by the number of previous antipsychotic prescriptions before cohort entry. Next, to consider only the patients recently exposed before switching, we restricted the analysis to patients who received antipsychotic prescriptions in the 3 months before cohort entry. Among these patients, we also examined whether the risk varied by the defined daily dose of the last antipsychotic drug used before cohort entry (eMethods 6 in the Supplement). To assess effect modification, we conducted analyses among adults only and among patients with a diagnosis of schizophrenia. Finally, we stratified the main analysis according to switched or added-on antipsychotic drug, defining add-on therapy by a concomitant antipsychotic prescription within 1 month after cohort entry. In these analyses, models were adjusted on the deciles of the propensity score.

Sensitivity Analyses

We performed 7 sensitivity analyses to assess the robustness of our results. First, we repeated the primary analysis with a 6-month follow-up. Second, to explore potential confounding from more severe patients being preferentially treated with aripiprazole when the drug became available on the market in 2005, we restricted the study cohort to patients who were switching to or adding aripiprazole or another antipsychotic medication to their treatment on or after January 1, 2006. Third, to minimize the potential for indication bias, we repeated the primary analysis by considering only users of second-generation of antipsychotic drugs. Fourth, to increase the specificity of the outcome definition, we considered only psychiatric hospitalizations with a diagnosis of schizophrenia; schizotypal, delusional, and other nonmood psychotic disorders; or mood disorders. Fifth, we repeated the primary analysis while identifying psychiatric treatment failure on the basis of Read codes for self-harm and suicide in the CPRD. Sixth, we used an as-treated exposure definition,

Figure 1. Flowchart of the Base and Study Cohorts



[a] At cohort entry, 4 patients (1 in the aripiprazole group and 3 in the other drugs group) were treated with a depot antipsychotic drug. Among the 3286 patients, 24 patients (0.7%; 11 in the aripiprazole group and 13 in the other drugs group) were exposed to at least 1 depot antipsychotic drug during follow-up. HES indicates Hospital Episode Statistics repository.

in which patients were followed up until the discontinuation of treatment or switch to another antipsychotic medication. Seventh, to explore the potential for misclassification of exposure, we repeated the as-treated analysis with an extended grace period of 60 days. All analyses were conducted with SAS, version 9.4 (SAS Institute Inc).

Results

We identified 229 049 patients who were initiating use of an oral antipsychotic drug between January 1, 2000, and March 31, 2015. Among these patients, 63 517 (27.7%) were eligible, forming the base cohort linked to the HES repository (**Figure 1**). The study cohort included 1643 patients (949 [57.8%] were women with a mean [SD] age of 42.1 [16.8] years) starting aripiprazole use; they were matched 1:1 to 1643 patients (871 [53.0%] were women with a mean [SD] age of 42.4 [17.1] years) starting use of another antipsychotic drug. The baseline characteristics of the matched cohort are shown in **Table 1**. Patients starting aripiprazole use had a similar baseline profile to those starting another antipsychotic drug, except for a slightly lower number of previous psychiatric admissions (300 [18.3%] vs 370 [22.5%]) or self-harm (49 [3.0%] vs 75 [4.6%]) in the 6 months before cohort entry and a higher number of different antipsychotic drugs (mean [SD], 0.9 [0.5] vs 0.7 [0.6]) before cohort entry.

During the 2692 person-years of follow-up, 391 incident psychiatric treatment failures occurred, yielding a crude incidence rate of 14.52 (95% CI, 13.16-16.04) per 100 person-years. **Table 2** presents the results of the primary analyses. Initiation to aripiprazole was not associated with an increased rate of psychiatric treatment failure, compared with initiation to another antipsychotic medication (HR, 0.87; 95% CI, 0.71-1.06). No association with psychiatric hospitalization (HR, 0.85; 95% CI, 0.69-1.06) or with self-harm or suicide (HR, 0.96; 95% CI, 0.68-1.36) was found when assessed separately.

Results of the secondary analyses are presented in **Table 3**. Initiation to aripiprazole was not associated with an increased rate of psychiatric treatment failure in various subgroups, including patients recently treated with antipsychotic drugs (HR, 0.87; 95% CI, 0.67-1.15) and patients with schizophrenia (HR, 0.82; 95% CI, 0.62-1.08). Similar patterns were observed when assessing psychiatric hospitalization and

Table 1. Baseline Characteristics by Exposure Status at Study Cohort Entry[a]

Variable	AP Prescription Used at Cohort Entry	
	Aripiprazole	Other AP Drug
All patients, No.	1643	1643
Age, mean (SD), y	42.1 (16.8)	42.4 (17.1)
Age group, y, No. (%)		
13-17	181 (11.0)	181 (11.0)
18-30	338 (20.6)	338 (20.6)
31-40	393 (23.9)	393 (23.9)
41-50	361 (22.0)	361 (22.0)
51-60	171 (10.4)	171 (10.4)
61-70	85 (5.2)	85 (5.2)
≥71	114 (6.9)	114 (6.9)
Male, No. (%)	694 (42.2)	772 (47.0)
Year of cohort entry, No. (%)		
2005-2008	439 (26.7)	509 (31.0)
2009-2011	554 (33.7)	599 (36.5)
2012-2016	650 (39.6)	535 (32.6)
Time since the first AP initiation, mean (SD), y	2.4 (2.5)	2.4 (2.5)
Comorbidities, No. (%)		
BMI, kg/m^2		
<25	459 (27.9)	452 (27.5)
25-30	397 (24.2)	398 (24.2)
>30	394 (24.0)	387 (23.6)
Unknown	393 (23.9)	406 (24.7)
Smoking status		
Never	465 (28.3)	494 (30.1)
Ever	1145 (69.7)	1112 (67.7)
Unknown	33 (2.0)	37 (2.3)
Alcohol abuse	102 (6.2)	92 (5.6)
Psychiatric diagnosis, No. (%)		
Schizophrenia	694 (42.2)	694 (42.2)
Bipolar disorder	220 (13.4)	220 (13.4)
Depression	325 (19.8)	325 (19.8)
Other psychiatric diagnoses[b]	37 (2.3)	37 (2.3)
Unknown	367 (22.3)	367 (22.3)
Coronary artery disease	33 (2.0)	32 (2.0)
Hypertension	127 (7.7)	109 (6.6)
Diabetes[c]	124 (7.6)	97 (5.9)
Hyperlipidemia	98 (6.0)	91 (5.5)
Stroke	33 (2.0)	28 (1.7)
Dementia	33 (2.0)	29 (1.8)
No. of psychiatric consultations, No. (%)[d]		
0	638 (38.8)	747 (45.5)
1-3	575 (35.0)	558 (34.0)
≥4	430 (26.2)	338 (20.6)
Severity 6 mo before cohort entry, No. (%)		
No. of AP prescriptions, mean (SD)	3.6 (4.1)	2.8 (4.1)
No. of different AP prescriptions, mean (SD)	0.9 (0.5)	0.7 (0.6)
Psychiatric admission	300 (18.3)	370 (22.5)
Self-harm	49 (3.0)	75 (4.6)
Most recent AP prescription before switch, No. (%)		
Olanzapine	581 (35.1)	479 (29.1)
Quetiapine fumarate	475 (28.7)	291 (17.7)
Risperidone	383 (23.1)	372 (22.6)
Haloperidol lactate	40 (2.4)	99 (6.0)
Chlorpromazine hydrochloride	36 (2.2)	102 (6.2)
FGA	156 (9.5)	446 (27.1)
SGA	1501 (91.4)	1201 (73.1)
Other psychotropic drugs, No. (%)[d]		
Antidepressants	1172 (71.3)	1137 (69.2)
Mood stabilizers	234 (14.2)	261 (15.9)
Sedative/hypnotics	524 (31.9)	544 (33.1)
ADHD medication	15 (0.9)	9 (0.6)
Drug used in alcohol dependence, No. (%)	18 (1.1)	18 (1.1)
Other drug type, No. (%)[d]		
Antihypertensive	332 (20.2)	312 (19.0)
Lipid lowering	210 (12.78)	185 (11.3)
Antiplatelet	133 (8.1)	117 (7.1)
Glucose lowering	93 (5.7)	77 (4.7)
Drug class, No. (%)[d]		
0-3	556 (33.8)	557 (33.9)
4-8	582 (35.4)	564 (34.3)
≥9	505 (30.7)	522 (31.8)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AP, antipsychotic; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FGA, first generation of antipsychotics; SGA, second generation of antipsychotics.

[a] A patient starting aripiprazole was matched 1:1 to a patient starting another AP drug on the basis of calendar year of cohort entry (within 5 years), time since the first antipsychotic prescription (within 6 months), psychiatric disease history (schizophrenia, bipolar disorder, depression, other psychiatric diseases, or unknown), age (in categories) and time-conditional propensity score.

[b] Other psychiatric diagnoses include ADHD, autism, obsessive compulsive disorders, and personality disorders.

[c] Diabetes type 1 or 2.

[d] Measured in the year before cohort entry.

self-harm or suicide separately (eTables 1 to 4 in the Supplement). Results were consistent in most sensitivity analyses (**Figure 2**; eTables 5 to 10 in the Supplement). In particular, using a more specific outcome definition for psychiatric hospitalization generated similar results.

Discussion

In this population-based study, we found no evidence of an increased rate of psychiatric treatment failure associated with initiating aripiprazole use compared with initiating use of other antipsychotic drugs in patients previously exposed to antipsychotic medications. Separate analyses for psychiatric hos-

Table 2. Crude and Adjusted Hazard Ratios for the Association Between Starting Aripiprazole and the Risk of Psychiatric Treatment Failure

Exposure	No. of Psychiatric Events	Person-Years	Incidence Rate (95% CI)[a]	Matched HR	Adjusted HR (95% CI)[b]
Composite outcome[c]					
Other AP prescription	209	1307	15.98 (13.96-18.31)	1 [Reference]	1 [Reference]
Aripiprazole	182	1384	13.15 (11.37-15.21)	0.83 (0.68-1.01)	0.87 (0.71-1.06)
Psychiatric hospitalization					
Other AP prescription	170	1327	12.81 (11.03-14.89)	1 [Reference]	1 [Reference]
Aripiprazole	147	1404	10.47 (8.91-12.31)	0.83 (0.67-1.02)	0.85 (0.69-1.06)
Self-harm/suicide					
Other AP prescription	70	1388	5.04 (3.99-6.37)	1 [Reference]	1 [Reference]
Aripiprazole	67	149	4.62 (3.64-5.87)	0.92 (0.66-1.29)	0.96 (0.68-1.36)

Abbreviations: AP, antipsychotic; HR, hazard ratio.

[a] Per 100 person-years.

[b] Adjusted for age, number of previous psychiatric admissions or self-harm in 6 months before cohort entry, number of different antipsychotic drugs before cohort entry, Index of Multiple Deprivation.

[c] Composite outcome comprises psychiatric hospitalization, self-harm, or suicide.

pitalizations, self-harm, and suicide showed no association. Similarly, among patients with schizophrenia, starting aripiprazole use was not associated with an increased rate of psychiatric treatment failure. Other secondary and sensitivity analyses led to the same results.

Consistent with our results, a recent meta-analysis[14] of adverse events reported in 22 clinical trials in schizophrenia found no association between psychotic worsening and switching to aripiprazole compared with other antipsychotic drugs (relative risk [RR], 1.17; 95% CI, 0.97-1.42), although the upper limit of the CI was compatible with a 42% increased risk. A greater rate of study discontinuation owing to a lack of efficacy with aripiprazole was found (RR, 1.46; 95% CI, 1.10-1.93).[14] However, this meta-analysis was based on clinical trials that were not designed to examine antipsychotic switch and in which psychiatric adverse events were not the primary outcome and switching antipsychotic was not the main intervention. Also, the accuracy of adverse psychiatric events assessment in these clinical trials was questionable, especially in the context of switching drugs and for psychiatric symptoms.[15] For example, a psychotic exacerbation after a switch to aripiprazole could reflect a psychotic worsening secondary to aripiprazole or a diminished response (lack of efficacy) with aripiprazole, compared with previous antipsychotic drugs used. Therefore, misclassification could affect nonserious and serious outcomes.[28]

In the past decade, numerous case reports have suggested that initiating aripiprazole use after previous antipsychotic exposure could be associated with psychotic worsening.[3-8] In a systematic review of 22 reported cases, psychiatric decompensations occurred in patients previously treated with an antipsychotic drug who either switched to or added aripiprazole.[10] In most cases (n = 19), patients were previously exposed to an antipsychotic dose that exceeded recommended guidelines, supporting the hypothesis that the risk of treatment failure could be higher in patients in a clinically vulnerable state (dopamine supersensitivity psychosis). The pharmacodynamic hypothesis is that long-term treatment and high doses of antipsychotic medications could up-regulate D_2 dopamine receptors and thereby induce a hyperdopaminergic state. In this context, starting a high-affinity partial D_2 dopamine agonist, such as aripiprazole, could worsen psychotic symptoms. Nevertheless, our findings suggest that the exacerbation of psychiatric symptoms may not lead to more serious psychiatric outcome, which is also clinically relevant. The results were also consistent when we stratified the analysis on the defined daily dose, with no association for higher dose (>1 defined daily dose) of the last antipsychotic used before cohort entry. To date, only 1 cohort study has evaluated the risk associated with aripiprazole and serious psychiatric outcomes.[17] That study found no increased risk of psychiatric hospitalization in 444 patients who switched to aripiprazole compared with 521 patients who switched to other antipsychotic medications (RR, 0.92; 95% CI, 0.67-1.26).[17] However, the cohort was small, limited to patients with schizophrenia, with a maximum follow-up of 6 months, and may have included previous use of aripiprazole.

We extended these previous findings in a large cohort of patients with various psychiatric diseases. No association was found between both psychiatric hospitalization and self-harm or suicide and initiation of aripiprazole use. However, for self-harm or suicide, the upper limit of the CI of 1.36 does not rule out an HR of 1.36.

Switching to aripiprazole might be associated with psychotic worsening in some patients, but it could be hypothesized that these patients present with symptoms that are manageable in an outpatient setting or that these patients could discontinue aripiprazole before further worsening of symptoms. The latter may explain the apparent protective effect of aripiprazole in the as-treated analysis. However, we could not exclude a potential risk of psychiatric treatment failure in patients with more severe psychiatric disease. Thus, further investigation is needed in patients who were highly exposed to antipsychotic drugs before switching to aripiprazole.

Strengths and Limitations

This study has several strengths. First, the prevalent new-user design allowed for a comparison of patients who switched or added treatment of antipsychotic drugs in a population-based cohort of new users of antipsychotic drugs.[24] Indeed, using time-based exposure sets and matching on time-conditional propensity score increases the comparability be-

Table 3. Crude and Adjusted Hazard Ratios for the Association Between Starting Aripiprazole and the Risk of Psychiatric Treatment Failure (Secondary Analyses)

Subgroup	No. of Patients	No. of Psychiatric Events	Person-Years	Incidence Rate (95% CI)[a]	Matched HR (95% CI)	Adjusted HR (95% CI)[b]
No. of previous AP prescriptions						
1-3						
Other AP prescription	608	77	484	15.91 (12.73-19.90)	1 [Reference]	1 [Reference]
Aripiprazole	426	43	359	11.99 (8.89-16.16)	0.76 (0.52-1.11)	0.81 (0.55-1.20)
4-12						
Other AP prescription	537	68	432	15.75 (12.41-19.97)	1 [Reference]	1 [Reference]
Aripiprazole	581	53	500	10.60 (8.10-13.88)	0.68 (0.48-0.97)	0.68 (0.47-0.98)
≥13						
Other AP prescription	498	64	392	16.34 (12.79-20.87)	1 [Reference]	1 [Reference]
Aripiprazole	636	86	525	16.37 (13.25-20.22)	1.01 (0.73-1.40)	1.05 (0.75-1.49)
Among patients exposed 3 mo before cohort entry						
Other AP prescription	861	109	681	16.00 (13.26-19.31)	1 [Reference]	1 [Reference]
Aripiprazole	1054	115	896	12.83 (10.69-15.41)	0.81 (0.63-1.06)	0.87 (0.67-1.15)
DDD of the last antipsychotic prescribed before cohort entry						
≤1 DDD						
Other AP prescription	610	70	493	14.19 (11.23-17.94)	1 [Reference]	1 [Reference]
Aripiprazole	778	71	665	10.67 (8.46-13.47)	0.76 (0.55-1.05)	0.82 (0.58-1.15)
>1 DDD						
Other AP prescription	251	39	188	20.74 (15.16-28.39)	1 [Reference]	1 [Reference]
Aripiprazole	276	44	231	19.06 (14.18-25.61)	0.94 (0.61-1.44)	0.99 (0.62-1.58)
Among adults only						
Other AP prescription	1616	203	1288	15.76 (13.74-18.09)	1 [Reference]	1 [Reference]
Aripiprazole	1611	179	1358	13.18 (11.38-15.26)	0.84 (0.69-1.03)	0.89 (0.72-1.09)
Among patients with schizophrenia						
Other AP prescription	694	119	532	22.38 (18.70-26.78)	1 [Reference]	1 [Reference]
Aripiprazole	694	95	582	16.33 (13.36-19.97)	0.74 (0.57-0.97)	0.82 (0.62-1.08)
Switch or add-on AP drug						
Add-on[c]						
Other AP prescription	217	28	157	17.79 (12.28-25.76)	1 [Reference]	1 [Reference]
Aripiprazole	344	39	269	14.50 (10.59-19.84)	0.83 (0.51-1.33)	0.91 (0.56-1.48)
Switch						
Other AP prescription	1347	142	1018	13.94 (11.83-16.44)	1 [Reference]	1 [Reference]
Aripiprazole	1239	118	982	12.02 (10.03-14.39)	0.87 (0.68-1.11)	0.89 (0.68-1.15)

Abbreviations: AP, antipsychotic; DDD, defined daily dose; HR, hazard ratio.

[a] Per 100 person-years.

[b] Adjusted for age, number of previous psychiatric admissions or self-harm in 6 months before cohort entry, number of different antipsychotic drugs before cohort entry, Index of Multiple Deprivation, and deciles of the propensity score.

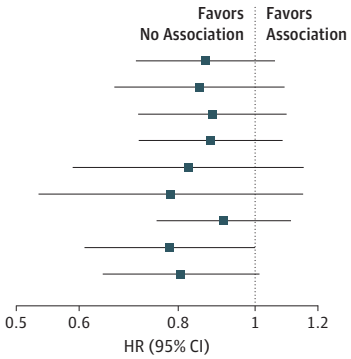
[c] *Add-on* defined as a concomitant AP prescription within 1 month after cohort entry.

tween exposure groups and thus minimizes residual confounding. Second, comparing aripiprazole with other antipsychotic drugs used by patients with similar psychiatric history likely minimized confounding by indication. Third, the results remained consistent across 7 sensitivity analyses. Fourth, we used data from the CPRD, which provides prospectively recorded data on prescriptions and medical history, including diagnoses. Finally, with respect to our outcome definition, we expect minimal misclassification bias, given that the *ICD-10* codes used to identify psychiatric hospitalization, self-harm, or suicide in the HES repository and ONS mortality database have already been used in a previous CPRD study.[25]

This study is observational in nature and thus is subject to some potential limitations. First, prescriptions in the CPRD represent those issued by general practitioners, and we had no information on medications prescribed by specialists. Therefore, patients with unstable psychiatric disease who had a follow-up exclusively with a psychiatrist may not have been captured. However, the general practitioners are central to the UK national health system, and most prescriptions are re-

Figure 2. Forest Plot of the Association Between Switching to Aripiprazole and Psychiatric Treatment Failure

Sensitivity Analysis Cycle	HR (95% CI)
Primary analysis	0.87 (0.71-1.06)
Primary analysis with 6-mo follow-up	0.85 (0.67-1.09)
Study cohort after January 1, 2006	0.88 (0.71-1.09)
Users of SGAs	0.88 (0.72-1.08)
Hospitalization with a diagnosis of schizophrenia	0.82 (0.59-1.15)
Hospitalization with a diagnosis of mood disorders	0.78 (0.53-1.15)
Using Read Codes for self-harm and suicide	0.91 (0.75-1.11)
As-treated analysis (30-day grace period)	0.78 (0.61-1.00)
As-treated analysis (60-day grace period)	0.81 (0.64-1.01)



HR indicates hazard ratio; SGAs, second-generation of antipsychotics.

newed by general practitioners, even when the treatment has been initiated by a specialist. We also had no information on patient compliance or adherence to their prescribed treatment. However, because all patients in the study cohort were treated with antipsychotic drugs, this misclassification is likely to be nondifferential between comparison groups.

Second, we identified episodes of psychiatric decompensations leading to hospital admission, self-harm, or suicide, which are clinically relevant outcomes in psychiatry. However, our outcome definition of psychiatric hospitalization may have lacked specificity to distinguish psychotic worsening from other reasons for hospitalization. Thus, we performed sensitivity analyses that considered only psychiatric hospitalizations with a diagnosis of schizophrenia or with a diagnosis of mood disorders, which generated similar results. Finally, as with any observational study, confounding remains possible. For instance, physicians may preferentially prescribe aripiprazole to patients with less severe psychiatric disease and who were less likely to experience psychiatric treatment failure. To mitigate this potential limitation, we formed a homogeneous cohort of patients treated with oral antipsychotic drugs, compared them with patients matched on propensity score and other important potential confounders (such as psychiatric disease diagnosis), and adjusted all models for several additional covariates.

Conclusions

The results of this population-based cohort study indicate that, compared with initiation of another antipsychotic drug, starting aripiprazole use after a previous exposure to antipsychotic medication was not associated with psychiatric hospitalization, self-harm, or suicide. However, these findings do not exclude a differential risk for nonserious psychiatric exacerbations that do not lead to psychiatric hospitalization. In addition, we could not eliminate a potential risk for psychiatric treatment failure in patients with prolonged antipsychotic treatment before initiation of aripiprazole use. Therefore, patients should still be monitored for psychiatric exacerbations when they switch to or add aripiprazole. These results warrant replication in larger population-based studies.

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