Antipsychotic drug use and the risk of developing diabetes mellitus in UK: a retrospective cohort study

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SUMMARY

Background: Drug-induced diabetes mellitus has been reported in the literature for both conventional and atypical antipsychotics. However, no large-scale epidemiological studies have been carried out that systematically assessed the risk of developing diabetes for patients taking these agents. In this retrospective cohort study, we explored the UK General Practice Research database (GPRD) to determine the hazard ratio of diabetes for patients prescribed antipsychotics compared with the general adult population in the UK.
Methods: A conventional antipsychotic cohort (N= 44,046), an atypical antipsychotic cohort (N=2,527), and a general patient population cohort (N=269,049) derived from the GPRD database were studied. The Cox proportional hazard regression model was used to determine the hazard ratio (HR) of diabetes development between these cohorts. The covariates included in the model were age, sex, and the presence or absence of obesity.
Findings: As compared to the conventional antipsychotic cohort, the atypical antipsychotic cohort had a higher risk of developing diabetes (HR= 2.6; 95% CI=1.3-5.3). The most commonly prescribed agents were thioridazine (44%) and fluopenthixol (22%) among conventional antipsychotics, and risperidone (71%) and olanzapine (21%) among atypical antipsychotics. The incidence of diabetes during exposure to either class of antipsychotics was higher than that during the periods when they were not exposed to these agents. As compared to the general population cohort in the UK, patients exposed to either class of antipsychotics had a higher risk of developing diabetes [HR=3.3 (95% CI= 1.7-6.5) for the atypical antipsychotic cohort; and HR= 1.3: (95% CI=1.003-1.8) for the conventional antipsychotic cohort].

INTRODUCTION

Studies over several decades suggest that diabetes, impaired glucose tolerance (IGT), and insulin resistance are more common among patients with major mood disorders and schizophrenia than among the general population (1, 2, 3, 4). It remains to be determined whether this disturbance in glucose homeostasis is attributable to the underlying psychiatric conditions, to the drugs used for their treatment, or both. Shortly after the

introduction of chlorpromazine in the early 1950s, there were reports of an association between exposure to this drug and emergence of hyperglycemia and diabetes (5, 6). The possibility that antipsychotic exposure might be a risk factor for diabetes, independent of neuropsychiatric disorders, was also suggested by studies showing the emergence of hyperglycemia in normal animals treated with chlorpromazine (7, 8). However, the diabetogenic potential of this drug was not supported by all investigations (9).

Drug-induced glucose intolerance was also reported for other conventional antipsychotics (10, 11, 12), as well as for atypical antipsychotics (13, 14, 15, 16, 17). A recent study suggested that patients treated with clozapine, an atypical antipsychotic, developed IGT or diabetes more often than those treated with conventional antipsychotics (13). This finding, together with the greater potency of atypical antipsychotics in inducing weight gain, raise the possibility that atypical antipsychotics as a class might be associated with a higher incidence of diabetes than conventional antipsychotics. Reports of an association between antipsychotics and diabetes are largely anecdotal, and consisted mostly of either single case reports or small case series. As of this date, there are no large scale epidemiological studies published that have determined the incidence of diabetes in patients treated with these two classes of antipsychotics or studies that compare these incidences with that of the general population. In the present retrospective cohort study, the incidence of diabetes mellitus was determined in the UK in patients exposed to conventional and atypical antipsychotics, and in the general population using the UK-based General Practice Research Database (GPRD). Hazard ratios of diabetes for patients exposed to these classes of antipsychotics and to individual antipsychotics were determined relative to the general UK patient population.

METHODS

Study population and data source

A detailed description of the baseline population from which the GPRD data were generated has been described elsewhere (18, 19, 20). Briefly, the database is comprised of over 8 million residents in the UK enrolled by selected general practitioners who had agreed to enter patient data using computers provided by VAMP Medical irrespective of future research hypotheses. It is a longitudinal database that contains patient information on sex, age, weight, height, diagnoses, prescriptions, hospitalizations, and doctor visits. The general practices contributing information were chosen to ensure that they were representative of the UK both geographically and in the number of partners at each practice. The accuracy and completeness of these data have been validated (21, 22) and numerous epidemiological studies have been published using this database for determining the incidence of diseases (20).

Identification of patients treated with antipsychotics

The study population was comprised of adults 18 years of age or older as of 1994, who were registered in standard general practices, and were prescribed an antipsychotic between January 1, 1994 and December 31, 1999. The retrospective cohorts studied included a general patient population cohort, a conventional antipsychotic cohort, an atypical anitpsychotic cohort, and monotherapy antipsychotic cohorts. The general population cohort consisted of a random sample of subjects registered continuously between January 1, 1996 and December 31, 1997 who had received at least one prescription for any drug during this two-year period. The conventional antipsychotic cohort included patients who were started on one or more conventional antipsychotics regardless of disease indications between January 1, 1994 and December 31, 1999. Patients who had taken atypical antipsychotics during this period were excluded. Antipsychotics classified as conventional for these studies are chlorpromazine, fluphenazine, methotrimeprazine, pericyazine, perphenazine, pipothiazine, promazine, thioridazine, trifluoperazine, benperidol, droperidol, flupenthixol, haloperidol, loxapine, pimozide, and zuclopenthixol. Only patients who were continuously registered for the

two-year period prior to starting antipsychotics were included. This two-year prior period was used to determine the baseline incidence of diabetes for this cohort. The atypical antipsychotic cohort was comprised of patients whose atypical antipsychotic(s) were started after January 1, 1994 for any psychiatric indications. Antipsychotics classified as atypical for these studies are clozapine, olanzapine, quetiapine, amisulpride and risperidone. Conventional antipsychotics were the most commonly prescribed antipsychotics in the United Kingdom, and relatively small numbers of patients were prescribed atypical antipsychotics. Consequently, the number of patients who took atypical antipsychotics in the GPRD database was small. To maximize the number of patients eligible for the atypical antipsychotic cohort, the requirement for continuous registration for the two-year period prior to initiation of the atypical antipsychotics was waived. Patients who had taken conventional antipsychotics prior to commencement of atypical antipsychotics were eligible for this cohort. However, those who had taken conventional antipsychotic(s) concurrently with atypical antipsychotics were excluded.

Identification of patients with diabetes mellitus

Any patient who had a computer-recorded diagnosis of type1or type 2 diabetes mellitus (as defined by one or more of the Oxford Medical Information System diagnostic codes for diabetes mellitus) or who were prescribed any hypoglycemic agent(s) indicated for the treatment of diabetes was considered as having diabetes. For a given subject, the date when the diagnosis of diabetes was first made by physician, and the date when hypoglycemic drug(s) was prescribed for the first time were determined, and the earlier date of these two was regarded as the date for a new case of diabetes. In determining the incidence of diabetes during exposure to conventional antipsychotics, patients with a personal history of diabetes prior to the first prescription of antipsychotic(s) were excluded. New cases of diabetes that occurred during the antipsychotic prescription period plus 15 days of washout period were considered as treatment-emergent diabetes. The washout period was defined as the 15 day period that immediately followed the discontinuation of a given antipsychotic drug or class of drugs. Two prescriptions separated by less than 16 days were counted as one continuous prescription.

Methods of Analysis

The Knowledge Manager software (Real Enterprise Solutions, Massachusetts, USA) in conjunction with SAS programs were used for identifying subjects eligible for various cohorts and for identifying incident cases of diabetes.

The incidence of diabetes prior to exposure to conventional antipsychotics was calculated based on the number of new cases of diabetes in the two-year period prior to the initiation of these antipsychotics. The incidence of diabetes prior to exposure of atypical antipsychotics was not determined because 72% of these patients had taken conventional antipsychotics prior to atypical antipsychotics. 95% confidence intervals for these incidences were calculated based on a method described elsewhere (23). For determining incidence of diabetes during exposure and after discontinuation of antipsychotics throughout the evaluation period, patients were followed until December 31, 1999, or until they left the clinical practices they were registered at , whichever came first. The cumulative antipsychotic treatment duration of each patient was determined and used to calculate diabetes incidence per 1000 patient-years.

Cox proportional hazards regression was used to determine statistically significant ($p<0.05$) predictors of diabetes for consideration of their inclusion as covariates in the regression model, and for estimating the hazard ratios (risk ratios) of diabetes between various cohorts mentioned above. The PHREG procedure in SAS was used for fitting the proportional hazard models. The covariates for these models were age, and the presence or absence of obesity. Subjects were classified as obese by a physician's diagnosis of obesity or by a body mass index equal to or greater than 30 kg/m^2 (NIH criteria). The classification of obesity was determined during the four-year period prior to exposure to antipsychotics for the antipsychotic cohorts and between 1992 and 1995 for the general population cohort. The most recent body mass index or obesity diagnosis was used for each subject. 27.4% and 55.7% of patients had such information in the two-year period and four-year prior to antipsychotic exposure, respectively. The age categories 18-44, 45-64, and 65 or older (used as covariates in the regression model) showed a near doubling of incidence with each transition in age category) as determined in the 1990-92

National Health Insurance Survey in the United States (24). All three-age categories were included in the model used to determine the hazard ratio of the conventional antipsychotic cohort, the atypical antipsychotic cohort, and the general population cohort. For hazard ratio determination in the monotherapy cohort (comprised of patients who received a specific antipsychotic as monotherapy) only two age categories were included in the model, 65 or above, and 18-64.. The 18-44 age category was not included because the trifluoperazine cohort did not have new cases of diabetes in this age category. The possibility that an increased frequency of physician visits might increase the probability of uncovering diabetes was evaluated. Since the hazard ratio for this covariable was equal to 1.0, whether it was included as a continuous or categorical covariate, it was not included in the regression models in this study. Family history is an established risk factor for type 2 diabetes but examination of the GPRD database showed that this information was missing in the great majority of the patients. As less than 1% of patients had recorded family history of diabetes (OXMIS code F250A), family history was not included as a covariate in the regression model.

RESULTS

The characteristics of the general patient cohort, the conventional antipsychotic cohort and the atypical antipsychotic cohort are shown in Table 1. The percentages of subjects with information on body mass index were comparable between all cohorts. The average age of patients in the general population cohort was less than that of the antipsychotic cohorts. In particular, the percentage of subjects in the 65 years and older category of the general population cohort was smaller than that of the antipsychotic cohorts. The average and median durations of exposure to atypical antipsychotics were higher than that of conventional antipsychotics. The percentage of males in the atypical antipsychotic cohort was slightly higher than in the other cohorts.

Table 1. The Characteristics of Major Cohorts Studied

	General patient population	Conventional antipsychotic cohort	Atypical antipsychotic cohort
Total number of subjects	269,049	44,046	2,527
Average age, yr.	50.9	58.9	55.9
18-44 years of age	41%	32%	41%
45-64 years of age	33%	25%	19%
65 years of age and older	26%	43%	40%
Sex: male, %	42%	40%	49%
Presence of obesity*, %	13%	15%	16%
Average duration of exposure to antipsychotic(s) per person**	----	164 days	222 days

* Based on the number of subjects with body mass index greater than or equal to 30 kg/meter^2 or with a diagnosis of obesity during the four year-period prior to the commencement of antipsychotics.

** The cumulative days of exposure to a given antipsychotic were calculated for those with multiple treatment episodes.

Table 2. Proportional Hazard Analysis of Diabetes Mellitus for Covariates in the Cox Regression Model

Variable	Hazard Ratio	95% confidence interval	P value
Conventional Antipsychotic Cohort (N= 44,046)			
Presence of Obesity	3.0	1.8-4.9	0.0001
Age >=65 years	5.9	2.3-15.1	0.0002
Age 45-64 years	4.5	1.7-11.9	0.0022
Sex (male)	0.9	0.5-1.5	0.68
Atypical Antipsychotic Cohort (N= 2,527)			
Presence of Obesity	4.14	1.0-17	0.047
Age >=65 years	4.5	0.7-28	0.10
Age 45-64 years	4.05	0.7-23	0.12
Sex (male)	1.5	0.39-5.8	0.55
General Adult Patient Population (N= 269,049)			
Presence of Obesity	4.6	3.9-5.4	0.0001
Age >=65 years	3.6	2.9-4.5	0.0001
Age 45-64 years	2.4	1.9-3.0	0.0001
Sex (male)	1.7	1.4-2.0	0.0001

Separate Cox regression analyses were performed to evaluate potential risk factors of diabetes for each cohort. All the covariates used for the Cox regression model in the present study are shown in Table 2. Judging from the overlapping of the 95% confidence intervals between cohorts, the hazard ratios of diabetes for each of the various risk factors were comparable between the cohorts. Obesity is an established risk factor for type 2 diabetes, and was found to have an important effect on the emergence of diabetes in the present study. Like studies around most parts of the world (see Diabetes in America, 26),

the incidence of diabetes in all cohorts in the present study increased with age. Gender has a small but significant effect for the general population.

The incidences and the hazard ratios of diabetes for the various antipsychotic cohorts and for the general population cohort are shown in Table 3. The incidence in the general population cohort was 3.7 per 1000 patient-years (CI: 3.4-4.0), and this was lower than the incidence of diabetes during exposure to any of the antipsychotics evaluated. The incidence during exposure to conventional antipsychotics (7.6 per 1000 patient-years; CI: 6.3-8.8) was significantly higher than the incidence during the two-year period prior to exposure to (5.5 per 1000 patient-years; CI: 5.0-6.0), as well as the period after discontinuation of these drugs (4.0 per 1000 patient-years; CI: 3.5-4.5).

The incidence during exposure to atypical antipsychotics was 13.6 per 1000 patient-years, and was significantly higher than the period after these drugs were discontinued (1.6 per 1000 patient-years, CI: 0-4.0). In this case, the 95% confidence interval is inaccurate as only 2 new cases of diabetes were noted during the period after these drugs were discontinued. The incidence prior to exposure to atypical antipsychotics was not calculated as most subjects in this cohort (72%) had prior exposure to conventional antipsychotics. The incidences of diabetes during periods of exposure and non-exposure to conventional and atypical antipsychotics are shown in Figure 1.

The incidences and hazard ratios of the commonly prescribed antipsychotics in each class were determined (Table 3). The general population cohort in UK was the reference group used for calculating these hazard ratios. During the period 1994-1999, the most commonly prescribed conventional antipsychotics in UK in descending order (% subjects exposed in parenthesis) were thioridazine (44%), flupenthixol (22%), trifluoperazine (13%), haloperidol (14%), and chlorpromazine (12%). As compared to the general patient population cohort, patients in the conventional antipsychotic cohort had significantly higher risk of developing diabetes (hazard ratio = 1.3; CI= 1.003-1.8). Some patients had taken more than one antipsychotic. The hazard ratios of patients who received monotherapy of specific antipsychotics were determined. A significant hazard

ratio was noted only for the thioridazine cohort, the largest monotherapy cohort. Risperidone and olanzapine were the two most commonly prescribed atypical antipsychotics in the UK, representing 71% and 21% of the atypical antipsychotic cohort, respectively. Less than 120 patients received monotherapy of clozapine, quetiapine or amisulpride. The risk of diabetes in the atypical antipsychotic cohort was significantly higher than that of the general population cohort (HR=3.3; p value =0.0004), and that of the conventional antipsychotic cohort (HR= 2.6; p value= 0.008; data not shown in Table 3).

Table 3. Incidence and Hazard Ratio of Diabetes in Adult Patients while taking Antipsychotics

COHORT	No. of new cases	No. of patients	Mean exposure (days)	No. of patient-years	Incidence (per 1000 patient-years)		Hazard ratio*		
					Rate	95% CI	Ratio	95% CI	p-value
CONVENTIONAL ANTIPSYCHOTICS									
All antipsychotics combined	149	44,046	164	19,720	7.6	6.3-8.8	1.3	1.003-1.8	0.048
Thioridazine only	56	15,160	174	7172	7.8	5.7-9.9	1.5	1.009-2.3	0.045
Fluopenthixol only	13	8,0031	116	2538	5.1	2.3-8.0	0.86	0.4-2.0	0.86
Trifluoperazine only	12	3,887	158	1,675	7.2	3.0-11.3	1.2	0.5-3.0	0.66
Chlorpromazine only	5	334	127	1156	4.3	0.5-8.2	0.37	0.05-2.6	0.37
Haloperidol only	13	3609	108	1059	12.3	5.5-19.1	1.6	0.7-4.0	0.28
ATYPICAL ANTIPSYCHOTICS									
All antipsychotics combined	21	2527	222	1,549	13.6	7.6-19.5	3.3	1.7-6.5	0.0004
Risperidone only	16	1685	228	1,067	15.0	7.5-22.5	3.2	1.4-7.1	0.006
Olanzapine only	2	526	193	279	7.2	0-17.3	--***	--	--
GENERAL POPULATION	1,589	269,049	--	430,892	3.7**	3.4-4.0	1.0	--	--

* Reference group was the general patient population cohort. Three age categories were included as a covariate in the model for the "antipsychotic combined", but only two age categories for individual monotherapy cohorts.

** Incidence for the general population regardless of their exposure to antipsychotics

*** The number of cases of new onset diabetes during exposure to olanzapine was too small for a meaningful calculation of hazard ratio.

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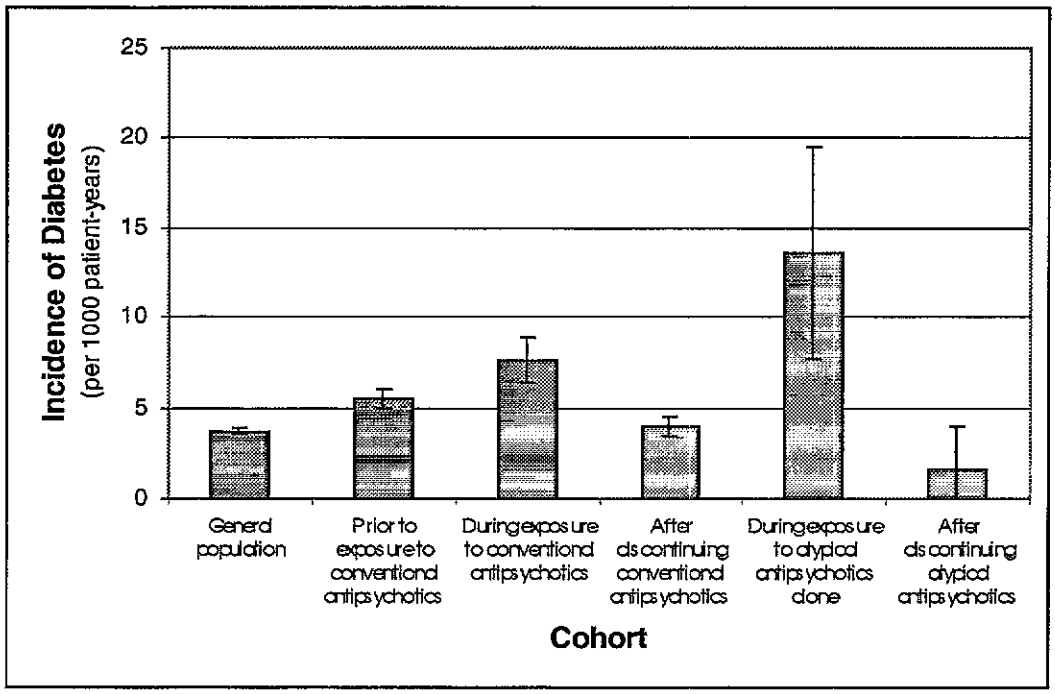
Figure 1. Incidence of Diabetes Mellitus in the United Kingdom (General Patient Population versus Antipsychotic Cohorts)



DISCUSSION

This study shows that patients treated with either conventional or atypical antipsychotics had a higher risk of developing diabetes during exposure to the drugs. This conclusion is supported not only by significantly higher hazard ratios for developing diabetes in these antipsychotic cohorts relative to the general patient population, but also by the significantly higher incidence during antipsychotic exposure than during the period prior to commencement or after discontinuation of these drugs. In the latter comparison, patients served as their own control for underlying risk factors for diabetes, such as obesity and age. Though a higher risk of diabetes was associated with treatment with either class of antipsychotics, it remains to be determined whether all antipsychotics increase glucose intolerance. Though the current study suggests a higher risk of developing diabetes for the atypical antipsychotics relative to the conventional antipsychotics, the comparison was limited by the predominance of patients who received risperidone in the atypical antipsychotic cohort (71%). Studies of other databases with a much larger number of patients who took atypical antipsychotics are needed to assess the potential of other atypical antipsychotics to induce glucose intolerance. Comparison of the activity of the two classes of antipsychotics in increasing glucose intolerance is of limited value as antipsychotics with each class may vary widely in such activity. Among the conventional monotherapy cohorts, only thioridazine (the largest monotherapy cohort) had a statistically significant hazard ratio. A sample size of about 11,900 is needed for a study with 80% power and 95% confidence level in detecting a significantly different hazard ratio of 1.5. Due to the modest risk associated with the use of conventional antipsychotics, the sample size of other cohorts were too small to discern risks of developing diabetes significantly different from that of the general patient population.

Findings from this study are consistent with a separate epidemiology study that we have conducted with patients in the United States using the AdvancePCS Inc.'s prescription claim database. This US study, with a conventional antipsychotic cohort of 19,782 patients, and a much more robust atypical antipsychotic monotherapy cohort (38,969

patients), confirms that treatment with either conventional or atypical antipsychotics were associated with higher risks of developing diabetes.

A number of strengths in the present study are noteworthy. First, only monotherapy antipsychotic cohorts were evaluated. This avoids confounding of risk assessment by concomitant antipsychotic. If such concomitants were included in our cohorts, the results would have been confounded when there were imbalance in frequency of use of such agents between cohorts. Second, it is uncommon for subjects in the GPRD longitudinal database to have more than 5 or even 10 years of record before the evaluation period used for identifying new onset of diabetes during antipsychotic treatment. This enabled us to check the record of many patients for several years prior to the commencement of antipsychotics for excluding pre-existing diagnosis of diabetes or treatment with diabetes medications. However, the present study has the following limitations. First, the number of patients who received atypical antipsychotics was relatively small. Thus, the small number of new cases of diabetes and the number of patients who took antipsychotics other than risperidone were too small for accurate determination of the risks of diabetes associated with those drugs. Second, unlike the conventional cohort that was comprised of antipsychotic naive patients, the atypical cohort consisted mainly of patients who had prior exposure to conventional antipsychotics. If both classes of antipsychotics induced diabetes by the same mechanism, the selection of subjects for the atypical antipsychotic cohort may have enriched this cohort with subjects with relative resistance to developing diabetes, since patients who had developed diabetes while taking conventional antipsychotics were excluded. Third, paucity of information on the family history of diabetes in this database precluded a meaningful inclusion of this variable in our Cox regression model. Fourth, the diagnosis of diabetes in this retrospective study was ascertained by a physician's diagnosis or by a recorded use of a glucose-lowering drug in the database. Without the primary clinical data, an unqualified diagnosis of diabetes is uncertain. However, it is reasonable to assume that a patient diagnosed with diabetes or is receiving a glucose-lowering drug has a high likelihood of having diabetes.

While it appears that antipsychotic drugs differ in their activity in increasing the risk of developing diabetes, the mechanism is unclear. Potential mechanisms for antipsychotics in increasing glucose intolerance include a reduction in the production or secretion of insulin, or by an increase in insulin resistance. Though treatment of antipsychotic drugs are associated with weight gain, but the relationship between weight gain and subsequent development of diabetes during specific drug use cannot be determined from the present study as the weight of relatively small percentage of subjects were recorded during antipsychotic exposure. In addition, correlating the weight gain potentials of various antipsychotics from other studies to their potentials in inducing diabetes in this study was not feasible as only the hazard ratios of thioridazine and risperidol antipsychotic cohorts were statistically significant.

Patients with psychiatric disorders present unique challenges in determining the potential of antipsychotics to alter glucose metabolism. For example, obtaining fasting glucose levels is quite difficult due to reduced compliance with fasting. While serial glucose tolerance tests would be valuable in assessing a particular drug's ability to alter glucose metabolism, such studies are also potentially difficult due to the nature of the underlying psychiatric illness. Further, patients with psychotic disorders often favor high carbohydrate diets, further compromising the ability to accurately determine glucose homeostasis.

In conclusion, the present study suggests a higher risk of developing diabetes associated with both conventional and atypical antipsychotic drugs. The sample sizes of thioridazine and risperidone cohorts were sufficiently large to discern a statistically significant increase in the risk for diabetes relative to the general patient population cohort in UK. Though the sample size of other monotherapy cohorts were not adequately powered to discern a significant treatment effect, the 95% confidence interval of their hazard ratios provide an estimation of diabetes risk associated with these agents. Further epidemiological studies utilizing databases with larger number of subjects who were treated with atypical antipsychotic are needed.

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