Agomelatine and Risk of Hospitalization for Acute Liver Injury: Nested Case-Control Study in Spain, Germany, and Denmark

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CONFLICTS OF INTEREST

MP, JF, MCA, JA, JC (Castellsague), and SPG are full-time employees of RTI Health Solutions (RTI-HS), an independent, not-for-profit research organization that does work for government agencies and pharmaceutical companies. As coordinating center, RTI-HS received funding covering all research partners from Servier to conduct this study. The contract between RTI-HS and the sponsor includes independent publication rights.

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ND and EJ are employees of Servier.

BACKGROUND

- Agomelatine is a melatonergic agonist and 5-HT_{2C} antagonist indicated for major depressive episodes in adults.
- Hepatotoxicity is an identified risk in the European risk management plan for agomelatine and drives this postauthorization safety study.
- Results from the interim analysis are presented.

OBJECTIVE

- To evaluate the risk of acute liver injury (ALI) hospitalization associated with the use of agomelatine and other selected antidepressant drugs.

METHODS

Study Design and Data Sources

- Multinational, multidata-source, nested case-control study of new users of agomelatine and other selected antidepressants.
- Population-based data sources: SIDIAP (Catalonia, Spain), EpiChron (Aragon, Spain), GePaRD (Germany), and the Danish national registers.
- Study period started after agomelatine launch (in 2009 or 2010) and ended with the last year with available data (2013 or 2014).

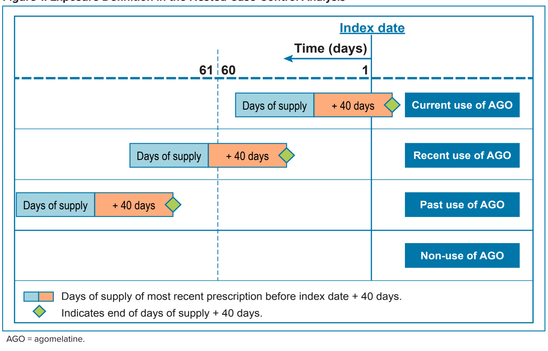
Study Population

- Inclusion criteria: 12-month continued enrollment and new use of:
  - Agomelatine (main exposure of interest)
  - Citalopram (common comparator)
  - Fluoxetine, paroxetine, sertraline, escitalopram, mirtazapine, venlafaxine, duloxetine, or amitriptyline
- Exclusion criteria:
  - < 18 years of age
  - Pregnancy at the start date of the first cohort entry
  - History of liver disease or risk factors for liver disease (e.g., alcohol use disorder, infectious hepatitis, chronic liver conditions, and cancer)

Definition of Cases and Controls

- ALI hospitalization was ascertained according to specific hospital discharge diagnoses codes (ICD-9 or ICD-10).
- All cases identified in the study cohort were included in the nested case-control study.
- Up to 20 controls were selected from the study cohort using density samppling and were matched to cases on age, calendar year of start date, and sex.
- Time at risk was categorized for each patient and each antidepressant into four mutually exclusive categories of exposure according to the days of supply for the most recent prescription fill received on or before the index date (see Figure 1).

Figure 1. Exposure Definition in the Nested Case-Control Analysis



AGO = agomelatine.

Statistical Analyses

- Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of ALI for each study antidepressant's current use were estimated via conditional logistic regression models using citalopram current use as the reference and using a prespecified list of confounders and backward selection based on the change in estimate.
- Meta-analytic techniques were used to combine the OR estimates from all data sources.

RESULTS

Study Population

- The cohort attrition results in each data source are presented in Table 1.

Table 1. Patients Included in the Study

	EpiChron	SIDIAP	GePaRD	Denmark
	N (% of All Users)	N (% of All Users)	N (% of All Users)	N (% of All Users)
Citalopram	9,089 (47.1%)	41,295 (59.4%)	229,895 (36.6%)	200,378 (56.3%)
Agomelatine	8,881 (83.0%)	3,243 (69.2%)	30,155 (43.0%)	18,044 (81.5%)
Fluoxetine	15,423 (56.3%)	19,235 (53.0%)	38,162 (34.5%)	15,651 (49.5%)
Paroxetine	23,659 (54.0%)	31,392 (53.8%)	27,599 (33.6%)	15,603 (48.3%)
Sertraline	11,173 (50.4%)	21,148 (56.6%)	43,461 (34.2%)	114,511 (68.2%)
Escitalopram	46,429 (62.2%)	23,107 (53.8%)	39,287 (36.7%)	44,864 (45.2%)
Mirtazapine	19,687 (56.4%)	14,161 (54.7%)	160,771 (34.0%)	124,736 (60.7%)
Venlafaxine	10,636 (46.8%)	11,840 (47.4%)	74,850 (35.7%)	71,754 (61.4%)
Duloxetine	21,025 (65.1%)	10,368 (53.8%)	32,357 (30.5%)	30,241 (61.1%)
Amitriptyline	20,830 (65.5%)	27,312 (64.2%)	140,535 (34.1%)	30,078 (65.0%)
Total	**186,832 (58.4%)**	**203,101 (56.1%)**	**817,072 (35.1%)**	**665,860 (59.1%)**

Main Results

- As shown in Figure 2, the number of cases exposed to agomelatine was very low: only 1 case in EpiChron, 1 case in GePaRD, fewer than 5 cases[1] in Denmark, and no cases in SIDIAP. Citalopram was the study antidepressant with the most cases, ranging from 2 in EpiChron to 57 in Denmark.
- In the multivariable-adjusted models, the OR of ALI hospitalization for current use of agomelatine compared with current use of citalopram was below 1 in all data sources, and all CIs were wide and included the null value.
- The combined OR of ALI hospitalization for current users of agomelatine compared with current users of citalopram was 0.39 (95% CI, 0.11-1.39).
- Sertraline and duloxetine also showed ORs of 1 or below in all data sources. For the rest of the antidepressants included in the study, the point estimates did not show any consistent pattern being either below or above the null value.
- Adjusted combined ORs for other antidepressants ranged from 0.72 among current users of escitalopram to 1.92 among current users of paroxetine. All 95% CIs were wide.

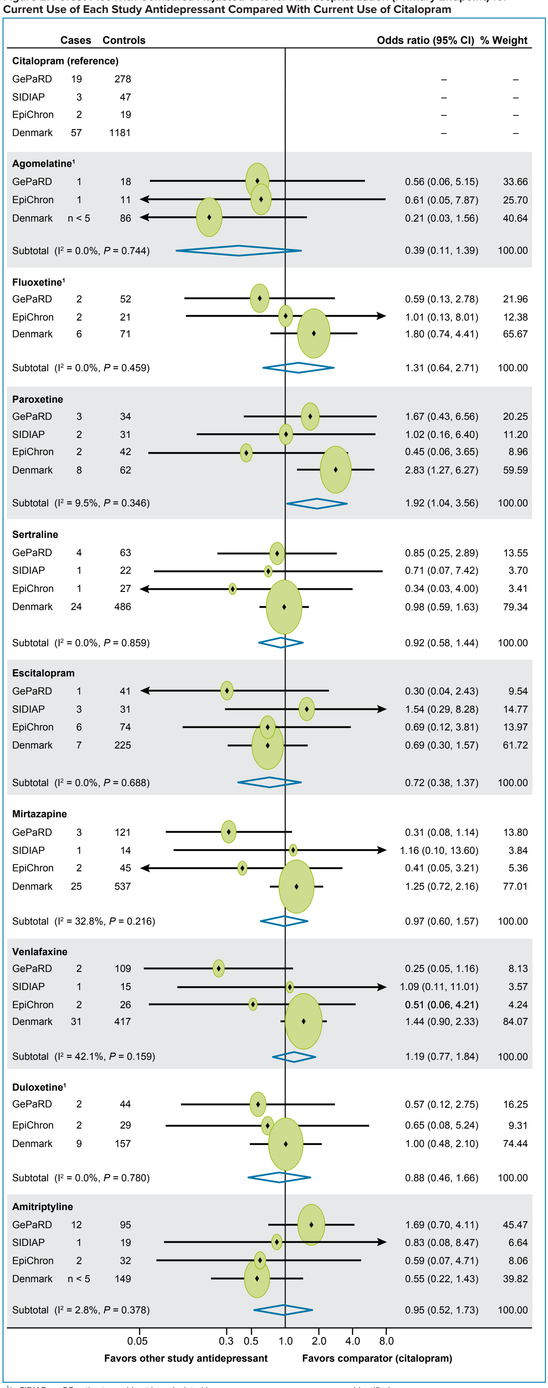
[1] Because of data protection laws in Denmark, the precise number of cases cannot be provided when the number is below 5.

DISCUSSION

Strengths

- Large cohort of more than 1.8 million new users of antidepressants, including more than 60,000 new users of agomelatine.
- The use of a new user design and restriction to patients without a history of liver disease or risk factors for liver disease to control for confounding.
- The use of four data sources from three different countries allowed evaluation of the research question in data sources with different health care systems and types of clinical information available.

Figure 2. Forest Plot With Combined Adjusted ORs for ALI Hospitalization (Primary Endpoint) for Current Use of Each Study Antidepressant Compared With Current Use of Citalopram



[1]In SIDIAP, an OR estimate could not be calculated because no cases among users were identified.

The size of the circle represents the weight of each data source to the combined OR point estimate.

In GePaRD and Denmark, estimates were adjusted for the following confounding factors: Charlson Comorbidity Index score, concurrent use of hepatotoxic drugs, concurrent use of other antidepressants, diabetes, history of peptic ulcer disease, hyperlipidemia and hypertriglyceridemia, hypertension, indication for anxiety disorders, indication for major depression, indication for other mental and behavioural disorders, number of hospitalizations, number of liver tests performed, number of outpatient visits, , and obesity or overweight. In Denmark, estimates were additionally adjusted for acute biliary and pancreatic disease, acute alcohol intoxication, history of rheumatic disease, time since first antidepressant, number of emergency department visits, and number of different antidepressants used at any time before the index date.

In SIDIAP and EpiChron, due to data sparsity, estimates were adjusted only for Charlson Comorbidity Index score.

Limitations

- Potential sources of misclassification that were likely to result in nondifferential misclassification, potentially biasing the estimates toward the null.
- The codes selected to identify ALI hospitalization had the highest positive predictive values according to previous validation studies. However, the positive predictive values varied largely according to the codes and the study and were frequently lower than 60%.
- The type and completeness of the recorded information for variables collected to adjust for potential confounding.
- Low number of cases and imprecise estimates due to use of restriction and low incidence of ALI.

CONCLUSIONS

- Based on 60,323 patients with newly prescribed agomelatine, this analysis suggests that current use of agomelatine is not associated with higher risk of ALI hospitalization compared with current use of citalopram in any of the four populations in Spain, Germany, and Denmark.
- Although 1,872,865 new users of antidepressants were evaluated across the four data sources, the precision of the risk estimates was low because of the low number of events in all study antidepressant cohorts.
- Ongoing study analyses, which will include Sweden, additional endpoints (e.g., including outpatient cases), and validated cases in Spain and Denmark, will provide more insight into the research question.

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