Agomelatine and Other Antidepressants and the Risk of Acute Liver Injury, a Post-Authorisation Safety Study in 4 European Countries

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BACKGROUND

- Agomelatine is a melatonergic agonist and 5-HT2C antagonist indicated for major depressive episodes in adults.
- Hepatotoxicity, including acute liver injury (ALI), is an identified risk in the risk management plan for agomelatine, and hepatotoxic reactions have been observed with other antidepressants; however, population-based studies quantifying this risk are scarce.

OBJECTIVE

- To evaluate the risk of ALI associated with the use of agomelatine and other selected antidepressant drugs.

METHODS

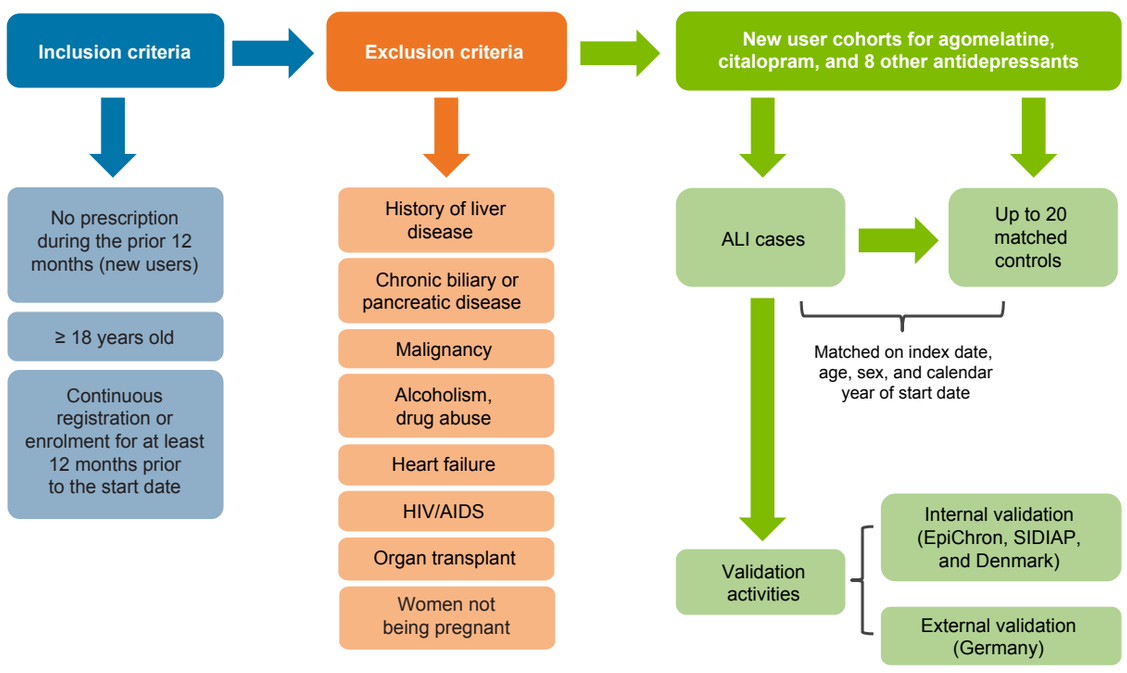
Study Design and Data Sources

- Multinational, multiple–data source, nested case-control study of new users of agomelatine and other selected antidepressants
- Population-based data sources: EpiChron (Aragon, Spain), SIDIAP (Catalonia, Spain), GePaRD (Germany), and Danish and Swedish national registers

Study Population

- The selection of cases and controls is described in Figure 1.

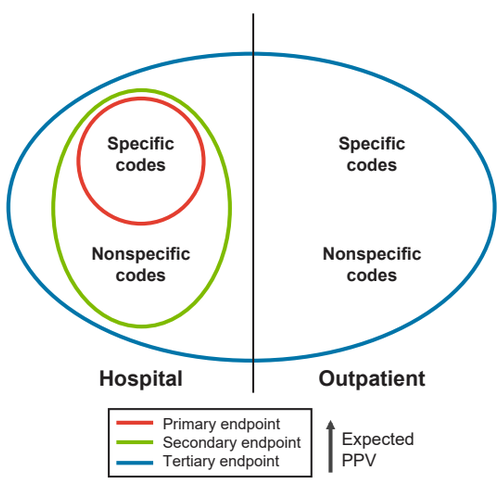
Figure 1. Selection of Cases and Controls



Definition of ALI

- Three ALI endpoints were defined (see Figure 2).

Figure 2. Definition of the Three Study Endpoints



Secondary and tertiary endpoints were validated in Denmark and Spain. In Germany, PPVs of the primary and tertiary endpoints were estimated (external validation).

Code	Description
Specific codes	
ICD-9-CM	
570.x	Acute and subacute necrosis of liver
572.2	Hepatic coma
573.3	Hepatitis unspecified
ICD-10-CM	
K71.0	Toxic liver disease with cholestasis
K71.1	Toxic liver disease with hepatic necrosis
K71.2	Toxic liver disease with acute hepatitis
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K71.9	Toxic liver disease, unspecified
K72.0	Acute and subacute hepatic failure
K72.9	Hepatic failure, unspecified
K75.9	Inflammatory liver disease, unspecified
K76.2	Central hemorrhagic necrosis of liver
Nonspecific codes	
ICD-9-CM	
573.8	Other specified disorders of liver
573.9	Unspecified disorders of liver
782.4	Jaundice, unspecified, not of newborn
V42.7	Liver transplant
790.4	Nonspecific elevation of transaminase or lactic acid dehydrogenase
789.1	Hepatomegaly
ICD-10-CM	
K76.8	Other specified diseases of liver
K76.9	Liver disease, unspecified
R17	Unspecified jaundice, excludes neonatal
R16.0	Hepatomegaly, not elsewhere classified
R16.2	Hepatomegaly with splenomegaly, not elsewhere classified
R74.0	Nonspecific elevation of transaminase and lactic acid dehydrogenase
Z94.4	Liver transplant

PPV = positive predictive value.

Statistical Analyses

- Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of ALI for current use of each study antidepressant compared with current use of citalopram were estimated via conditional logistic regression models that used a prespecified list of confounders, and other potential confounders were added after a backward selection process.
- Meta-analytic methods were employed to obtain the pooled adjusted ORs (random models were used when heterogeneity was present, i.e., $I^2 \geq 30\%$).
- Several preplanned sensitivity analyses (SAs) were done to check the robustness of results, and 2 post hoc SAs (requested by the European Medicines Agency), one applying no liver-related exclusion criteria and one with all exclusion criteria but alcohol and drug abuse, were implemented to check the robustness of the results.

CONFLICTS OF INTEREST

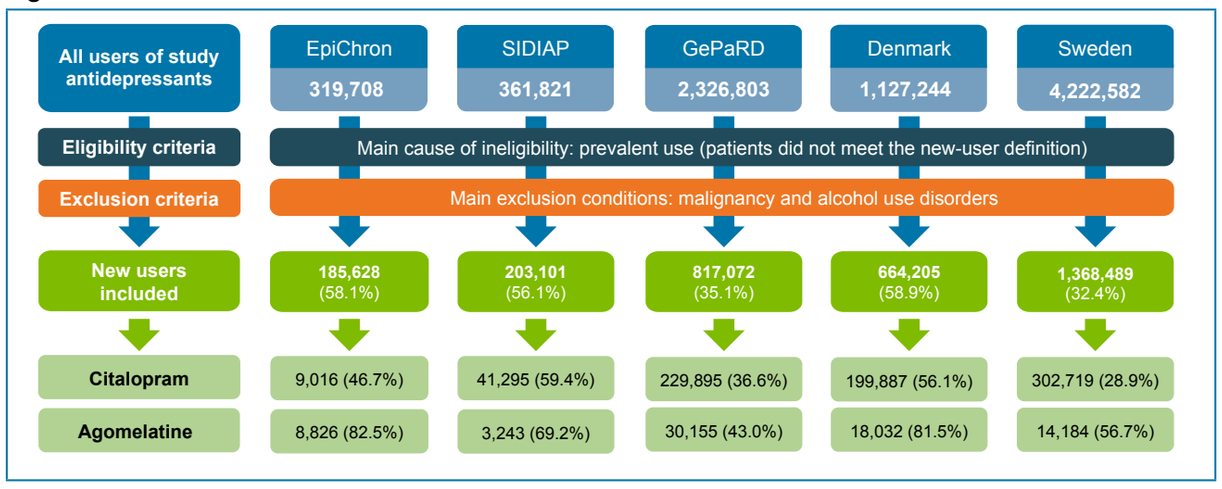
The study was funded by Servier under a contract with RTI Health Solutions that grants the research team independent publication rights. MP, JF, MCA, JA, JC, and SPG are employees of RTI Health Solutions. AP, TS, JR, RM, BPP, AT, MH, TR, DH, MGS, APT, JH, BK, LB, JC, BF, and GP worked on other projects funded by pharmaceutical companies in their institutions that were not related to this study and were without personal profit. GP reports participation in research projects funded by pharmaceutical companies. GP also received royalties and reports travel and participation in meetings funded by pharmaceutical companies. ND and EJ are employees of Servier.

RESULTS

Study Population

- There were 3,238,495 new users of study antidepressants (74,440 new users of agomelatine).
- The cohort attrition process in each data source is presented in Figure 3.

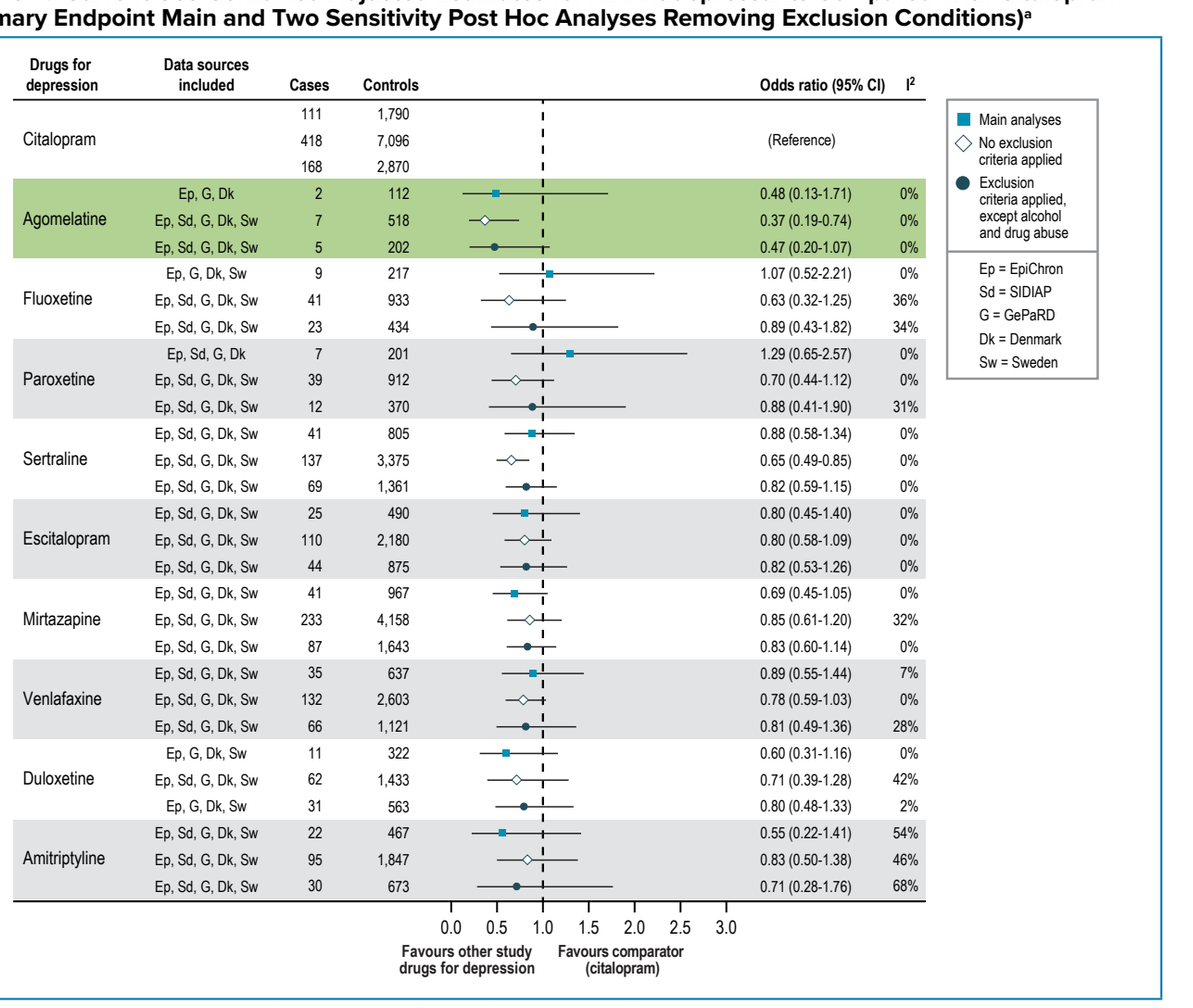
Figure 3. Cohort Attrition



Main Results

- The main results for agomelatine and the other antidepressants for the primary endpoint are presented in Figure 4. A total of 472 cases for the primary endpoint was identified. PPVs for the primary endpoint ranged from 60% to 84%.
- A total of 178 cases (confirmed by validation) for the secondary endpoint and 17,118 cases for the tertiary endpoint was identified. Agomelatine results for the secondary (OR, 0.40; CI, 0.05-3.11) and tertiary endpoints (OR, 0.79; CI, 0.50-1.25) were similar to the results of the primary endpoint. PPVs for the tertiary endpoint ranged from 8% to 47%.
- For the other study antidepressants that were compared with citalopram, most OR point estimates were also below 1.00 except for the tertiary endpoint, for which paroxetine and venlafaxine showed an increased risk of ALI.
- Results of the planned SAs for agomelatine and the other antidepressants were, in general, consistent with the main analysis and produced combined OR point estimates for agomelatine below 1.00 for current use.

Figure 4. Current Use Combined Adjusted Estimates for All Antidepressants Compared With Citalopram (Primary Endpoint Main and Two Sensitivity Post Hoc Analyses Removing Exclusion Conditions)[a]



[a] OR estimates were adjusted for confounding factors. The list of confounders differed by data source and type of analysis (main vs. sensitive analyses). The following confounders were included in most analyses: obesity, hyperlipidaemia and hypertriglyceridaemia, diabetes, hypertension, indication of treatment with drugs for depression for major depression, indication of treatment with drugs for depression for anxiety disorders, indication of treatment with drugs for depression for other mental and behavioural disorders, Charlson Comorbidity Index, number of liver tests performed, concurrent use of hepatotoxic drugs, and concurrent use of other drugs for depression.

DISCUSSION

Strengths

- Large, multinational, and multiple–data source study including nine different antidepressants compared with citalopram
- Validation activities
- Three different endpoints with different incidences of ALI and different PPVs

Limitations

- Low ALI incidence and low precision in the main analyses of risk estimates and PPVs
- Despite the pharmacoepidemiological methods used to minimize its presence, bias as a result of potential misclassification of exposures or endpoints, and of residual confounding, is still possible.

CONCLUSIONS

- The results of this study do not suggest that the risk of ALI with the use of agomelatine constitutes a public health problem, at least among patient populations in health care systems with prescription patterns and risk-minimisation measures similar to those in this study.
- When compared with citalopram, most antidepressants evaluated had OR point estimates for ALI below 1.00. However, specific studies to investigate this potential association of citalopram with ALI would be needed.

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