ANTIDEPRESSANTS AND HEPATOTOXICITY: A COHORT STUDY AMONG 5 MILLION INDIVIDUALS REGISTERED IN THE FRENCH NATIONAL HEALTH INSURANCE DATABASES

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BACKGROUND

Hepatotoxicity may be a concern when prescribing antidepressants.[1] Drug-induced liver injuries are rare and generally emerge once the drug is widely available.[2-3] They are usually unpredictable, without a clear dose relationship and generally appear between several days and 6 months after the drug initiation.[1]

Nevertheless, this risk remains poorly quantified for Serotonin and Noradrenaline Reuptake Inhibitors, SNRIs (venlafaxine, milnacipran and duloxetine) and "other antidepressants" (mianserin, mirtazapine, tianeptine and agomelatine), particularly in comparison with Selective Serotonin Reuptake Inhibitors, SSRIs, which are by far the most commonly prescribed antidepressants.

OBJECTIVE

To quantify the short-term risk of serious liver injury associated with new use of SNRIs and "other antidepressants" compared to SSRIs, in real-life practice.

METHODS

Design, setting

- A cohort study was conducted using the French national health insurance databases (Système National d'Information Inter-Régimes de l'Assurance Maladie, SNIIRAM and Programme de Médicalisation des Systèmes d'Information, PMSI) covering almost the entire French population (65.3 million inhabitants), from January 1, 2010 to December 31, 2015.
- Beneficiaries of the general scheme (approximately 77% of the French population), aged >24 years, with a first reimbursement of SSRIs, SNRIs, or "other antidepressants" between January 2010 and June 2015 and without history of cancer, human immunodeficiency virus infection, hepatic injury or alcohol use disorders were included and followed up to 6 months.

Exposure & Outcome definition

- Initiators of venlafaxine, milnacipran, duloxetine, mianserin, mirtazapine, tianeptine and agomelatine were compared to initiators of SSRIs regarding the risk of occurrence of serious liver injury resulting in hospitalization within the 6 months following antidepressant initiation.
- Serious liver injuries were identified using initial diagnosis of hospital stays recorded in the PMSI (validated ICD-10 codes K71.0, K71.1, K71.2, K71.6, K71.8, K71.9, K72.0, K75.2, K75.9, K76.2, K76.7, Z94.4).

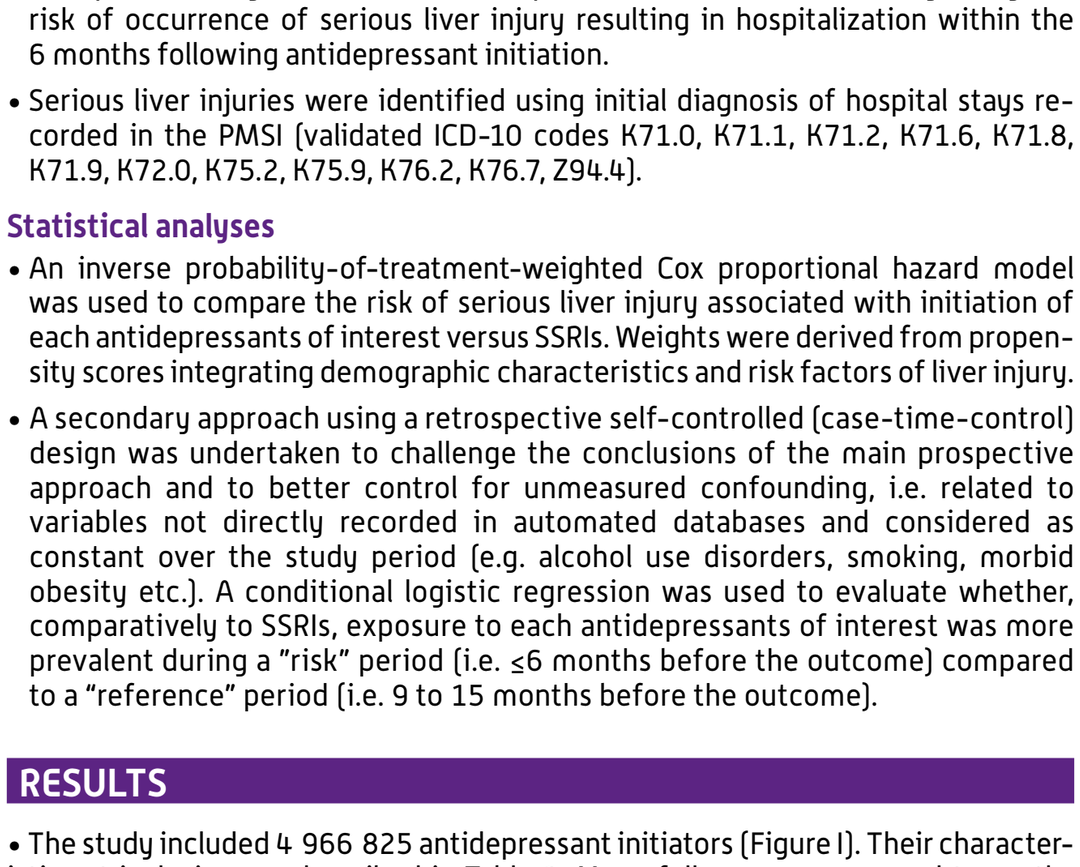
Statistical analyses

- An inverse probability-of-treatment-weighted Cox proportional hazard model was used to compare the risk of serious liver injury associated with initiation of each antidepressants of interest versus SSRIs. Weights were derived from propensity scores integrating demographic characteristics and risk factors of liver injury.
- A secondary approach using a retrospective self-controlled (case-time-control) design was undertaken to challenge the conclusions of the main prospective approach and to better control for unmeasured confounding, i.e. related to variables not directly recorded in automated databases and considered as constant over the study period (e.g. alcohol use disorders, smoking, morbid obesity etc.). A conditional logistic regression was used to evaluate whether, comparatively to SSRIs, exposure to each antidepressants of interest was more prevalent during a "risk" period (i.e. ≤6 months before the outcome) compared to a "reference" period (i.e. 9 to 15 months before the outcome).

RESULTS

- The study included 4 966 825 antidepressant initiators (Figure I). Their characteristics at inclusion are described in Table 1. Mean follow-up was around 4 months and for 40% to 50% of initiators, only one reimbursement of antidepressant was retrieved during the follow-up.

Figure I: Diagram of inclusion



Abbreviations: HIV, human immunodeficiency virus; SSRI, selective serotonin reuptake inhibitors.
a. No prescription of antidepressant in the previous 6 months.
b. 1 072 879 individuals with change in health plan, 351 139 twins and 440 individuals with cancelled antidepressant prescription were not included in the study population.

TABLE 1. Main characteristics of antidepressant initiators at inclusion

	SSRIs	Venlafaxine	Milnacipran	Duloxetine	Mianserin	Mirtazapine	Tianeptine	Agomelatine
	n = 3 543 559	n = 436 155	n = 37 577	n = 247 250	n = 293 484	n = 128 593	n = 181 289	n = 98 918
Mean age (sd), years	51 (17)	50 (16)	51 (16)	53 (16)	62 (20)	59 (20)	59 (19)	49 (15)
Women, n (%)	2 433 101 (69)	294 671 (68)	27 306 (73)	167 668 (68)	197 485 (67)	80 810 (63)	128 499 (71)	66 761 (68)
Complementary universal health insurance, n (%)	283 099 (8)	35 111 (8)	3 511 (9)	23 390 (10)	21 818 (7)	13 920 (11)	13 163 (7)	10 828 (11)
Prescriber, n (%)								
General practitioner	2 929 581 (83)	350 920 (81)	25 003 (67)	176 656 (71)	225 490 (77)	81 761 (64)	154 469 (85)	67 894 (69)
Hospital practitioner	293 607 (8)	42 361 (10)	5 469 (15)	37 733 (15)	45 371 (16)	32 590 (25)	12 938 (7)	13 814 (14)
Private practice psychiatrist	219 627 (6)	30 058 (7)	3 765 (10)	13 659 (6)	12 236 (4)	10 810 (8)	8 249 (5)	14 988 (15)
Clinical characteristics, n (%)								
Psychiatric history[a]	1 490 307 (42)	200 642 (46)	19 170 (51)	111 575 (45)	156 919 (54)	73 257 (57)	86 237 (48)	52 186 (53)
Diabetes[a]	232 970 (7)	26 231 (6)	2 540 (7)	33 808 (14)	32 364 (11)	12 712 (10)	18 112 (10)	5 741 (6)
Heart failure[a]	48 122 (1)	4 705 (1)	394 (1)	3 299 (1)	12 070 (4)	4 924 (4)	5 570 (3)	675 (1)
Chronic renal failure[a]	26 204 (1)	2 588 (1)	209 (1)	2 102 (1)	6 786 (2)	2 934 (2)	2 522 (1)	432 (0)
Measurable history of smoking[b]	285 243 (8)	35 522 (8)	3 279 (9)	23 259 (9)	24 838 (9)	12 048 (9)	15 148 (8)	8 597 (9)
Morbid obesity[a]	49 472 (1)	5 898 (1)	648 (2)	6 950 (3)	5 398 (2)	2 331 (2)	2 944 (2)	1 471 (2)
Measurable history of substance abuse[b]	23 554 (1)	3 613 (1)	303 (1)	1 527 (1)	3 461 (1)	2 736 (2)	912 (1)	1 080 (1)
Hepatotoxic drugs use[c]	1 454 984 (41)	172 691 (40)	17 281 (46)	129 046 (52)	141 553 (48)	57 982 (45)	86 439 (48)	41 382 (42)

Abbreviations: SSRIs, selective serotonin reuptake inhibitors.
[a] Measured up to one year before inclusion. [b] Measured up to 36 months before inclusion. [c] Measured up to 6 months before inclusion.

- 382 serious liver injuries were identified and occurred within a mean delay of 2 months after treatment initiation. No event was identified for milnacipran. Initiation of antidepressants of interest was not associated with an increased risk of serious liver injury when compared to SSRIs (Table 2).
- In the secondary approach using a case-time-control design the conclusions remained unchanged (Table 3).

TABLE 2. Risk of hospitalization due to serious liver injury in initiators of antidepressants of interest versus SSRIs in the cohort study (main approach)

Antidepressant	Initiators n = 4 966 825	Events n = 382	Event incidence (per 100 000 person-years)[a]	Hazard Ratios (95% CI)	
				Crude	Adjusted[b,c]
SSRIs	3 543 559	258	19	1.00 [Reference]	1.00 [Reference]
Venlafaxine	436 155	36	22	1.15 (0.81-1.63)	1.17 (0.83-1.64)
Milnacipran	37 577	0	0	-	-
Duloxetine	247 250	12	13	0.70 (0.39-1.24)	0.54 (0.28-1.02)
Mianserin	293 484	29	22	1.43 (0.97-2.10)	0.90 (0.58-1.41)
Mirtazapine	128 593	15	33	1.65 (0.98-2.77)	1.17 (0.67-2.02)
Tianeptine	181 289	24	32	1.93 (1.27-2.94)	1.35 (0.82-2.23)
Agomelatine	98 918	8	25	1.18 (0.58-2.38)	1.07 (0.51-2.23)

Abbreviations: SSRIs, selective serotonin reuptake inhibitors.
[a] Standardized on gender and age categories (<50 or ≥50 years), SSRI initiators served as the reference group.
[b] Inverse probability of treatment weighting considering the following covariates: inclusion year, gender, age, deprivation index and complementary universal health insurance at inclusion; diabetes, heart failure, chronic renal failure, measurable history of smoking, morbid obesity and measurable history of substance abuse up to 12 to 36 months before inclusion; aminotransferase testing at inclusion ±1 month.
[c] Additional adjustment on age categories, prescriber specialty at inclusion; psychiatric history in the 12 months before inclusion; hepatotoxic drugs, other antidepressants and aminotransferase testing reimbursed during the follow-up.

TABLE 3. Risk of hospitalization due to serious liver injury in initiators of antidepressants of interest versus SSRIs in each case-time-control study performed by antidepressant of interest (second approach)

Antidepressant of interest in each case-time-control study[a]	Cases		Odds ratio (95% CI)	
	Reference period (n =)[b]	Risk period (n =)[b]	Crude	Adjusted[c]
Venlafaxine	21	28	1.00 (0.56-1.81)	0.94 (0.51-1.72)
Milnacipran	5	2	0.43 (0.08-2.36)	0.86 (0.12-5.98)
Duloxetine	13	18	1.09 (0.52-2.30)	1.15 (0.53-2.53)
Mianserin	16	21	1.07 (0.54-2.11)	0.91 (0.42-1.97)
Mirtazapine	11	13	0.93 (0.40-2.18)	1.13 (0.43-3.00)
Tianeptine	17	7	0.94 (0.37-2.36)	1.06 (0.40-2.82)
Agomelatine	5	4	0.69 (0.18-2.69)	0.87 (0.12-6.34)

Abbreviations: SSRIs, selective serotonin reuptake inhibitors.
[a] Eligible profiles in each case-time-control study performed by antidepressant of interest: users of antidepressant of interest without SSRIs in one of the two periods, i.e. risk of reference and of SSRIs without antidepressant of interest in the other period.
[b] Number of individuals with the following conditions: (i) at least one prescription of the antidepressant of interest and no prescription of SSRIs during the period considered (risk of reference) (ii) at least one prescription of SSRIs and no prescription of the antidepressant of interest during the other period.
[c] Adjusted for variations in hepatotoxic drug and other antidepressant reimbursement between the reference and the risk periods.

CONCLUSION

To our knowledge the present study is the first observational study having compared hepatotoxicity of antidepressants both in real life and on the basis of such a large and nationwide representative sample. Its sample size warranted identifying rare outcomes such as serious, including fatal, drug-induced liver injuries.

This cohort study conducted on almost 5 million antidepressant initiators did not provide arguments in favour of an increased risk of serious liver injury associated to SNRIs (venlafaxine, milnacipran and duloxetine) or "other antidepressants" (mianserin, mirtazapine, tianeptine and agomelatine) when compared to SSRIs.

In real-life practice, hepatotoxicity of antidepressants proposed as first line does not seem markedly differing across products.

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