ORIGINAL ARTICLE

Adverse effects of gender-affirming hormonal therapy in transgender persons: Assessing reports in the French pharmacovigilance database

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Abstract

Limited data are available on adverse drug reactions (ADRs) of gender-affirming hormone therapy (HT), mainly due to the lack of population-based studies with adequate controls, thus making spontaneous reporting systems a valuable tool to detect potential side reactions. In this nationwide retrospective study, we aimed to analyze ADRs related to gender-affirming HT reported in the French pharmacovigilance database (FPVD). We requested all the individual case safety reports related to gender-affirming HT recorded in the FPVD before May 27, 2020. We excluded previously published cases and those where gender-affirming HT was not the suspected drug. A total of 28 reports of ADRs were identified. Six concerned transgender men (21–40 years) and 22 transgender women (22–68 years). In transgender men taking testosterone enanthate, all reported ADRs were cardiovascular events, with pulmonary embolism in 50% of cases. Median time to onset (TTO) was 34 months. In transgender women, antiandrogens, mainly cyproterone acetate, were involved in 68% of cases, and estrogens in 77% of cases, mostly in association with progestin or cyproterone acetate. Meningiomas were the principal ADRs, followed by cardiovascular events, with a median TTO of 5.3 months. Our data show a previously unreported, non-negligible proportion of cases indicating cardiovascular ADRs in transgender men younger than 40 years. In transgender women, cardiovascular events were the second most frequent ADR. Further research is necessary to identify risk factors that might help to the individualization of treatment strategies. There is a necessity to increase awareness, implement preventive and education measures.

KEYWORDS
adverse drug reactions, pharmacovigilance, sex steroid hormones, transgender persons

1 | INTRODUCTION

Transgender and gender nonconforming people ("transgender", "trans", "gender nonbinary", "gender incongruent") hold gender identities that do not align

with the genders commonly assumed for their sex assigned at birth. Gender nonbinary people identify with genders that are neither man nor woman: their gender identity does not sit comfortably with "man" or "woman" or they feel that their gender identity involves being both a man and a woman, or that it is fluid, in between, or outside of that binary. The 11th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-11)[1] has recently redefined gender identity-related health, replacing diagnostic category "transsexualism" with "gender incongruence of adolescence and adulthood".[1] Gender dysphoria, according to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5),[2] is defined as a clinically significant distress or impairment related to a strong desire to be of another gender. Not all transgender or gender diverse people experience dysphoria. Some transgender and gender nonconforming people want to modify their appearance to be consistent with their self-identified gender identities. This is known as transition or gender affirmation. In females transitioning to males and in males transitioning to females, exogenous cross-sex steroids are prescribed to favor the development of secondary characteristics of the desired sex, while endogenous hormone production is inhibited. Gender-affirming hormonal treatment (HT) strategies are based on the Endocrine Society Practice Guidelines[3]; however, available empirical evidence is scarce in young subjects and the elderly.

Available data on adverse outcomes of HT in transgender persons are limited by the lack of cohort studies with adequate controls. The use of estrogens in transgender women seems to confer an increased risk of myocardial infarction and ischemic stroke; however there is no convincing evidence supporting the existence of adverse cardiovascular effects of testosterone administration in transgender men.[4] Fundamental questions also concern the role of preexisting comorbidities on the development of adverse drug reactions (ADRs) related to gender-affirming HT, including oncological risk.

Earlier, five case reports of gender-affirming HT-induced ADRs were identified in the French Pharmacovigilance Database (FPVD).[5] Out of these, one was related to a voluntary overdose and one to a prescription error. However, the methodology was limited to searching the term "transsexual" in the full text of identified reports. Given the lack of available data, our objective was to describe adverse drug reactions (ADRs) recorded in the FPVD concerning gender-affirming HT using a more robust strategy.

2 | MATERIAL AND METHODS

The data source used was the French Pharmacovigilance Database (FPVD).[6] Briefly, the FPVD was created in 1973 and, since 1985, all spontaneous reports of ADRs have been recorded in it. According to French law, every health professional *must* report any adverse drug reactions (ADR) to the regional centers of pharmacovigilance, either "serious" or not, either "expected" or not. Moreover, every patient *can* report such ADRs. For each ADR report, information about the patient (age, sex, medical history), drug exposure (to the suspected drug and other associated non-suspected drugs), drug discontinuation, and ADR characteristics [delay of onset, severity recorded as "serious" or "non-serious," expectedness, causality assessed through semiological, chronological and bibliographical criteria[7] and outcome] are recorded in the FPVD. ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA). All documented cases are fully anonymized. The FPVD is approved by the French Data Protection Agency (CNIL) and compliant with the European General Data Protection Regulation Law.

For our study, the FPVD was queried on the 27th of May 2020 for all ADRs cases involving gender-affirming HT, based on the Anatomical Therapeutic Chemical Classification (ATCC). Precisely, three complementary queries were performed. The first one was searching for female transgender cases, i.e., the combination between the sex criterion "female" and all authorized androgens used as medicaments (G03B according to the ATCC). We did the same for male transgender cases, i.e., a combination of the sex criterion "male" and authorized estrogens (G03C) and/or progestin (G03D) used as drug therapies. The second query consisted of looking for the medical history of patients using the following MedRA terms: "gender disorders" (as a high-level term available in the MedRa version 23.0) and "transsexualism" (as preferred term known in the previous versions).

As both medical history and indications for HT were not systematically recorded, we completed the previous queries by searching the terms "transsexual," "trans-sexual," "transgender," "trans-gender," and "gender dysphoria" in the full texts of all identified reports. An endocrinologist and a pharmacologist reviewed all anonymized recorded cases to select confirmed ADRs related to gender-affirming HT and discard those with any etiology other than iatrogenic. Previously published cases[5] and those for which gender-affirming HT was not the suspected drug were also excluded.

No additional approval was required for studies based on this database because all records respect the patient's and notifier's anonymity. Thus, this observational study did not require patient consent or ethics committee approval. Additionally, this study was approved by the French Network of Regional Pharmacovigilance Centres.

3 | RESULTS

A total of 38 reports of ADRs were identified. We excluded 5 cases where gender-affirming HT was not the suspected drug and five reports that have already been published.[5] Among the remaining reports, six concerned transgender men (age range 21–40 years) and 22 transgender women (age range 22–68 years). A majority of these identified reports were from the Regional Pharmacovigilance Centres in Nancy (five reports) and those of Brest (four reports) and Tours (three reports). To evaluate each story, we carried out a case-by-case evaluation by focusing on comorbidities and concomitant medications.

3.1 | Transgender men

Health professionals reported all six cases (Table 1). Treatment with testosterone enanthate was involved in all subjects. Prescribed dosages ranged from 250 mg every four weeks to 250 mg every two weeks, with the treatment duration from 15 days to 15 years, and a median time to onset (TTO) of 34 months. In one case, only a single dose was administered before the occurrence of an adverse event. Reported ADRs were cardiovascular and thromboembolic events: deep vein thrombosis (DVT; 1 patient), pulmonary embolism (PE; 3 patients), and ischaemic stroke (2 patients). One of the patients with ischaemic stroke also had polycythemia and hyperlipidemia. Therapy was discontinued in 50% of cases. In the present report, total recovery was noted in 3 subjects, and sequential recovery with sequelae was observed in one. One subject did not recover, and no follow-up information was available for the last patient.

3.2 | Transgender women

Twenty-two ADR cases were reported by health professionals (Table 2). Only three reports were self-declarations. Gender-affirming HT was prescribed with medical advice in most of the subjects (82%). One subject bought his/her HT on the Internet and self-medicated. Another one also self-medicated but did so with prescribed HT. This transgender woman was probably a drug-abuser and a "doctor-shopper." She managed to get prescriptions of 211 packages of estrogen-based menopause replacement therapy, 135 of Androcur®, 187 of various hypnotics, and 44 packets of multiple anxiolytics within 32 months. Besides self-medication, 2 cases were related to self-induced drug intoxications. In one subject, a self-induced drug intoxication was associated with the worsening of preexisting depression after the instauration of cyproterone acetate

TABLE 1 Adverse drug reactions (ADRs) of gender-affirming hormonal therapy reported in transgender men

Age of subject (ADR reporter)	Medical history	Gender-affirming hormonal treatment (duration)	Time to onset	ADRs	Dechallenge	Outcome
40 years (specialist physician)	Type 2 diabetes, obesity, vitiligo	Testosterone enanthate[a] (15 y)	15 y	PE, Diabetic ketoacidosis	Yes	Unknown
31 years (specialist physician)	NA	Testosterone enanthate[a] one dose	15 days	PE	Yes	Recovered
27 years (hospital pharmacist)	Smoking	Testosterone enanthate[a] 250 mg/3 weeks (NA)	7 mo	PE	No	Not recovered
21 years (specialist physician)	NA	Testosterone enanthate[a] 250 mg/4 weeks (1y)	8 mo	DVT	Yes	Recovered
36 years (hospital pharmacist)	NA	Testosterone enanthate[a] 250 mg/2 weeks (5–6 y)	5–6 y	Ischemic stroke	No	Partially recovered (right hemiparesis)
33 years (specialist physician)	NA	Testosterone enanthate[a] 250 mg/3 weeks (8 y)	8 y	TIA, polycythemia, lipid blood level increased	No	Recovered

DVT - deep vein thrombosis; IM - intramuscular injection; NA - not available; PE - pulmonary embolism; TIA - transient ischemic attack; mo - month; y - year.
[a]Testosterone enanthate (Androtardyl®) intramuscular administration.

TABLE 2 Adverse drug reactions (ADRs) of gender-affirming hormonal therapy reported in transgender women

Age of subject (ADR reporter)	Medical history	Gender-affirming hormonal treatment (duration)	Time to onset	ADRs	Dechallenge	Outcome
64 years (self-declaration)	NA	CPA[a] 50 mg/day + Estradiol hemihydrate[b] (25 y)	25 y	Meningioma	Yes	Not recovered
61 years (specialist physician)	Venous thromboembolism	CPA[a] 50 mg/day + Estradiol hemihydrate[b] 1 mg/day (7 y)	7 y	Meningioma	Yes (CPA)	Not recovered
48 years (specialist physician)	Venous thromboembolism	CPA[a] 70 mg/day + Estradiol hemihydrate[b] 0.5–1 mg/day (32 y)	32 y	Meningioma	Yes (CPA)	Not recovered
59 years (specialist physician)	NA	CPA[a] (21 y)	23 y	Meningioma	Yes	Not recovered
55 years (specialist physician)	NA	CPA[a] 150 mg/day + Estradiol hemihydrate (Provames[®]) 3 mg/day (7 y)	7 y	Meningioma	Yes	Not recovered
52 years (self-declaration)	NA	CPA[a] 50 mg/day (16 y)	15 y	Meningioma	Yes	Not recovered
37 years (specialist physician)	Self-induced drug intoxication	CPA[a] 100 mg/day (5 y)	4 y	Meningioma	Yes	Not recovered
41 years (specialist physician)	NA	CPA[a] 50 mg/day (9 y); Estradiol hemihydrate[b] 0,5 mg/day (5 y)	8 y + 4 y	Meningioma	Yes	NA
45 years (specialist physician)	Smoking (30 cigarettes/day) Alcoholism Gastric bypass	Estradiol hemihydrate[b] (1 y)	1 y	Ischemic stroke with aphasia and right hemiparesis, carotid atheroma	Yes	Recovering
35 years (specialist physician)	Smoking; HIV[c]	CPA[a] 100 mg/day + Estradiol hemihydrate (Femsept[®]) 1 patch 50 ug/day (> 1 y)	> 1 y	Acute coronary syndrome	Yes	Partially recovered (implantation of a coronary stent)
45 years (specialist physician)	Smoking, arterial hypertension (untreated)	17 beta estradiol (Oestrogel 0,06%[®]) 1,5 mg/day (28 mo)	28 mo	Malignant hypertension, secondary hyperaldosteronism, AV block, macular edema	Yes	Recovered
35 years (hospital pharmacist)	HIV[c]Shigella and Helicobacter pylori infection	CPA[a] (3 mo); Ethinyl estradiol 35 ug + Cyproterone acetate 2 mg (Diane[®])/day (2 mo)	3 mo + 2 mo	PE	Yes	Recovering
31 years (specialist physician)	Asthma, Obesity	Estradiol (5 mo) + Chlormadinone (11 mo)	5 mo + 11 mo	PE + DVT	Yes	Recovered
59 years (hospital pharmacist)	NA	CPA[a] 100 mg/day + Estradiol hemihydrate	1 y	DVT	Yes	Recovered

(Continues)

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TABLE 2 (Continued)

Age of subject (*ADR reporter*)	Medical history	Gender-affirming hormonal treatment (duration)	Time to onset	ADRs	Dechallenge	Outcome
		(Femsept®) 1 patch/week (1 y)			(replaced with triptorelin)	Recovered
45 years (*general practitioner*)	NA	Estradiol valerate 2 mg/+ Medroxyprogesterone acetate 10 mg (Divina®) (75 days)	15 days	Phlebitis, hypercholesterolemia	Yes	Recovered
24 years (*self-reported*)	Autism	Estradiol hemihydrate[b] (1 mo)	1 mo	Hot flushes	NA	Not recovered
68 years (*specialist physician*)	Severe hypochromic microcytic anemia at 66 y	CPA[a] + Estradiol hemihydrate[b]	NA	Severe hypochromic microcytic anemia	NA	NA
28 years (*general practitioner*)	NA	Estradiol + Progesterone (1 y)	1 y	Somnolence, muscular and abdominal pain, nausea, dizziness	Yes (estradiol)	Recovered
Self-medication with hormonal therapy						
35 years (*general practitioner*)	Abuse of anxiolytics and hypnotics	CPA[a] 300 mg/day + Estrogens (32 mo)	NA	Phlebitis, headache, depression, gynecomastia, pruritus	NA	NA
32 years (*town pharmacist*)	NA	Ethinyl estradiol (215 days) bought on the Internet	200 days	Breast tumefaction	Yes	Recovered
Self-induced drug intoxication with hormonal therapy						
22 years (*specialist physician*)	Depression Psychosis diagnosed at age 21 y treated with Venlafaxine, Fluoxetine, Olanzapine, Risperidone	CPA[a] 50 mg/day (1 mo);	1 mo	Worsening of psychosis and depression/ psychiatric disorders	No	Recovered[d]
27 (*specialist physician*)	NA	CPA[a] 30 mg/day, one administration + Estradiol hemihydrate[b] (NA) Non-hormonal drugs used for suicidal attempt: Spiramycine, Alprazolam, Loratadine	36 hours, aggravation at 42 hours	Hepatitis	Yes	Recovered

AV - atrioventricular; CPA - cyproterone acetate; DVT - deep vein thrombosis; NA - not available; PE - pulmonary embolism; mo - month; y - year.
[a] Cyproterone acetate (Androcur®).
[b] Estradiol hemihydrate (Estreva gel 0,1%®).
[c] Tritherapy (Dolutegravir + Abacavir + Lamivudine).
[d] Adaptation of anti-depressive therapy, introduction of estrogen treatment.

(CPA). In the other one, the circumstances of the suicidal attempt were not notified.

Antiandrogens, mainly CPA, were involved in 68% of reported cases. Estrogens were implicated in 77% of cases, mostly in association with progestins or CPA. Meningioma was the main ADRs observed (36%). CPA was involved in all of these cases. The daily antiandrogen dose ranged from 50 to 150 mg, and the length of therapy varied from 4 to 32 years. In one case, the posology was unknown. The second most frequent ADR were cardiovascular and thromboembolic events (36%), such as ischaemic stroke, acute coronary syndrome (ACS), malignant hypertension, DVT, and PE. Median TTO was 5.3 months. Miscellaneous ADRs such as anemia, hot flushes, tiredness, pruritus, breast tumefaction, and hepatitis (suicidal attempt) was also noticed. Of note, the patient with ACS and one with PE were HIV-seropositive treated with tri therapy (Dolutegravir + Abacavir + Lamivudine).

Gender-affirming HT was discontinued in 82% of transgender women, fully (n = 14) or partially (n = 4). In the patient with a suicidal attempt following the worsening of preexisting depression, estrogen therapy was introduced while maintaining CPA. Eight out of 22 transgender women recovered (37%), one recovered only partially, and two were recovering when their cases were reported. No recovery was observed in 8 other subjects; of those, 7 were cases of meningioma. The information was unknown for three patients, whose the 8th case of meningioma. Long-term outcome data are not available.

4 | DISCUSSION

To the best of our knowledge, this is the first nationwide report from FPVD showing the occurrence of cardiovascular ADRs in young transgender men receiving exogenous testosterone. In the present study, all identified reports in transgender men were related to cardiovascular and thromboembolic events with pulmonary embolism in 50% of cases. All subjects were 40 years old or younger. In transgender women, cardiovascular ADRs were the second most frequently reported ADRs. Only one study is available from FPVD reporting five ADRs, two related to voluntary overdoses and prescription errors. It is to note that no cardiovascular event was reported.[5] Therefore, our findings are significant and indicate the need to assess the benefits and risks of gender-affirming HT in this subpopulation.

Epidemiological data on gender incongruence in France are not available; consequently, the results of this study cannot be generalized to the whole transgender and gender-nonconforming population in France. In the University Hospital of Nancy, care of transgender and gender-nonconforming persons started in the 1990s, and the follow-up of individuals is done via the healthcare register since 2004.[8] Our gender identity center is among the largest centers in the Grand-Est region of France. At the time of this report, a total of 373 transgender persons (184 transgender men) were followed in our department (*personal data*). Previously, we retrospectively analyzed[9] records from 142 transgender women (mean age 40 ± 10 years with a mean follow-up of 6.8 ± 2 years), and from 104 transgender men (mean age 41 ± 7 years with a mean follow-up of 4.3 ± 2 years). Our analysis showed a frequency of arterial hypertension of 7% in transgender men and 10% in transgender women (*personal data)*.

In the general population in France, available data on the prevalence of cardiovascular diseases is based on the self-reporting health and disability survey on the sample of households and institutionalized adult subjects in France (2008–2009) with a prevalence of cardiovascular diseases of 3.7% for ischaemic heart disease, 2.3% for heart failure and 2% for stroke.[10,11] According to the literature, in cisgender women, unlike cisgender men, the prevalence of cardiovascular diseases is lower, and their manifestation occurs later in life.[12] Epidemiological studies demonstrated the protective effects of estrogens against cardiovascular diseases in pre-menopausal cisgender women.[13] However, in cisgender women after menopause and in cisgender men with and without hypogonadism, HT may be responsible for harmful effects.[14–17] In transgender men treated with exogenous testosterone, several reports indicated an increase in blood pressure, dyslipidemia, and visceral fat accumulation.[18–21]

Literature data are inconsistent regarding the parameters of lipid metabolism in transgender subjects receiving gender-affirming HT, Elbers et al[19] reported a significant decrease in HDL-cholesterol and increased triglycerides in 17 transgender men (mean age 23 +/− 5 years) one year after initiating gender-affirming HT. The same study showed significant increases in HDL-cholesterol and triglycerides and a significant decrease in LDL-cholesterol in 20 transgender women (mean age 26 +/− 6 years). Others showed[22] a substantial increase in LDL-cholesterol and decreased HDL-cholesterol in 35 transgender men (mean age 26 years). A significant decrease of LDL- and HDL-cholesterol and triglycerides was reported in 55 transgender women (mean age 34 years) one year after starting gender-affirming HT. A recent meta-analysis[18] of 29 studies, including 3231 transgender women (age range 19–44 years) and 1500 transgender men (age range 22–38 years), reported low-quality evidence suggesting that sex steroid therapy may increase LDL-cholesterol and triglyceride levels and decrease HDL-cholesterol in transgender men. In contrast, oral estrogens may increase triglycerides in transgender women 12–24 months after starting gender-affirming HT.

There is a lack of sufficient evidence enabling conclusions regarding the risk of venous thromboembolism,

myocardial infarction, and stroke in transgender persons receiving gender-affirming HT.[4,23] Existing data suggest that the cardiovascular and metabolic effects of gender-affirming HT differ in transgender men and transgender women.[20,21] Several studies reported a significantly higher incidence of venous thromboembolism, ischemic stroke, and myocardial infarction in transgender women receiving gender-affirming HT than in cisgender men and cisgender women.[23,24] However, no adjustments were made for hormonal regimens. In one retrospective single-center study including 676 transgender women taking oral 17β-estradiol for a mean of 1.9 years, only one subject (0.15% of the population) had venous thromboembolism.[25] All subjects took oral 17β-estradiol, and less than 10% took conjugated equine estrogen or oral progesterone and/or depot medroxyprogesterone acetate.

The occurrence of cardiovascular events in persons using sex hormones i.e estrogens, progestogens and testosterone seems to be related to the steroid used, route of administration, dose and duration of treatment, and to the age of patients. However, the literature data are not conclusive depending on the studies (type, design, duration …), population (cisgender or transgender people, age, number, history of cardiovascular diseases …) and the steroid considered.[4,14,26–28] More data are available in cisgender population. For instance, a recent meta-analysis including 5328 cisgender men (mean age 63 years) reported that, during the first year of treatment, testosterone supplementation was associated with an increased risk of cardiovascular events, especially with oral and transdermal use of testosterone.[14] Similarly, a recent cross-over analysis of health insurance data showed a short-term risk of acute cardiovascular events in older men following testosterone injection receipt.[26] Another study including 204 857 adult mean (mean age 61 years) reported, after a mean follow-up period of 5 years, increased risk with of cardiovascular events with the use of transdermal testosterone in participants with chronic medical conditions.[27] Finally, an increased cardiovascular risk with the use of transdermal testosterone was reported in 209 men (mean age 74 years) with pre-existing comorbidities (hypertension, diabetes, hyperlipidemia, obesity).[28] Recently, a marked increase in platelet activation and in coagulation marker concentrations has been reported in young 48 transgender women (median age 30 years) taking transdermal estradiol and CPA which may confer increased cardiovascular risk.[29] Others previously reported altered endothelial function in transgender men receiving testosterone.[30] Altogether, the literature data do not always allow conclusions and need to be completed by prospective long-term studies.

Fundamental questions also concern the role of pre-existing comorbidities and concomitant treatments on the development of ADRs related to gender-affirming HT. Two cardiovascular ADRs in the present study concern subjects treated with antiretrovirals. Interestingly, antiretrovirals and hepatitis C direct-acting antivirals were shown to influence the pharmacokinetics and/or pharmacodynamics of gender-affirming HT.[31] Non-nucleoside reverse transcriptase inhibitors may decrease plasma concentrations of steroid hormones (estradiol, cyproterone, 5α-reductase inhibitors, progestogens, and testosterone). Cobicistat-based treatments may increase the plasma exposure to estradiol. Ritonavir-containing regimens may increase or decrease exposure to estradiol, and both these drugs can increase exposure to cyproterone 5α-reductase inhibitors, progestins, and testosterone. Potential interactions and overlapping side effects should therefore be considered by clinicians when prescribing HT in transgender subjects. Besides, transgender persons taking gender-affirming HT may have an increased risk for depression, cardiovascular disease, dyslipidemia, and decreased bone mineral density; therefore, anti-retrovirals and or direct-acting antivirals with minimal side effects are recommended.[32]

In transgender women, the most frequent ADR identified in the present study was meningioma. Cyproterone acetate (CPA) was involved in all these cases. Our findings are in concordance with the literature indicating that long-term use of high-doses of CPA represents a risk of developing meningiomas.[33] Indeed, the labeling of CPA-related drugs was modified in 2009[34] to indicate that meningiomas have been reported in persons with prolonged use of CPA.[35] According to the recommendations of the French National Agency for Medicines and Health Products Safety (2019), new regulations for prescription of CPA (50–100 mg) are applied, including the necessity of an annual written consent signed by both the clinician and patient, and normal brain MRI scans.[36]

Given that transgender women on CPA have doses of 50–100 mg/day,[33] those using this medication are at an increased risk of developing meningiomas. In most of our patients, no recovery of the meningioma after discontinuation of CPA was observed at the time of the case report. Interestingly, literature data indicate a regression of some meningiomas even without invasive treatment after discontinuation of CPA. This has been demonstrated in a case series of 12 cisgender women with CPA-induced meningioma.[37] Discontinuing this medication led to a reduction in tumor size for 11 and a cessation of tumor growth in the remaining patient, with no recurrences after one year. In our series, the frequency of unrecovered patients may be explained by the lack of long-term outcome data.

We further identified two reports of ADRs in the subpopulation of transgender women that were related to self-medication. Notably, self-prescribed gender-

affirming HT use was reported in up to 30% of transgender women even before attending gender clinics. This may expose these persons to potential health risks.[38] Finally, we noted two cases of self-induced intoxication involving CPA. Interestingly, available data suggest that drug misuse, anxiety, and depression are more frequent among transgender persons than in the general population. Moreover, psychological outcomes may tend to improve during gender-affirming HT.[39]

4.1 | Limitations of the study

As this study is based on spontaneous reports, data are not exhaustive. Population-based studies are needed to confirm our findings. In particular, this study cannot quantify and stratify the cardiovascular risk because of under-reporting and the lack of population-based epidemiological data. Moreover, suspected, additional drugs cannot be ruled out, and additional confounding factors such as comorbidities, pharmacodynamic, and pharmacokinetic drug interactions. Furthermore, our study cannot evaluate the mental distress of transgender persons as these kinds of data are rarely provided. Nevertheless, our analysis has some strengths. The search strategy was more robust than the previous report,[5] combining standardized queries and verbatim research. Doing so allowed us to classify gender-affirming HT-related ADRs in transgender persons.

5 | CONCLUSION

The spontaneous reporting system of FPVD shows a previously unreported and non-negligible proportion of reports indicating cardiovascular ADRs in transgender men younger than 40 years taking testosterone enanthate. This may require clinical judgment on a case-by-case basis and the need to assess the benefits and risks of gender-affirming HT in this subpopulation. In transgender women, meningioma was the most frequently reported ADRs followed by cardiovascular events. These results should stimulate continued vigilance and encourage further research. It is essential to identify risk factors that might lead to the individualization of treatment strategies. It is also necessary to stratify the risk according to preexisting comorbidities, concomitant treatments, and biological variables such as age at the start of gender-affirming HT, chronological age, or sex at birth. Above all, our study highlights the necessity to increase awareness and implement preventive measures and therapeutic education interventions targeting transgender people.

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