Use of antidepressant and antipsychotic drugs in subjects with hemophilia of the Umbria Region in the period 2011-2022

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Abstract

Introduction. Chronic diseases, such as hemophilia, can evoke psychological sequelae and be associated with a higher risk of mental health disorders. The utilization of antidepressant and antipsychotic drugs in subjects with hemophilia is not completely understood and few data are available.

Objectives. The aim of this analysis is to describe use of antidepressant and antipsychotic drugs in subjects with hemophilia of the Umbria Region in the period 2011-2022. **Methods.** A descriptive, cross-sectional, and retrospective analysis based on data on filled prescriptions for antidepressants and antipsychotics has been carried out. The overall and annual prevalence of drugs use and consumption were calculated based on pharmaceutical prescriptions charged to the National Health Service in subjects with hemophilia and matched controls from general population.

Results. In the study period 170 subjects with hemophilia were identified; about 80% were male. About 20% and 8.2% received antidepressants and antipsychotics, respectively. A higher percentage of users and consumption were found in subjects with hemophilia compared to matched controls, although no statistically significant differences were observed.

Conclusions. Our analysis suggests that depression and psychosis are important comorbidities in subjects with hemophilia. Further larger studies are needed in order to confirm these data and better define the burden of mental health disorders in subjects with hemophilia.

INTRODUCTION

Hemophilia is a rare inherited blood coagulation disorder caused by a deficiency of clotting factor VIII (hemophilia A) and factor IX (hemophilia B) characterized by spontaneous and post-traumatic bleeding events in the joints, muscles, and other soft tissues [1]. The treatment of hemophilia has progressively reached new landmarks and with advances in diagnosis and the development of safe and effective treatment modalities, subjects with hemophilia now have an almost average life expectancy [2]. Despite evolving from a fatal disease to a chronic disorder, hemophilia causes significant morbidity and its psychosocial impact on patients and their caregivers remains considerable [3].

Data on the use of antidepressants and antipsychotics in the adult general population of high-income countries showed a meaningful use (up to 17% of adults are prescribed antidepressants and up to 2% antipsychotics) which is steadily increasing compared to the previous decades [4]. In 2022, 6.7% of the Italian population used antidepressants and 1.8% used antipsychotics [5]. Consumption of antidepressants is higher in fe-

• hemophilia

Key words

• antidepressants

• inherited blood coagulation disorders

- antipsychotics
- drug consumption

males and increases with age, reaching a prevalence of 27.7% in women aged more than 85 years. Conversely, the prevalence of use of antipsychotics increases with age and men use more doses than women on average in all age groups, with the exception of persons aged more than 85 years [5].

Chronic diseases are associated with a higher risk of mental health disorders and hemophilia is no exception [5] considering several factors that significantly impact quality of life such as the consequences of bleeding episodes, frequent hospital admissions, chronic arthropathy, and functional disability. These factors contribute to a high rate of mental health disorders, particularly depression, in patients with haemophilia, with more than 30% affected in several studies [6-24]. A systematic literature review and meta-analysis by Al-Huniti A and colleagues reported that at least 2 out of every 5 subjects with hemophilia suffer from depression and/ or anxiety [13]. Across studies, differences exist in the methodologies including questionnaires, face-to-face interviews and data from health data registries used. These differences were also influenced by demographic, socio-political, and health care system between countries. A recent descriptive, longitudinal, and retrospective analysis based on information from administrative health data registries found an increased consumption of antidepressant and anti-anxiety medications among subjects with haemophilia compared with controls, regardless of age or sex [25].

To date there is a lack of studies, especially large national studies, analysing broad hemophilia populations with a specific focus on strategies for management of depression, anxiety and psychiatric disorders. The aim of this analysis is to describe the prevalence of antidepressant and antipsychotic drugs in subjects with hemophilia in the Umbria Region in the period 2011-2022 and to evaluate the trend over this period. This study represents the first attempt to evaluate the burden of mental health disorders in the haemophilic population based on the drug prescription from a regional health data registry over a long time period. It could confirm data from international and national studies on this topic.

METHODS

All Italian citizens are enrolled in the Italian National Health Service (Servizio Sanitario Nazionale, SSN), which provides health care free of charge. We obtained data from the regional archive of drug prescriptions for the period 2011-2022, which contains all outpatient prescriptions filled within the SSN, and from the archive of SSN enrolees, which contains demographic data about inhabitants of Umbria Region.

We performed a descriptive, cross-sectional, and retrospective analysis based on data on filled prescriptions for antidepressant (Anatomical Therapeutical Chemical classification, ATC, N06A) and antipsychotic (ATC N05A) drugs in subjects with hemophilia. This study compares the prevalence of use of antidepressant and antipsychotic drugs, defined as the proportion (%) of a population with at least one prescription of aforementioned drugs either in each year during the whole study The study population comprised subjects with hemophilia identified through:

- ≥1 prescription of factor VIII or factor IX concentrates (ATC code B02BD02 or B02BD04) or
- bypassing agents during the study period or hospitalization between January 2000 and December 2022 with a diagnosis of "congenital factor VIII disorders" (International Classification of Disease – Clinical modification, ICD-9-CM, 286.0) or "congenital factor IX disorders" (ICD-9-CM 286.1).

Subjects diagnosed with other congenital hematological disorders (ICD-9-CM 286.2-Congenital factor XI deficiency, 286.3-Congenital deficiency of other clotting factors, 286.4-von Willebrand's disease, 286.5-Hemorrhagic disorder due to intrinsic circulating anticoagulants, antibodies, or inhibitors, 286.6-Defibrination syndrome, 286.7-Acquired coagulation factor deficiency, and 286.9-Other and unspecified coagulation defects) were excluded. For each year analysed, the proportion of subjects treated with antidepressants and antipsychotics was calculated, stratified by age, and gender.

Controls from the general population were identified through the same regional archive of drug prescriptions of the Umbria Region and randomly matched at a ratio of 1:100 using gender, age, and health district of reference. The study cohort was dynamic, including births and deaths as observed.

The defined daily dose (DDD) is the unit of measurement defined as the assumed average maintenance daily dose for a drug, approved and recommended by the World Health Organisation (WHO) for drug use studies and surveys (https://atcddd.fhi.no/atc_ddd_index_and_guidelines/guidelines/). The "DDDs per user" measure the mean duration of treatment per user. This measure has been used for many years in drugs consumption studies and comparisons at national and international level [5]. The total DDDs used were computed by summing all the DDDs for each prescribed package to obtain antidepressant and antipsychotic drugs consumption during the study period.

Differences in the main characteristics and drug use between subjects with hemophilia and controls were tested through the Chi-Square, Wilcoxon rank-sum and T-tests, with the significance level set at a p-value <0.05.

RESULTS

During the study period 170 subjects with hemophilia (both A and B) were identified, of whom 79.4% were male (n=135) and 20.6% female (n=35) (*Table 1*). The mean age was 42.7 years: 40.3 for males and 52.3 years for females. Approximately 76% of subjects (129 cases) had factor VIII deficiency while 24% (41 cases) had factor IX deficiency. Most subjects were identified through diagnosis codes (77%, 131 cases) while the remaining 23% (39 cases) through the prescription of factor VIII or factor IX concentrates. *Table 1* summarises key demographic and pharmacoepidemiological characteristics of the study population (n=170) and controls from the general population (n=16,916). As Demographic characteristics of subjects with hemophilia and matched controls from the general population

	Subjects with hemophilia	Matched controls	р
Total	170	16,916	
Mean age (±SD)	42.7 (±24.1)	43.0 (±23.9)	0.904
Gender (% male)	79.4	79.3	0.974
Age groups n. (%)			
<18 years	26 (15.3)	2,611 (15.4)	0.960
18-39 years	55 (32.4)	5,368 (31.7)	0.863
40-64 years	48 (28.2)	4,861 (28.7)	0.886
65-84 years	35 (20.6)	3,476 (20.5)	0.990
85+ years	6 (3.5)	600 (3.5)	0.990
Coagulation factors use (%)*	60.6	-	-

SD: standard deviation; *At least 1 prescription of factor VIII or factor IX concentrates or bypassing agents during the study period.

expected, no significant differences between these two groups in terms of distributions of age and gender was observed (*Table 1*).

In the period 2011-2022, the consumption between two groups was comparable except for the median DDD (p-value <0.001), mean number of prescriptions (p-value <0.001), and in the use of specific drug categories or classes. In particular, the use of drugs in the "Blood and blood forming organs" (ATC code B), "Systemic hormonal preparations, excluding sex hormones and insulins" (ATC code H) and "Nervous system" (ATC code N) categories has been found higher in subjects with hemophilia compared to matched controls (Table 1). These differences were especially driven by antihemorrhagics (ATC code B02) and antianemic preparations (ATC code B03) for the ATC Category "B" and by desmopressin (ATC code H01BA02) and Corticosteroids for systemic use (ATC code H02) for the ATC Category "H". Moreover, a higher use of drugs for Nervous system (ATC code N) was found in subjects with hemophilia, with Analgesics (ATC code N02) and Antidepressants (ATC code N06A) being among the fifteen most used therapeutic classes (Table 2).

In order to verify the results of the main analysis, data on drug utilisation in the last year available have been analysed. In 2022, a higher prevalence of use in subjects with hemophilia compared to the matched controls was confirmed (p-value <0.05). The consumption between two groups was comparable except for mean number of active principles (p-value <0.001). No significant differences compared to 2011-2022 were found for categories and therapeutic classes (*Table 2*).

The prevalence of use of antidepressants during the study period was 19.4% in subjects with hemophilia and 17.2% in matched controls. Concerning antipsychotics 8.2% of subjects with hemophilia and 5.9% of matched controls received at least one prescription during the study period (*Table 3*). Higher prevalence of use was found in both males and females with hemo-

philia compared to matched controls. The analysis by gender in both groups showed higher prevalence of use in female subjects for antidepressant and antipsychotic drugs.

Regarding the trends of the antidepressant drugs, an increase in prevalence of use was observed in Umbria Region from 2011 to 2022 for both subjects with hemophilia and matched controls. In subjects with hemophilia, the percentage of users increased from 4.79% in 2011 to 8.70% in 2022 (the highest observed value), with values remaining above 4% since 2012 except for the lowest value of 3.70% in 2017. A constant slight increase in prevalence of use of antidepressant drugs, from 3.90% in 2011 to 6.79% in 2022, was observed in matched controls (Figure 1). Notably, the prevalence of antidepressant use was higher (about 1.5-fold) in subjects with hemophilia compared to matched controls in each year considered, with the exceptions of 2017 and 2020. However, for each year considered, the difference between the two groups was not statistically significant.

The trend analysis of antipsychotic drugs showed an increase in their prevalence of use in Umbria Region from 2011 to 2022 both in subjects with hemophilia and matched controls. In subjects with hemophilia, the percentage of users increased from 0.60% in 2011 to 3.73% in 2022 (the highest observed value), with the prevalence remaining stable at 2.45% in the 2018-2020 period. A steady, slight increase in the prevalence of use of antipsychotic drugs was observed in matched controls, rising from 0.67% in 2011 to 2.26% in 2022, (*Figure 2*). The difference between the two groups for each year considered was not statistically significant.

Regarding the DDDs per user of antidepressant drugs, values showed a slight increasing tendency from 2011 to 2022 in subjects with hemophilia and a stable trend in matched controls. The DDDs per user in subjects with hemophilia showed higher values during the 2016-2020 period, reaching a peak in 2017 (320 DDDs per user). In the last two years (2021 and 2022), they showed a decrease returning to a level comparable with those registered in the 2011-2014 period. On the other hand, the DDDs per user in matched controls remained quite stable throughout the study period, ranging from 205 in 2011 to 221 DDDs per user in 2022 with a peak in 2015 (233 DDDs per user). For each year considered, the difference between the two groups was not statistically significant (*Figure 3*).

Regarding the DDDs per user of antipsychotic drugs, values showed a decreasing trend over time in subjects with hemophilia and a generally constant trend in matched controls. The DDDs per user in subjects with hemophilia showed higher values in 2011, 2013, and 2016 reaching a peak in 2017 (448 DDDs per user). In the 2018-2022 period they showed a steady decline to values lower than 170 DDDs per user with the lowest value of 71 DDDs per user registered in 2022. On the other hand, the DDDs per user in matched controls remained quite stable throughout the study period, ranging from 140 in 2011 to 91 DDDs per user in 2022 reaching a peak in 2012 (161 DDDs per user). The difference between the two groups was not statistically sig-

Table 2

Drug utilization in subjects with hemophilia and matched controls from the general population in the 2011-2022 period and year 2022

	2011-2022			2022		
	Subjects with hemophilia	Matched controls	p	Subjects with hemophilia	Matched controls	p
Prevalence of use (%), any drugs	99.4	94.1	<0.05	80.7	62.6	<0.05
Defined daily dose median*	2,213	700	<0.001	390	495	0.186
Mean number of active principles	14.9	13.1	0.075	4.6	5.8	<0.001
Mean number of prescriptions	393	243	<0.001	48.3	41.5	0.281
ATC≠1st level categories n. (%)						
Alimentary tract and metabolism (A)	110 (64.7)	10,370 (61.3)	0.822	54 (33.5)	5,492 (33.9)	0.915
Blood and blood forming organs (B)*	149 (87.6)	7,202 (42.6)	<0.05	77 (47.8)	3,380 (20.9)	<0.05
Cardiovascular system (C)	84 (49.4)	7,799 (46.1)	0.389	52 (32.3)	5,544 (34.3)	0.601
Dermatologicals (D)	12 (7.1)	1,054 (6.2)	0.657	1 (0.6)	221 (1.4)	0.417
Genitourinary system and sex hormones (G)	30 (17.6)	2,701 (16.0)	0.552	16 (9.9)	1,213 (7.5)	0.243
Systemic hormonal preparations, excluding sex hormones and insulins (H)	109 (64.1)	7,618 (45.0)	<0.05	37 (23.0)	2,291 (14.2)	<0.05
Antiinfectives for systemic use (J)	155 (91.2)	14,699 (86.9)	0.099	59 (36.6)	5,787 (35.8)	0.817
Antineoplastic and immunomodulating agents (L)	14 (8.2)	879 (5.2)	0.077	6 (3.7)	398 (2.5)	0.303
Musculo-skeletal system (M)	76 (44.7)	8,078 (47.8)	0.429	25 (15.5)	2,864 (17.7)	0.472
Nervous system (N)	82 (48.2)	5,745 (34.0)	<0.05	30 (18.6)	2,205 (13.6)	0.066
Antiparasitic products, insecticides and repellents (P)	10 (5.9)	1,207 (7.1)	0.527	1 (0.6)	171 (1.1)	0.590
Respiratory system (R)	80 (47.1)	7,121 (42.1)	0.192	25 (15.5)	1,747 (10.8)	0.055
Sensory organs (S)	8 (4.7)	974 (5.8)	0.558	2 (1.2)	430 (2.7)	0.265
Various (V)	3 (1.8)	189 (1.1)	0.426	0 (0.0)	49 (0.3)	0.484
ATC≠ 2nd level therapeutic classes n. (%)						
Antibiotics	152 (89.4)	14,556 (86.0)	0.208	55 (34.2)	5,607 (34.7)	0.896
Corticosteroids for systemic use	87 (51.2)	6,965 (41.2)	<0.05	25 (15.5)	1,639 (10.1)	0.024
Anti-peptic, antiulcer and GERD***	86 (50.6)	7,861 (46.5)	0.284	40 (24.8)	3,126 (19.3)	0.078
Antihypertensives	80 (47.1)	7,221 (42.7)	0.252	49 (30.4)	5,040 (31.1)	0.845
Antihemorrhagics	77 (45.3)	377 (2.2)	<0.05	9 (5.6)	57 (0.4)	<0.05
Drugs for asthma and COPD***	74 (43.5)	5,871 (34.7)	<0.05	21 (13.0)	1,250 (7.7)	<0.05
NSAIDs£	66 (38.8)	7,240 (42.8)	0.297	17 (10.6)	1,921 (11.9)	0.608
Analgesics	56 (32.9)	3,623 (21.4)	<0.05	12 (7.5)	899 (5.6)	0.296
Antianemic preparations	41 (24.1)	2,979 (17.6)	<0.05	10 (6.2)	939 (5.8)	0.826
Drugs for osteoporosis	36 (21.2)	3,149 (18.6)	0.394	12 (7.5)	1,192 (7.4)	0.967
Anticoagulants	34 (20.0)	4,449 (26.3)	0.063	4 (2.5)	1,180 (7.3)	<0.05
Antidepressants	33 (19.4)	2,913 (17.2)	0.452	14 (8.7)	1,099 (6.8)	0.340
Systemic hormone preparations, excluding sex hormones and insulins	28 (16.5)	71 (0.4)	<0.05	3 (1.9)	16 (0.1)	<0.05
Antibiotics for topical use	27 (15.9)	2,701 (16.0)	0.976	6 (3.7)	455 (2.8)	0.486
Drugs for genitourinary disorders	26 (15.3)	2,293 (13.6)	0.510	15 (9.3)	1,117 (6.9)	0.230

*ATC: Anatomical Therapeutic Chemical Classification System; *Excluding coagulation factors and bypassing agents; **GERD: Gastroesophageal reflux disease; ***COPD: chronic obstructive pulmonary disease; ENSAIDs: Nonsteroidal anti-inflammatory drug.

nificant for most years; however, according to Wilcoxon rank-sum test a statistically significant difference was found only in 2016 (p-value 0.029) and 2017 (p-value 0.021) (*Figure 4*).

DISCUSSION

Our descriptive, cross-sectional, and retrospective analysis showed that 20% of subjects with hemophilia received at least one antidepressants prescription and

Table 3

Prevalence of use and consumption of antidepressant and antipsychotic drugs in subjects with hemophilia and matched controls from the general population

	Hamanhilla			Metched controls				
		Hemophilia			Matched controls			
	Males	Females	Total	Males	Females	Total		
N. of subjects (%)	135 (79.4)	35 (20.6)	170 (100)	13,416 (79.3)	3,500 (20.7)	16,916 (100)		
Mean age in years (±SD)	40.3 (23.4)	52.3 (24.5)	42.7 (24.1)	40.5 (23.2)	52.2 (24.3)	43.0 (23.9)		
Antidepressant drugs								
Users n. (%)	22 (66.7)	11 (33.3)	33 (100)	1,900 (65.2)	1,013 (34.8)	2,913 (100)		
DDDs per user	942.4	1,035.1	973.3	717.9	1,004.6	817.6		
Mean age in years (±SD)	57.4 (17.8)	72.9 (20.9)	63.2 (20.2)	58.9 (19.7)	67.8 (18.1)	62.5 (19.8)		
Prevalence of use (%)	16.3	31.4	19.4	14.2	28.9	17.2		
Antipsychotic drugs								
Users n. (%)	10 (71.4)	4 (28.6)	14 (100)	675 (67.1)	331 (32.9)	1,006 (100)		
DDDs per user	535.6	181.2	434.3	368.9	193.4	311.1		
Mean age in years (±SD)	61.2 (20.6)	74.8 (11.1)	65.8 (19.2)	64.9 (22.3)	76.2 (18.1)	69.2 (21.9)		
Prevalence of use (%)	7.4	11.4	8.2	5.0	9.5	5.9		

SD: Standard Deviation; DDD: defined daily dose.

8.2% at least one antipsychotics prescription during the study period. A higher percentage of users and higher consumption were found in subjects with haemophilia compared to matched controls, although no statistically significant differences were observed. Antidepressants use was highest among users aged 70 or older, especially females. Additionally, antidepressant users increased from 7.1% in 2011 to 10.4% in 2022, while antipsychotic users increased from 0.6% in 2011 to 4.4% in 2022.

In 2022, 6.7% of the Italian population used antidepressants and 1.8% antipsychotics [5]. Consumption of antidepressants is higher in females and increases with age, reaching a prevalence of 27.7% in women aged over than 85 years. On the other hand, the prevalence of antipsychotics use increases with age and men use more doses than women on average in all age groups, except for those aged over 85 years [5]. In particular, 8.5% of the Umbria Region population used antidepressants and 2.3% antipsychotics with differences in terms of consumption between genders (11.2% in females vs 5.3% in males for antidepressants and 2.2% in females vs 1.8% in males for antipsychotics) [5]. These data place the Umbria Region among the Italian region with the highest consumption of antidepressant and antipsychotic drugs [5].

Previous studies have reported a higher rate of mental health disorders in patients with hemophilia compared to controls [6-24], with depression (formal diagnosis) and depressive symptoms/anxiety interesting 40-50% of subjects with hemophilia. The methodology used in the abovementioned studies varied significantly and demographic, health care and social care differences between studied populations should be taken into account. Our findings are substantially in line with a recent systematic review and meta-analysis, which reported about two-fold or higher increased risk



Figure 1

Prevalence of use of antidepressant drugs trend in subjects with hemophilia and matched controls from general population (Umbria Region, 2011-2022).



Figure 2

Prevalence of use of antipsychotic drugs trend in subjects with hemophilia and matched controls from general population (Umbria Region, 2011-2022).



Figure 3

Trend of defined daily doses (DDDs) per user of antidepressant drugs in subjects with hemophilia and matched controls from general population (Umbria Region, 2011-2022).



Figure 4

Trend of defined daily doses (DDDs) per user of antipsychotic drugs in subjects with hemophilia and matched controls from general population (Umbria Region, 2011-2022).

of depression, anxiety, or both in subjects with hemophilia compared with the general population [13], as well as with those from a descriptive, longitudinal, and retrospective analysis based on data from four Nordic countries National Health Data Registers during 2007-2017 [25]. This study showed higher likelihood of antidepressants use in subjects with hemophilia compared to matched controls, especially in women and carriers subgroups [25].

Considering that no information was available in our health flow data about private purchases by citizens, the use of drugs (e.g., benzodiazepines) and non-pharmacological interventions in mild to moderate mental health disorders, the prevalence of antidepressants and antipsychotics use observed in our study underestimates the real burden of mental health disorders, especially depression and depressive symptoms. Our study had some limitations: the relatively small number of patients identified in the study explains the variability in the prevalence of use and consumption trends in subjects with hemophilia. Some variables that are significant predictors of depression, such as the severity of hemophilia, persistent pain, and joint impairment, were not considered. The definition of subject with haemophilia based on diagnosis in hospital care and prescriptions of factor VIII or factor IX concentrates includes also female carriers of hemophilia. Moreover, the broad inclusion criteria could include people with other bleeding disorders where hemophilia A or B had been registered with an uncorrected code. Finally, information about diagnosis of depression and psychotic disorders was unavailable.

Despite these limitations, we believe this study is of particular importance as it provides data on the use of antidepressants and antipsychotics in subjects with haemophilia. A strength of the study is that information on all filled prescriptions for drugs used in the management of depression, and psychosis was available during the 12-year study period.

CONCLUSIONS

Despite significant improvements in morbidity and mortality outcomes, the quality of life for subjects with haemophilia remains endangered, with emerging evidence suggesting that chronic diseases are associated

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with mental health disorders. In addition to direct or indirect impact that mental health disorders have on physical health of subjects, some evidence includes depression and anxiety among modifiable factors that can decrease adherence to factor replacement therapy, thus increasing the risk of disease complications [26, 27]. This study suggests that mental health disorders, such as depression and psychosis, are relevant comorbidities in subjects with hemophilia and should be considered by clinicians to ensure appropriate treatment and improve patients' quality of life. Although our sample size was sufficient considering the prevalence of haemophilia, the generalizability of the results should be interpreted with caution. Further studies with larger, preferably multicenter, regional, or national cohorts are warranted to validate these findings and establish more robust conclusions.

Authors' contributions

GM, RA and RDC designed the study. RER, GB and MR retrieved and prepared the data. RDC, MC, AA and GM carried out the statistical analysis. GM, RA, RER, AA, MC, GB, RDC and MR wrote the manuscript. All Authors critically revised and approved the final version of the manuscript. The corresponding Author attests that all listed Authors meet authorship criteria and that no others meeting the criteria have been omitted.

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