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Iatrogenic triggers for anorexia nervosa and bulimia nervosa: A WHO safety database disproportionality analysis

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ABSTRACT

Eating disorders, characterized by abnormal eating, weight control behaviors or both include anorexia nervosa (AN) and bulimia nervosa (BN). We investigated their potential iatrogenic triggers, using real-world data from the WHO safety database (VigiBase®). VigiBase® was queried for all AN and BN reports. The reports were classified as 'pediatric' or 'adult' according to age. Disproportionality analyses relied on the Information Component (IC), in which a 95% confidence interval lower-end positivity was required to suspect a signal. Our queries yielded 309 AN and 499 BN reports. Isotretinoin was disproportionately reported in pediatric AN (IC 3.6; [2.6–4.3]), adult AN (IC 3.1; [1.7–4.0]), and pediatric BN (IC 3.9; [3.0–4.7]). Lamivudine (IC 4.2; [3.2–4.9]), nevirapine (IC 3.7; [2.6–4.6]), and zidovudine (IC 3.4; [2.0–4.3]) had the highest ICs in adult AN. AN was associated with isotretinoin, anticonvulsants in minors, and antiretroviral drugs in adults. In adults, BN was related to psychotropic and hormonally active drugs. Before treatment initiation, an anamnesis should seek out mental health conditions, allowing the identification of patients at risk of developing or relapsing into AN or BN. In addition to misuse, the hypothesis of iatrogenic triggers for AN and BN should also be considered.

1. Introduction

Eating disorders (EDs) represent a significant burden on patients, their families, and society resulting in the loss of over 3.3 million healthy life years worldwide (Galmiche et al., 2019; Devoe et al., 2023; van Hoeken and Hoek, 2020). Their prevalence has increased over the last few decades, further amplified by the COVID-19 pandemic (Devoe et al., 2023). EDs are the third most common chronic illness among adolescents. They are characterized by abnormal eating and/or weight control behaviors (Gonzalez et al., 2007; Treasure et al., 2020). EDs are inheritable through intertwining genetic factors, breeding patterns, and peer or social media pressures (Castillo and Weiselberg, 2017). However, as treatment possibilities are developing, access to care remains challenging (Castillo and Weiselberg, 2017; Hay, 2020; Herpertz-Dahlmann

and Dahmen, 2019; Werz et al., 2021).

In anorexia nervosa (AN) and bulimia nervosa (BN), body image, through the overvaluation of weight and shape, is essential to a patient's self-view (Hay, 2020). Therefore, patients are prone to moving from one disease to another (Castillo and Weiselberg, 2017). The lifetime prevalence of AN is 0.5%–1%, with a clear predominance in women (sex ratio 8:1) (Zipfel et al., 2015). Its diagnosis relies on a restriction of energy intake (and a subsequent loss of weight), an intense fear of gaining weight or becoming fat, and body image disturbance (DSM-5TM, 2013). Amenorrhea, resulting from hypothalamic-pituitary dysfunction, is often a core symptom of this disorder (Attia and Roberto, 2009). One-fifth of AN-related fatalities are caused by suicide (Arcelus et al., 2011). In contrast, the lifetime prevalence of BN ranges from 0.9% to 3%, with a lower female dominance (sex ratio 3:1) (Campbell and

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Peebles, 2014). BN involves recurrent episodes of binge eating, inappropriate compensatory behaviors, and the contingency of self-confidence in weight and shape (Herpertz-Dahlmann and Dahmen, 2019).

Some authors consider both AN and BN as syndromes resembling addiction, given the relentlessness with which individuals pursue starvation, bingeing episodes, or both, and the narrowing of their behavioral repertoire (Barbarich-Marsteller et al., 2011; Hudson et al., 2007). Abnormal neurotransmission, mostly involving dopamine, has been investigated under shared neurobiology (Hadad and Knackstedt, 2014; Kaye et al., 2013; Umberg et al., 2012).

Consistently, there is a high rate of comorbidity between AN, BN, substance abuse, food restriction/bingeing episodes, and drugs of abuse that reciprocally modulate their reinforcing effects (Barbarich-Marsteller et al., 2011; Carr, 2002; Kaye et al., 2013). More than one-third of patients with BN have a substance use disorder, often stemming from impulsivity and attempts to control weight (Bahji et al., 2019; Castillo and Weiselberg, 2017; Nagata et al., 2002). Similarly, AN may precede the onset of substance use disorders, indicating that patients with AN may initially engage in substance use to enhance weight loss (Baker et al., 2010).

In this context, there is a high prevalence of misuse of various drugs, such as laxatives, diuretics, amphetamine derivatives, metformin, topiramate, orlistat, and thyroid hormone supplements, often leading to detrimental effects (Castillo and Weiselberg, 2017; Crow et al., 1997; Geer et al., 2019; Halmi et al., 1991; Kakunje et al., 2020; Kovacs and Palmer, 2004; Mehler, 2011; Roerig et al., 2010; Sharma and Kar, 2015; Welch and Fairburn, 1996; Westmoreland et al., 2016; Wiederman and Pryor, 1996). Fornari et al. emphasized the importance of drug consumption in diagnosing BN, including the possibility of intentional substance and drug misuse/abuse, with a weight control/loss objective. They considered the following situations: 1) drugs prescribed for the treatment of given medical conditions that deviated from their original purpose, 2) drugs not prescribed for a person and taken improperly, and 3) illegal substances taken to lose weight (Fornari et al., 1990). Indeed, there is growing evidence that drug misuse/abuse and eating behaviors influence each other, particularly via the regulation of the monoaminergic system (Clineschmidt and Bunting, 1980; Cole, 1978; Khera et al., 2016; Merino et al., 2022; Menkes, 1992). For instance, the severity of caloric restriction predicted psychostimulant use irrespective of the ED type (Wiederman and Pryor, 1996). Laxative-abusing patients tend to exhibit body dissatisfaction, a drive for thinness, and depressive and somatic symptoms (Kovacs and Palmer, 2004).

These misuse situations are often difficult to distinguish from cases of ED potentially induced by drug consumption. As the causes and consequences of AN and BN are difficult to differentiate, we aimed to distinguish self-medication as a compensatory behavior from using treatments, possibly leading to the onset/relapse of AN or BN. In this respect, our objective was to investigate the potential iatrogenic factors contributing to anorexia nervosa and bulimia nervosa. For this purpose, we relied on disproportionality analyses of the World Health Organisation (WHO) safety database (VigiBase®, Uppsala Monitoring Centre, Sweden) (Lanteri et al., 2018; Lindquist, 2008).

2. Methods

2.1. Data source

The WHO mandates that the Uppsala Monitoring Centre (UMC) oversees drug safety and gathers evidence about adverse drug reactions (ADRs), potentially leading to the identification of safety signals (Centre, n.d.; Uppsala Monitoring Centre, n.d.). Since 1967, Individual Case Safety Reports issued by more than 172 national pharmacovigilance network members and pharmaceutical companies have been gathered by VigiBase®. VigiBase® ensures anonymity for both patients and notifiers (Lindquist, 2008). According to French clinical research

law, review by an ethics committee is not required for observational studies such as ours. Informed consent was not required because all data from VigiBase® were de-identified.

Each Individual Case Safety Report (ICSR) contains sociodemographic characteristics of the patient (age, sex), administrative information (country, reporter qualification), suspected drug(s) (indication (s), start and cessation dates, dose), other drug(s) administered (concomitant), and characteristics of adverse drug reactions (s) (reaction(s), seriousness, onset, and outcome). An ADR is defined as an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product, which usually predicts hazards from future administration and warrants prevention, specific treatment, or alteration of the dosage regimen, or withdrawal of the product (Aronson and Ferner, 2005). From a pharmacovigilance perspective, an ADR is deemed serious if it requires hospitalization or prolongation, causes a congenital malformation results in persistent or significant disability or incapacity, is life-threatening, results in death, or requires significant medical intervention to prevent one of these outcomes (FDA, n.d.; Gautron et al., 2018).

2.2. Query

According to the Medical Dictionary for Regulatory Activities (MedDRA, version 25.1), a Standardised MedDRA Query (SMQ) is an exhaustive, validated, predetermined collection of Preferred Terms (PTs) intended to help in investigating drug safety issues in pharmacovigilance ("Standardised MedDRA Queries | MedDRA," n.d.). A PT is a distinct descriptor for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical, social, or family history characteristic (MedDRA, n.d.).

We first queried VigiBase® for all reports featuring the PT 'Anorexia Nervosa' registered between November 14, 1967 (first reports in VigiBase®) and February 13, 2023. By applying the same method, cases involving the PT 'Bulimia Nervosa' were also gathered. Then, queried reports involving patients under 18 were classified into a 'pediatric population' category, whereas older patients were classified into an 'adult population' category. These groups were further subdivided as follows:

- Pediatric population
 - o Infants: 0 days to 23 months
 - o Children: 2 to 11 years
 - o Adolescents: 12 to 17 years
- Adult population
 - o Young adults: 18 to 44 years
 - o Middle-aged adults: 45 to 64 years
 - o Elderly: ≥ 65 years

Cases were classified according to the year of notification to assess the evolution of AN and BN reporting. We aimed to detect potential notoriety biases associated with specific periods.

2.3. Primary analyses

Qualitative variables are described using proportions. Quantitative variables were described as means with standard deviations (\pm SD). Statistical analyses were performed using the R software (version 4.1.2).

After that, a disproportionality analysis was performed (Bate and Evans, 2009). Using each ED (AN or BN) age category (pediatric or adult population) combination, potential drug safety signals were sought for each drug, accounting for the following:

- At least 3 cases if the total number of cases was \leq 75
- At least 5 cases if the total number of cases was \geq 75

In pharmacovigilance, disproportionality analyses are used to detect

and assess drug safety signals (Bate and Evans, 2009; Gahr et al., 2015). The superiority of the proportion of reports involving a specific ADR and a given drug (cases) over the proportion of reports with the same ADR and other drugs (non-cases) suggests an association between this drug and ADR. The Information Component (IC) compares the observed and expected values for any drug-ADR combination, enabling us to check for a potential association. The UMC has validated this tool (Bate et al., 1998; Lindquist, 2008). Especially in the case of a low expected ADR frequency in the database, the IC favors reducing the risk of false-positive signals, allowing for more specific signal detection than other measures, such as the reporting odds ratio (van Puijenbroek et al., 2002). The positivity of IC indicates that the number of observed reports was higher than expected. The lower boundary of the 95% confidence interval (CI) of the IC, called $IC_{0.25}$, must be positive by the UMC to statistically confirm the detection of a signal in VigiBase® (Bate et al., 1998; Lindquist, 2008).

In this disproportionality analysis, potential drug-ADR associations were selected using $IC_{0.25}$, calculated using R (version 4.1.2).

2.4. Secondary Analyses

2.4.1. Assessment of misuse and abuse

As patients are prone to drug misuse (weight loss or compensatory behaviors) and drug abuse (with high rates of addictive comorbidities), we aimed to distinguish between potentially contributing iatrogenic factors and consumption related to EDs or comorbid drug abuse. For this purpose, we queried VigiBase® for all reports featuring both narrow SMQ 'drug abuse, dependence and withdrawal' and the PT of the ED of interest (either AN or BN). The information contained in the ICSRs was collected as previously described. The proportion of reports coded with abuse and AN or BN was calculated, and these cases were retained for the general disproportionality analysis. Our objective was to investigate

reports that combined these two subtypes of addictive disorders more accurately.

2.4.2. Cases issued by healthcare professionals

We performed additional disproportionality analyses of the cases issued by healthcare professionals to mitigate potential coding heterogeneity and increase the specificity of our findings. Therefore, another disproportionality analysis was conducted on AN and BN reports that met this criterion. The methodology used is described above (see Primary analyses).

3. Results

3.1. Anorexia nervosa

3.1.1. Overall characteristics

As of February 13, 2023, the 'Anorexia Nervosa' query in VigiBase® yielded 309 reports, mainly involving females (224, 77.5%). Young adults (aged 18 to 44 years) were the most represented age group (101, 32.7%), and the United States of America provided approximately one-third of the reports (100, 32.4%). Healthcare professionals reported most of the cases (206, 66.7%). Isotretinoin was the most frequently used drug (21, 6.8%), followed by COVID-19 vaccines (15, 4.9%), topiramate (13, 4.2%), and lamivudine (11, 3.6%). Overall, 177 (57.3%) cases were deemed serious, 13 of whom were fatalities (4.2%). When the outcome was available (163, 52.8%), the majority of patients recovered or were recovering at the time of the analysis (96, 58.9%), 54 (33.1%) did not recover, and four (2.4%) had recovered with sequelae. The distribution of AN reports showed a peak in notifications from 2012 to 2014, as displayed in Fig. 1. The most frequently reported drugs among the 35 AN cases reported in 2013 were clobazam (6, 17.1%), carbamazepine (5, 14.3%), and valproic acid (4, 11.4%) (Table 1).

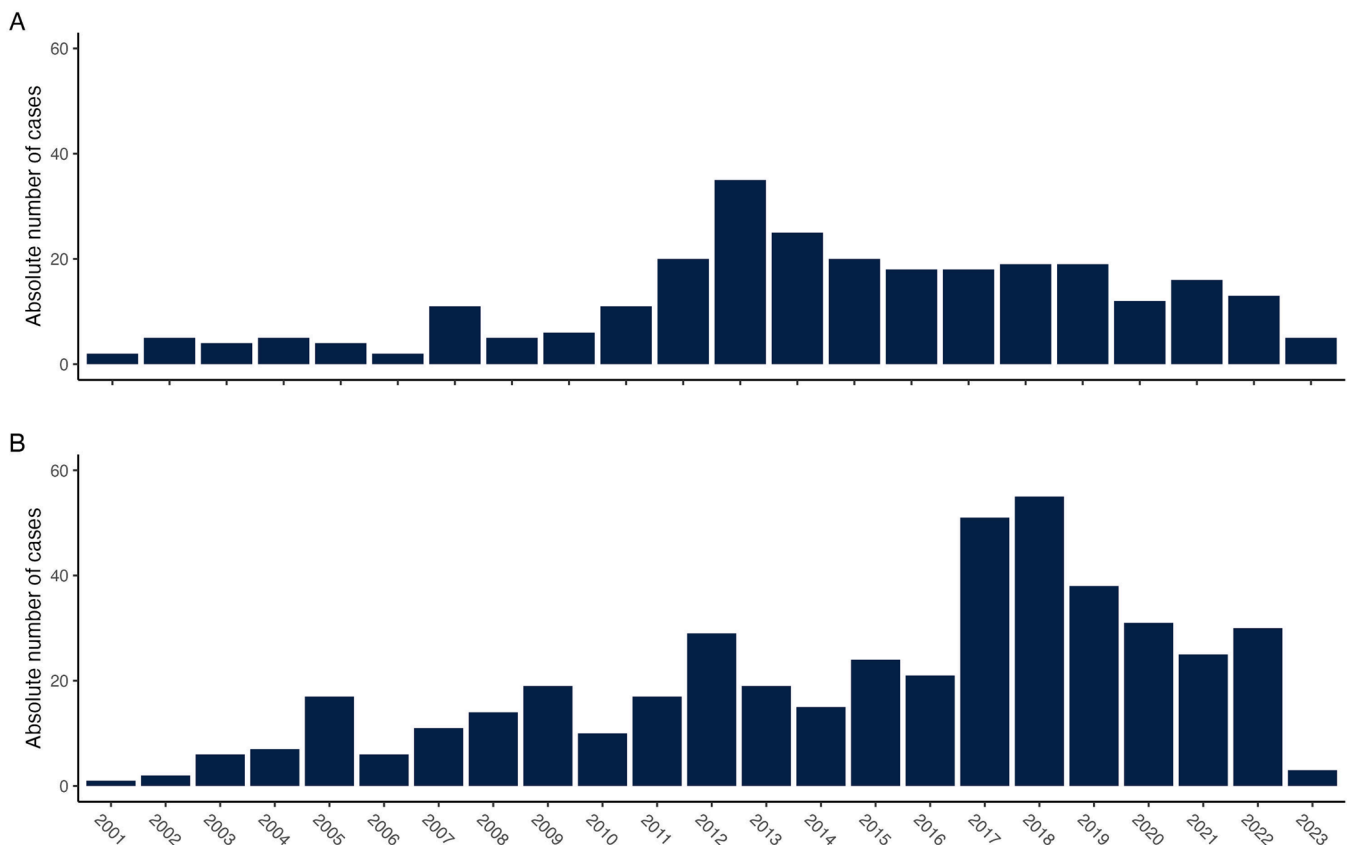


Fig. 1. Temporal distribution of notification of cases of anorexia nervosa (A) and bulimia nervosa (B).

Table 1
Characteristics of the reports of patients.

Characteristics	Number of reports (%)			
	Anorexia nervosa		Bulimia nervosa	
Age category	Pediatric	Adult	Pediatric	Adult
Total	79 (100)	174 (100)	51 (100)	291 (100)
Sex				
Female	56 (70.9)	134 (77.0)	35 (68.6)	235 (80.8)
Male	22 (27.8)	38 (21.8)	14 (27.5)	53 (18.2)
Unknown	1 (1.3)	2 (1.1)	2 (3.9)	3 (1.0)
Age group				
Infants	1 (1.3)		2 (4.0)	
Children	22 (27.8)		8 (15.7)	
Adolescents	56 (70.9)		41 (80.4)	
Young adults		101 (58.0)		151 (51.9)
Middle-aged adults		45 (25.9)		107 (36.8)
Elderly		28 (16.1)		33 (11.3)
Unknown	56 (18.1)		157 (31.5)	
Region				
Region of the Americas	29 (36.7)	42 (24.1)	31 (60.7)	85 (29.2)
Eastern Mediterranean Region		3 (1.7)		1 (0.3)
European Region	27 (34.1)	56 (32.1)	16 (31.4)	183 (62.9)
South-East Asia and Western Pacific Region	22 (27.8)	56 (32.1)	4 (7.8)	17 (5.8)
African Region	1 (1.3)	17 (9.8)		7 (2.4)
Reporter qualification				
Healthcare professional	59 (74.7)	117 (67.2)	38 (74.5)	164 (56.4)
Physician	22 (27.8)	65 (37.4)	23 (45.1)	118 (40.5)
Pharmacist	2 (2.5)	25 (14.4)	3 (5.9)	22 (7.6)
Other Health Professional	35 (44.3)	27 (15.5)	12 (23.5)	24 (8.2)
Others	9 (11.4)	41 (23.5)	19 (37.3)	121 (41.5)
Lawyer		1 (0.6)	5 (9.8)	9 (3.1)
Consumer	9 (11.4)	40 (23.0)	14 (27.5)	112 (38.5)
Unknown	14 (17.7)	29 (16.7)	6 (11.8)	33 (11.3)

3.1.2. Pediatric population

One-quarter of the anorexia nervosa reports involved the pediatric population (79, 25.1%), with a majority of adolescents (aged between 12 and 17 years) (56, 70.9%) and a mean age of 10.6 (±4.4) years. The mean recorded weight was 27.9 kg (±16.8). Weight loss (12 patients, 15.2%), depression (11 patients, 13.9%), and amenorrhea (5, 6.3%) were the most frequently reported symptoms. Suicidal ideation and attempts accounted for two (2.7%) and one (1.3%) case(s), respectively. The most frequently reported drugs were isotretinoin (11, 13.9%), topiramate (8, 10.1%), the HPV vaccine (8, 10.1%), and valproic acid (6, 7.6%). The co-reported drugs included lorazepam (11, 3.8%), fluoxetine (9, 3.1%), and citalopram (8, 2.7%).

In this age group, more than half of the cases were deemed serious (51, 64.6%), among which 24 (30.4%) involved hospitalizations, six (7.6%) were disabling, and two (2.5%) were life-threatening reactions. When follow-up data were available (46, 58.2%), most patients recovered or were recovering (31, 67.4%), whereas 14 (30.4%) did not recover.

Topiramate (IC 3.8; 95% CI:2.6–4.6) and isotretinoin (IC 3.6; 95% CI:2.6–4.3) were leading in disproportionality, as shown in Table 2.

Table 2
Disproportionality analysis of reports involving pediatric and adult populations with anorexia nervosa.

Pediatric population		
Active Ingredient	Number of reports (%)	IC [95%CI]
Isotretinoin	11 (13.9)	3.6 [2.6–4.3]
Topiramate	8 (10.1)	3.8 [2.6–4.6]
HPV vaccine ^a	8 (10.1)	1.5 [0.3–2.3]
Valproic acid	6 (7.6)	2.7 [1.3–3.6]
Clobazam	5 (6.3)	3.3 [1.7–4.3]
Adult population		
Active Ingredient	Number of reports (%)	IC [95%CI]
Lamivudine	11 (6.3)	4.2 [3.2–4.9]
Nevirapine	8 (4.6)	3.7 [2.6–4.6]
Zidovudine	6 (3.4)	3.4 [2.0–4.3]
Isotretinoin	6 (3.4)	3.1 [1.7–4.0]
Esomeprazole	5 (2.9)	2.5 [1.0–3.5]

^a HPV: Human Papillomavirus.

3.1.3. Adult population

Among anorexia nervosa cases, more than half occurred in the adult population (174, 56.3%), including a majority of young adults (101, 58.0%), with a mean age of 39.3 (±18.3) years and a weight of 55.6 kg (±15.6).

The main co-reported symptoms were depression (23, 13.2%), weight decreased (20, 11.5%), and asthenia (14, 8.0%). Suicidal ideation was noted in five (2.9%) patients, and suicide attempts were reported in three (1.7%) patients. In terms of the absolute number of reports, 11 were involving lamivudine (6.3%), nine involved COVID-19 vaccines (5.2%), eight involved nevirapine (4.6%), and six involved zidovudine (3.4%). Valproic acid, folic acid, and metoclopramide were co-reported in 2 (3.9%) cases.

Regarding seriousness, 85 (48.9%) reports were deemed serious, including 56 (32.2%) hospitalizations, 14 (8.0%) disabling reactions, nine (5.2%) life-threatening reactions, and nine (5.2%) fatalities. Among the cases displaying follow-up (93, 53.4%), more than half recovered or were recovering (54, 58.1%), whereas less than one-third did not (30, 32.3%). The strongest disproportionality signals were reached by antiretroviral drugs (ARTs) lamivudine, nevirapine, and zidovudine, shown in Table 2.

3.2. Bulimia nervosa

3.2.1. Overall characteristics

Our VigiBase® query using the 'Bulimia Nervosa' term yielded 499 cases, with a majority of women (394, 79.0%). Young adults were the prevailing age group (151, 30.3%). Nearly one-third of the cases originated in the United States (164, 32.9%), and more than half were issued by healthcare professionals (236, 52.7%). Levothyroxine (45, 9.0%), isotretinoin (24, 4.8%), olanzapine (21, 4.2%), and quetiapine (19, 3.8%) were mainly involved. Nearly half of the cases were considered serious (247, 49.5%), including nine fatalities (1.8%). Among cases displaying an outcome (235, 47.1%), most patients recovered or were recovering (126, 53.6%), 103 (43.8%) did not recover, and four (1.7%) recovered with sequelae. Since 2017, a trend toward an increase in BN reporting has been observed, as shown in Fig. 1. Indeed, in 2018, 55 new cases of BN were collected in VigiBase®, among which 18 (32.7%) involved levothyroxine.

3.2.2. Pediatric population

The pediatric population was involved in 51 (10.2%) bulimia nervosa reports. Although adolescents accounted for over three-quarters of the cases (41, 80.4%), the mean patient concerned was 11.0 (±4.1) years. The mean recorded weight was 55.5 kg (±16.3). The main co-reported symptoms were depression (12, 23.5%), weight increased

(11, 21.6%), and decreased appetite (10, 19.6%). Suicidal ideation and attempts accounted for seven (13.7%) and five (9.8%) cases, respectively. Regarding number of reports, isotretinoin (12, 23.5%) was followed by topiramate (9, 17.6%), valproic acid (4, 7.8%), and sertraline (3, 5.9%). The co-reported drugs included sulfamethoxazole, trimethoprim (10, 5.7%), levothyroxine (7, 4.0%), and alprazolam (6, 3.4%).

Seriousness criteria were met in 31 (60.8%) cases, including 11 (21.6%) hospitalizations, four (7.8%) disabling reactions, four (7.8%) congenital anomalies, three (5.9%) life-threatening reactions, and one fatality (0.2%). In cases displaying follow-up (16, 31.4%), most patients did not recover (9, 56.3%), whereas six (37.5%) recovered or were recovering at the time of the analysis.

Topiramate (IC 4.1; 95% CI:3.0–4.9) and isotretinoin (IC 3.9; 95% CI:3.0–4.7) accounted for the strongest potential signals regarding disproportionality analysis, as displayed in [Table 3](#).

3.2.3. Adult population

Adult cases of bulimia nervosa accounted for 58.3% (291) of the total number of reports. Young adults were involved in more than half of the reports (151, 51.9%), with a mean age of 40.5 (± 15.9) years. The mean recorded weight was 69.7 kg (± 24.2). Weight increased (60, 20.6%), depression (54, 18.6%), and insomnia (35, 12.0%) were the most frequently reported terms. Suicidal ideation was noted in 20 (6.9%) patients and suicide attempts were reported in five (9.8%) patients. Levothyroxine (16, 5.5%), quetiapine (14, 4.8%), olanzapine (13, 4.5%), and aripiprazole (10, 3.4%) were the most frequently reported drugs. Nystatin, amlodipine, and valganciclovir were co-reported in three (3.8%) cases.

Among the reports considered serious (135, 46.4%), 41 (14.1%) hospitalizations, 13 (4.5%) disabling reactions, 11 (3.8%) life-threatening reactions, two (0.7%) congenital anomalies, and five (1.7%) fatalities were reported. When outcomes were available (159, 54.6%), the majority of patients recovered or were recovering (92, 57.9%), 64 (40.3%) did not recover, and two (1.3%) recovered with sequelae. Pramipexole (IC 4.1; 95% CI:3.1–4.9) and levothyroxine (IC 3.6; 95% CI:2.8–4.2) reached the highest signals.

Potential safety signals detected using disproportionality analyses are summarized in [Figs. 2 and 3](#).

Table 3
Disproportionality analysis of reports involving children and adults with bulimia nervosa.

Pediatric population		
Active Ingredient	Number of reports (%)	IC [95%CI]
Isotretinoin	12 (23.5)	3.9 [3.0–4.7]
Topiramate	9 (17.6)	4.1 [3.0–4.9]
Valproic acid	4 (7.8)	2.5 [0.7–3.5]
Sertraline	3 (5.9)	2.5 [0.5–3.7]
Adult population		
Active Ingredient	Number of reports (%)	IC [95%CI]
Levothyroxine	16 (5.5)	3.6 [2.8–4.2]
Quetiapine	14 (4.8)	3.4 [2.6–4.1]
Olanzapine	13 (4.5)	3.5 [2.6–4.2]
Aripiprazole	10 (3.4)	3.5 [2.5–4.2]
Pramipexole	10 (3.4)	4.1 [3.1–4.9]
Fluoxetine	9 (3.1)	3.0 [1.9–3.8]
Mirtazapine	9 (3.1)	3.5 [2.4–4.3]
Levonorgestrel	8 (2.7)	1.7 [0.6–2.6]
Valproic acid	6 (2.1)	2.5 [1.1–3.4]
Drospirenone; Ethinylestradiol	6 (2.1)	2.7 [1.3–3.7]
Paliperidone	6 (2.1)	3.1 [1.7–4.0]
Sertraline	5 (1.7)	2.2 [0.7–3.2]
Bupropion	5 (1.7)	2.3 [0.8–3.3]
Zolpidem	5 (1.7)	2.6 [1.1–3.6]
Venlafaxine	5 (1.7)	2.3 [0.8–3.3]
Semaglutide	5 (1.7)	3.0 [1.5–4.0]

3.3. Secondary analyses

3.3.1. Assessment of misuse and abuse

Among the 309 AN cases gathered in VigiBase®, six (1.9%) also belonged to the SMQ 'drug abuse, dependence and withdrawal'. All of these cases were considered serious. Half (3, 50%) of the cases involved adolescents, whereas the other half involved young adults. The cases were shared equally between the sexes (three cases each). Codeine and hydrocodone were the most frequently reported drugs (two cases each). Among these cases, one was recorded as the result of intentional product misuse involving dexamfetamine, alprazolam, and sodium oxybate.

Out of the 499 bulimia nervosa reports collected, 24 (4.8%) were coded as cases potentially involving drug abuse or dependence. Most of these cases (23, 95.8%) were deemed serious. Most patients were women (20, 83.3%), with a predominance of young and middle-aged adults (five cases each). Quetiapine (six cases, 25.0%), sertraline (three cases, 12.5%), and fluoxetine (three cases, 12.5%) were noted. Among these reports, two were related to drug misuse, with one case involving quetiapine and one involving the laxative bisacodyl.

3.3.2. Cases issued by healthcare professionals

Healthcare professionals reported 201 out of the 309 AN cases yielded in VigiBase®. ARTs such as lamivudine, nevirapine, and zidovudine are still disproportionately reported in this ED. Healthcare professionals notified 256 cases of BN. Pramipexole, zolpidem, and olanzapine signals were also detected. The anticonvulsants topiramate and valproic acid, as well as isotretinoin were still disproportionately reported for both AN and BN, as shown in [Table 4](#).

4. Discussion

4.1. Overall

Our analysis of the WHO pharmacovigilance database sheds light on age-dependent profiles and drugs potentially associated with AN and BN. Indeed, in the pediatric population, both EDs were associated with isotretinoin, topiramate, and valproic acid. In the adult population, AN was mostly imputed to ARTs, whereas BN involved several drug classes, such as atypical antipsychotics (AAPs), antidepressants, and hormonal contraceptives. Isotretinoin exhibited potential signals for AN (in both populations) and BN in the pediatric population. The main concern was to distinguish the drugs potentially triggering AN or BN from those used in the context of compensatory behaviors ([Fig. 4](#)). No signals involving laxatives or diuretics, often used for weight control, were detected.

4.2. Pediatric population

The drug label of isotretinoin mentions the possibility of psychiatric ADRs such as depression, psychosis, suicidal ideation, and aggressive behaviors, which warrants a preliminary interview regarding the history of psychiatric disorders in patients. In addition, their potential occurrence must be monitored and assessed during follow-up visits ([FDA, n.d.](#)). Our study strengthens the previous findings on ED imputed to isotretinoin ([Singer et al., 2019](#)). Since psychiatric disorders are well-known promoters of EDs, patients treated with isotretinoin may show decreased self-esteem (due to persistent acne). In that respect, body image control might be a greater preoccupation in these patients, further increasing the risk of AN and BN ([Öner and Hacinecioglu, 2022](#)). In both EDs, a secondary analysis focusing on healthcare professionals' reports concurred with our primary findings.

The antiepileptic drug topiramate can trigger psychiatric ADRs such as mood disorders, anxiety, and anorexia ([FDA, n.d.](#)). Its potential association with BN seems consistent with the drug label, as AN and BN are likely to exist on a pathophysiological continuum in the same patient, depending on cognitive flexibility and impulse control ([Howard et al., 2020](#)). Its combination with phentermine obtained marketing

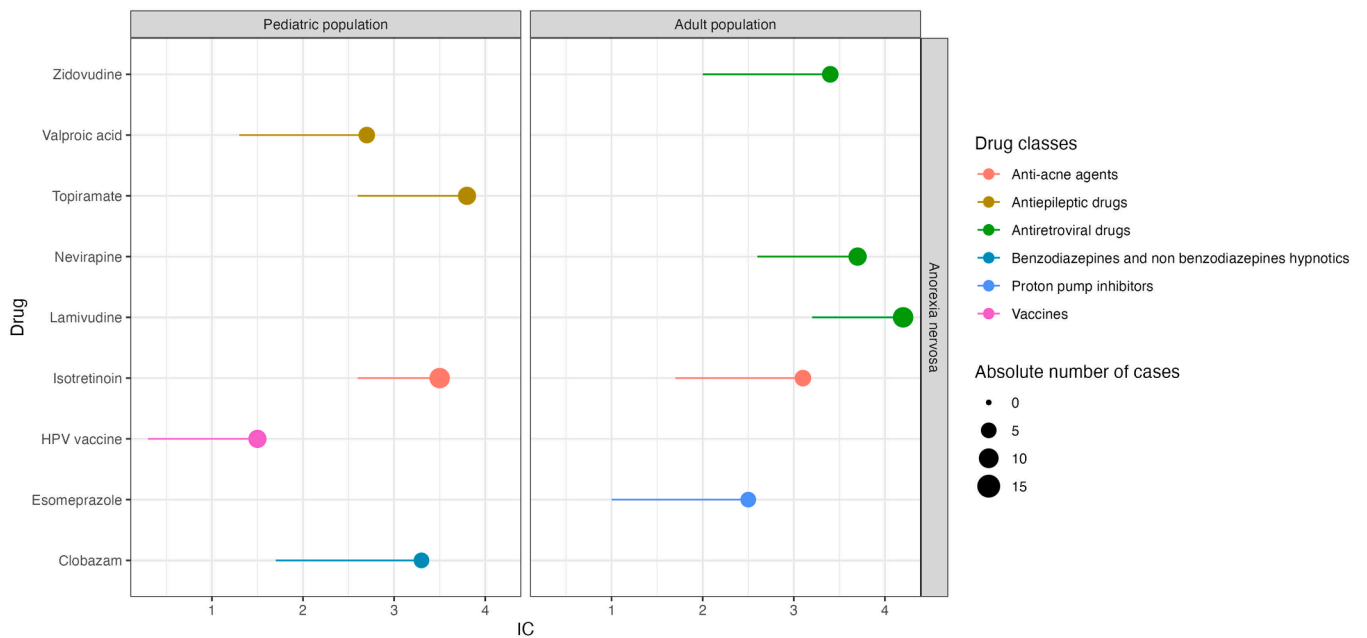


Fig. 2. Summary of disproportionality analyses of anorexia nervosa.

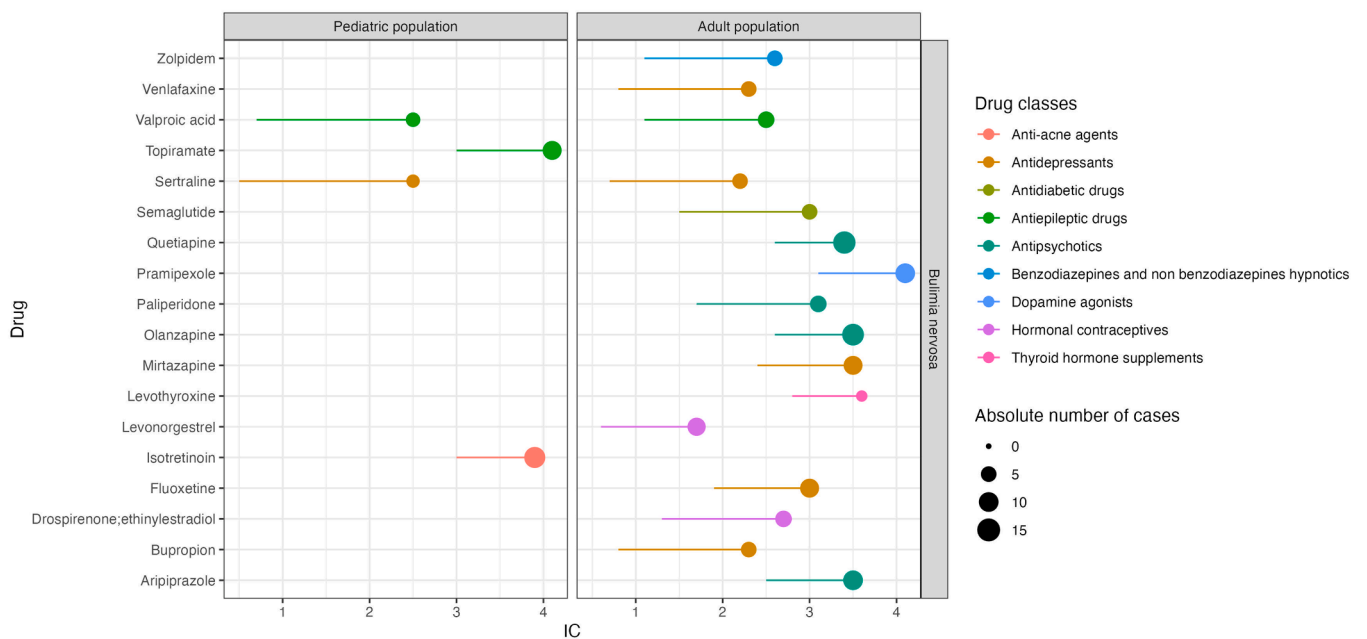


Fig. 3. Summary of disproportionality analyses of bulimia nervosa.

authorization from the Food and Drug Administration (FDA) in 2011 to treat obesity (FDA, n.d.). However, topiramate is also considered a promising approach for the treatment of BN, binge-eating disorder (BED), and substance abuse (especially alcohol and cocaine use disorders) (Himmerich et al., 2021; Nouredine et al., 2021). The use of topiramate in these conditions may be a confounding factor, as patients with AN and BN are predisposed to other addictive disorders, and topiramate may be misused for weight loss or control purposes (Herpertz-Dahlmann and Dahmen, 2019; Kakunje et al., 2020; Khera et al., 2016).

Valproic acid is an antiepileptic drug used as a mood stabilizer, which exhibited potential safety signals in our study. It can trigger psychiatric alterations such as psychosis, psychomotor hyperactivity, and aggressive behaviors, especially in the pediatric population

(Depakene - FDA-Approved Drugs, n.d; Résumé des caractéristiques du produit - DEPAKOTE 250 mg, comprimé gastro-résistant - Base de données publique des médicaments, n.d). Valproic acid has been investigated as a treatment option for AN and could effectively alleviate psychiatric comorbidities (e.g., mood disorders) of AN and BN (McElroy et al., 2009; Prucoli and Parmeggiani, 2022). However, its association with weight gain suggests a possible link to the onset of bulimic symptoms. Our disproportionality analysis of notifications from healthcare professionals supported signals involving both antiepileptic drugs.

Clobazam, an antiepileptic benzodiazepine, accounts for a potential signal in AN afflicting the pediatric population. Frequently consumed in the context of substance abuse disorders, the risk of dependence it underpins, in addition to potential weight loss during withdrawal, may foster excessive concerns about the food (FDA, n.d.). Additionally,

Table 4
Disproportionality analysis of reports of anorexia nervosa and bulimia nervosa issued by healthcare professionals.

Anorexia nervosa		
Active Ingredient	Number of reports (%)	IC [95%CI]
Lamivudine	11 (5.5)	3.9 [3.0–4.7]
Topiramate	11 (5.5)	3.9 [2.9–4.6]
Isotretinoin	10 (5.0)	3.4 [2.4–4.2]
Nevirapine	8 (4.0)	3.5 [2.3–4.3]
Tacrolimus	8 (4.0)	2.8 [1.6–3.6]
Valproic acid	6 (3.0)	2.4 [1.0–3.3]
Zidovudine	6 (3.0)	3.1 [1.7–4.1]
Carbamazepine	6 (3.0)	2.5 [1.2–3.5]
Clozapine	6 (3.0)	1.5 [0.1–2.4]
Clobazam	6 (3.0)	3.5 [2.1–4.4]
Mycophenolic acid	5 (2.5)	2.3 [0.7–3.3]
Phenytoin	5 (2.5)	2.4 [0.9–3.4]
Bulimia Nervosa		
Active Ingredient	Number of reports (%)	IC [95%CI]
Topiramate	12 (4.7)	3.9 [3.0–4.6]
Olanzapine	11 (4.3)	3.2 [2.3–4.0]
Isotretinoin	10 (3.9)	3.3 [2.2–4.0]
Pramipexole	10 (3.9)	4.1 [3.1–4.9]
Aripiprazole	9 (3.5)	3.1 [2.0–3.9]
Valproic acid	8 (3.1)	2.6 [1.4–3.4]
Fluoxetine	7 (2.7)	2.9 [1.7–3.8]
Zolpidem	6 (2.3)	2.8 [1.4–3.7]
Quetiapine	6 (2.3)	2.4 [1.0–3.3]
Bupropion	6 (2.3)	2.8 [1.5–3.8]
Methylphenidate	6 (2.3)	2.9 [1.5–3.8]
Mirtazapine	5 (2.0)	2.7 [1.2–3.7]

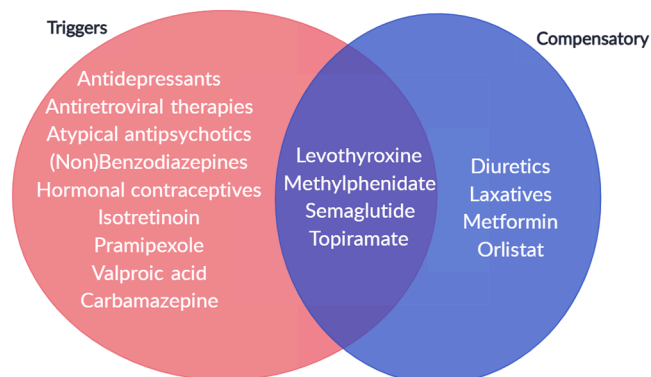


Fig. 4. Summary of potential drugs triggering anorexia nervosa or bulimia nervosa, misused in compensatory behaviors or both.

anxiolytic drugs are often consumed in the context of drug abuse comorbid with EDs. In such situations, the risk of transfer, multiple addictions, or both is not rare and must be considered.

4.3. Adult population

ARTs are the main safety signals in adult populations with AN. Indeed, people living with HIV or AIDS (PLWHA) may experience ART-induced lipodystrophy (Guzman and Vijayan, 2022). Eventually, having to face body ideal transgression, PLWHA subjected to such body changes may exhibit a desire for thinness and compensatory behaviors (Kelly et al., 2009). In this context, PLWHA may also be considered at risk for AN (and other EDs). All these signals were strengthened by our analysis of healthcare professionals' reports.

Our safety database analysis of BN yielded four signals involving AAPs. As this class is prone to foster weight increase, olanzapine is (although controversially) considered a treatment option in AN

(FDA-Approved Drugs: Zyprexa, n.d.; Treasure et al., 2020; Zipfel et al., 2015). AAPs enhance cognitive restraint (a key factor in ED development), disinhibition, and susceptibility to hunger, which may promote the occurrence of BN in predisposed patients (Blouin et al., 2008). Similarly, five antidepressants exhibited potential signals for BN. While they usually trigger an increase in appetite, multiple attempts at the pharmacological treatment of EDs (including binge behaviors) have been made, some of which have been successful (e.g., fluoxetine in BN and bupropion in BED) (FDA, n.d.; Himmerich et al., 2021; White and Grilo, 2013). However, depressive symptoms are known to be either a cause or a consequence of BN (Himmerich et al., 2021) and may partly confound these signals.

Additionally, we found a safety signal for the association between levothyroxine and BN. Hyperthyroidism may promote the transition from AN to BN in predisposed patients, by reducing the inhibition (Fonseca et al., 1990; Schmidt and O'Donoghue, 1992). Conversely, a correlation has been found between caloric intake (during binge episodes) and TSH levels, suggesting that food bingeing may stimulate thyroid activity (Altemus et al., 1996; Spalter et al., 1993). In addition to the potential misuse derived from the desire for weight control, inappropriate levothyroxine dosages may have contributed to the emergence of this signal. However, in 2017 in France, changes in excipients of the main brand name thyroid hormone supplement led to a massive upsurge in notifications, which may have explained the peak of BN reporting in the following period (Fig. 1) (Romani et al., 2022). However, our secondary analysis, focusing on the healthcare professionals' notifications, did not support this signal.

Hormonal contraceptives, which accounted for two signals in our study, may also trigger BN. As they tend to foster affect lability and increase appetite and weight, a decreasing effect on cholecystokinin concentrations (carrying a satiating effect) has been previously suggested (Metz et al., 2022). Drugs with high androgenic activity (such as levonorgestrel) may promote bulimic symptoms by reducing impulse control (FDA, n.d.; Hirschberg, 2012). Similarly, drugs that foster behavioral disinhibition, such as pramipexole (a dopamine agonist) or zolpidem (a non-benzodiazepine hypnotic drug), may increase the risk of loss of food control (Center for Drug Evaluation and, 2018; Merino et al., 2022).

4.4. Strengths and limitations

This study relied on a comprehensive and unprecedented analysis of the WHO safety database. Nonetheless, this is hindered by the inherent limitations of spontaneous reporting systems and post-marketing pharmacovigilance approaches, such as lack of follow-up and under-reporting (Hazell and Shakir, 2006). Furthermore, AN and BN are frequently subject to underdiagnosis (or misdiagnosis) and poor adherence to treatment, and the rates of reporting of these potential ADRs may have been substantially reduced (Falvey et al., 2021). Sometimes, these diagnoses may have been confounded by isolated persistent aphagia or polyphagia, worsening coding heterogeneity. The latter also affected co-reported terms; for instance, weight decrease was scarcely co-reported in AN, although greater percentages might be expected. The paucity of data in the ICSRs did not allow us to calculate body mass indices, that are relevant in analyzing eating disorders.

Potential confusion between the treatment and potential causation of the disease (e.g., topiramate (Castillo and Weiselberg, 2017), fluoxetine (Hay, 2020)) might have partially confounded our findings. Although the pharmacological aspects of some drugs may foster alterations in eating behaviors, the possibility of their misuse for weight control/loss purposes cannot be excluded. Nonetheless, regarding weight loss and compensatory behaviors, no signals involving laxatives or diuretics were found, and our analysis of healthcare professional reports did not confirm the levothyroxine signal. The latter strengthens our primary findings, supporting the potential contributions of ARTs, antiepileptic drugs, and isotretinoin. Therefore, the impact of these limitations should

not be overestimated. Outside the scope of VigiBase®, data regarding illegal substance consumption (particularly prevalent in BN) could not be considered in our analysis (Herpertz-Dahlmann, 2015).

Notwithstanding this limitation, the scarcity of reports on misuse or abuse supports the reliability of our findings. Some drugs (e.g., COVID-19 vaccines and levothyroxine), because of intense media coverage, may have been subject to the Weber effect, with a potentially undue increase in reporting (Romani et al., 2022). Overall, pharmacovigilance studies characterize potential drug safety signals rather than determining their causality. Further population-based studies should help reassess these outcomes.

5. Conclusions

In this study, based on a comprehensive analysis of anorexia nervosa and bulimia nervosa reports gathered from the WHO safety database, we raised awareness about the potential pharmacovigilance signals corresponding to different age categories. While AN was mostly associated with isotretinoin and anticonvulsants in the pediatric population, ARTs were the leading signal in the adult population. In adults and elderly patients, BN was associated with psychotropic drugs (AAPs and antidepressants) and hormonally active substances. We confirmed previous data regarding the possible involvement of isotretinoin and ARTs in EDs with an additional analysis focusing on the reporting of healthcare professionals.

Multiple authors have investigated drugs taken by patients with EDs as part of compensatory behaviors. Considering the complexity of the interactions between drug consumption and eating behaviors, we attempted to shed light on drugs likely to induce or worsen AN, BN, or both. In this respect, we broadened the assumptions of Fornari et al. and raised awareness on medications whose pharmacological properties could explain the emergence or strengthening of such disorders (Fornari et al., 1990). Before treatment initiation, careful anamnesis should seek a potential psychiatric history, allowing the identification of young patients at risk of developing AN or BN and older patients at risk of relapse. Conversely, in cases of new-onset (or recurrence) anorectic or bulimic symptoms, the hypothesis of an iatrogenic trigger should be considered, beyond drug misuse as part of weight control behaviors. As the pathophysiology of EDs is complex and multifactorial, with a profound impact on patients' quality of life and major barriers to treatment possibilities, identifying potential contributing factors is crucial.

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Research involving human participants, animals or both

The authors carried out no animal or human studies for this article.

Ethics approval

Ethics committee approval was not required for this observational study because the analysis was performed on an anonymized pharmacovigilance database according to French Clinical Research Law.

Informed consent

Because all data from VigiBase® were de-identified, informed consent was not required.

Data, Materials, Code availability, or both

The data supporting this study's findings are available from the Uppsala Monitoring Center (UMC); however, restrictions apply to the

availability of these data, which were used under license for the current study, and so are not publicly available. Access to VigiBase is available without a fee to Dr. Fanny Rocher. However, the data are available from the authors upon reasonable request and with permission from the UMC.

CRediT authorship contribution statement

Diane Merino: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Alexandre Olivier Gérard:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Alexandre Destere:** Formal analysis, Writing – review & editing. **Florence Askenazy:** Writing – review & editing. **Emmanuelle Dor:** Writing – review & editing. **Michel Benoit:** Writing – review & editing. **Faredj Cherikh:** Supervision, Writing – review & editing. **Milou-Daniel Drici:** Supervision, Writing – review & editing.

Declaration of Competing Interest

None.

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