Efficacy of Medications Approved for the Treatment of Alcohol Dependence and Alcohol Withdrawal Syndrome in Female Patients: A Descriptive Review

Roberta Agabio^a Pier Paolo Pani^b Antonio Preti^c Gian Luigi Gessa^{a, d}
Flavia Franconi^e

^aDepartment of Biomedical Sciences, Section of Neuroscience and Clinical Pharmacology, University of Cagliari,

^bSocial-Health Services, Cagliari Health Public Trust (ASL Cagliari), ^cUnit of Psychosomatics and Clinical Psychiatry, University Hospital, University of Cagliari, ^dNeuroscience Institute, National Research Council of Italy, Section of Cagliari, Cagliari, and ^eDepartment of Biomedical Sciences, University of Sassari, Sassari, Italy

Key Words

Alcohol dependence · Alcohol withdrawal syndrome · Women · Pharmacotherapy · Gender differences

Abstract

The aim of this study was to evaluate whether the number of women recruited for studies to establish the efficacy of medications approved for treatment of alcohol dependence (AD) and of alcohol withdrawal syndrome (AWS) is sufficient to reveal possible gender differences in the response to these medications and in suggesting the use of different doses in female patients. Our results show that the rates of women recruited for studies evaluating the efficacy of disulfiram (1%), benzodiazepines (3%), and anticonvulsants (13%) were too low to establish possible gender differences. The rates of women recruited for studies evaluating the efficacy of acamprosate (22%), naltrexone (23%), and nalmefene (30%) were higher and allowed evaluation of data obtained for female patients. Women receive medications for treatment of AD and/or AWS for which efficacy has been demonstrated in studies in which men were more largely represented.

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Introduction

Pharmacotherapy is emerging as a valuable tool for the treatment of alcohol dependence (AD), but only a few medications are available to date. Currently, medications approved in the United Kingdom and/or in the United States for AD treatment to help patients achieve abstinence, or at least to reduce alcohol consumption, comprise disulfiram, naltrexone, acamprosate, nalmefene and gamma-hydroxybutyrate (GHB) [1–3].

Briefly, disulfiram is the oldest medication for the treatment of AD, approved by the FDA since 1948 [3]. Its mechanism of action involves inhibition of aldehyde dehydrogenase (ALDH), the enzyme responsible for converting acetaldehyde to acetate during alcohol metabolism, which leads to the accumulation of acetaldehyde after alcohol intake [4]. Accumulation of acetaldehyde causes a consequent aversive reaction that deters further alcohol use [5]. Accordingly, disulfiram is indicated for the prevention of relapse in abstinent patients.

G.L.G. and F.F. contributed equally to this work.

Naltrexone is a competitive antagonist of μ -opioid receptors, approved by the FDA in 1994 for the treatment of AD [2, 3]. Its mechanism of action is not fully understood [2]. As the rewarding effects of alcohol are partly mediated through the opioid receptors, blocking of these receptors could explain the reduction in reward effects induced by alcohol consumption and subsequently the reductions in intake and cravings for alcohol [6]. Concerns about low adherence for oral formulations led to the development of slow-release formulations of naltrexone [6].

Nalmefene is a μ -opioid antagonist, like naltrexone, but, compared to naltrexone, nalmefene has a longer plasma half-life, higher bioavailability, and lower liver toxicity [7]. This medication has been recently approved by the European Committee for Medicinal Products for Human Use for the treatment of AD [8].

In the United States, acamprosate is currently the most widely prescribed medication to prevent AD relapse [9, 10]. The mechanism of action of acamprosate is not completely known. It shares similarities with several amino acids, such as glutamate, gamma-aminobutyric acid, aspartate, glycine, and taurine [11]. Converging evidence indicates that acamprosate normalises a hyper-glutamatergic state caused by extensive alcohol exposure and repeated phases of alcohol withdrawal, restoring the balance between inhibitory and excitatory neurotransmitters, and attenuating alcohol craving [12].

GHB is an endogenous neurochemical currently marketed in some European countries for the treatment of AD [13]. The mechanism of action of GHB in the treatment of AD is substitutive [1]. While substitution therapy carries a lower risk than the use of the substance of abuse, the substitute also has a potential for abuse, and cases of GHB intoxication have been reported [14, 15]. For this reason, in the United States, GHB has not been approved for the treatment of AD [13].

Finally, medications approved in the Europe and/or the United States for the treatment of alcohol withdrawal syndrome (AWS) comprise benzodiazepines (e.g. diazepam, chlordiazepoxide, and lorazepam), anticonvulsants (e.g. carbamazepine, valproic acid, and phenytoin), and GHB [16–18].

Unfortunately, AD medications are not effective in all patients, and the magnitude of the response to these medications is generally modest [3]. To improve the efficacy of AD medications, there is growing interest in investigating possible factors that mediate the response to pharmacotherapy, such as different patient characteristics and genetic factors [19, 20]. It is notable that women and men vary largely in terms of biological and psychosocial-cultural factors involved in the response to medical treatments, and sex differences in response to medications have been described for several treatment methods [21–25].

For instance, it has been observed that women eliminate the hypnotic medication zolpidem more slowly than men do, and lower doses of this medication have been recommended for women compared to men [26, 27]. Similarly, women could differ from men in the response to medications approved for treatment of AD and/or AWS.

Women differ from men with regard to several AD aspects [28–34]. This mental disorder is twice as prevalent in men as in women [35], although women suffer serious negative consequences of alcohol consumption much early in life and to a greater degree than men. In addition, women also experience specific alcohol-related problems, such as the risk of foetal alcohol syndrome if alcohol is consumed during pregnancy [36, 37]. The higher vulnerability to the development of alcohol-related consequences in women is, at least in part, due to sex differences in alcohol pharmacokinetics. The risk of medical consequences is related to blood alcohol concentration, and after drinking equivalent amounts of alcohol, women achieve higher blood alcohol concentration than men of similar body weight [38–40]. This occurs because women have a smaller volume of distribution (due to a higher proportion of body fat and lower body water than men) and a lower first-pass metabolism of alcohol than men (because of lower levels of the gastric enzyme that metabolises alcohol: alcohol dehydrogenase) [38]. For these reasons, women are advised to consume lower amounts of alcohol than men do.

Gender difference has also been described as an important factor in determining alcohol consumption, as well as the response to alcohol at comparable blood alcohol concentration. For instance, in humans and non-human adult primates, males consume higher amounts of alcohol than females [33, 41] do, while in rodents, females consume higher amounts of alcohol than males [42, 43]. Moreover, aggressive behaviour after alcohol consumption is less evident in women than in men [44], and female rats are more sensitive than males to alcohol-induced hypothermia [45]. Both animal and clinical studies have found that females tend to develop less severe AWS than males [31, 46]. Complex interactions between intrinsic sex differences in brain organization and the activational effects of circulating gonadal steroids, neuroactive steroids (steroids synthesised in the brain, adrenals, and gonads that affect neuronal excitability), and stress hormones have been proposed to explain these findings [47, 48]. For instance, as allopregnanolone, a metabolite of

progesterone, has shown an anticonvulsant effect in some preclinical models, the current hypothesis is that females and males might have different sensitivity to AWS owing to the effects of neurosteroids [47, 49]. Some of the sex differences observed in alcohol consumption and/or in responses to alcohol have been attributed to differences in levels of oestrogens and androgens between women and men. Indeed, it has been observed that oestrogen and androgen levels modulate the mesocorticolimbic 'reward' dopaminergic system [50], and that women release less amounts of dopamine in the ventral striatum compared to men after acute alcohol consumption [51]. Human and preclinical studies have also shown that the pattern of alcohol consumption varies throughout the different phases of the menstrual cycle, and these differences have been attributed, at least in part, to different levels of oestrogens and progesterone [50].

In view of all these sex differences, it can be hypothesised that women and men might also differ in their response to medications approved for treatment of AD and/or AWS, and might require different doses of these medications. To test this hypothesis, we performed a descriptive review of studies on the efficacy of these medications to evaluate: (a) whether a sufficient number of women were recruited to evaluate possible sex differences in the response; (b) if the number of women was sufficient, whether sex differences in the response were observed; and (c) the doses administered in these studies. To this end, recent meta-analyses evaluating the efficacy of AD and/or AWS medications were selected. From these meta-analyses, data on female patients and medication doses administered were collected. When this information was not available in the selected meta-analyses, the primary clinical trials were examined.

Methods

Search Methods for Identification of Reviews

A systematic search was conducted on PubMed/Medline and the Cochrane database of Systematic Reviews to identify meta-analyses on the efficacy of medications approved for AD and AWS treatment. A first systematic search was conducted using the keywords 'pharmacological treatment (mesh) AND alcohol dependence (mesh)', and a second systematic search using the keywords 'pharmacological treatment (mesh) AND alcohol withdrawal syndrome'. In both searches, the filters meta-analysis, Humans, and English language were activated. The search was performed in August 2014. When no meta-analysis was found for a medication, a manual search throughout the reading of the other selected meta-analyses was conducted. When more than one eligible meta-analysis was available for the same medication, the more recent one was selected.

Criteria for Considering Reviews for Inclusion

Only meta-analyses on the efficacy of medications already approved for AD and/or AWS treatment were included. Other inclusion criteria were (1) use of rigorous methods to minimise bias, (2) diagnosis of AD and/or AWS according to appropriate standard criteria (e.g. the criteria of Diagnostic and Statistical Manual of Mental Disorders), and (3) comparison between the results obtained by patients treated with the pharmacological intervention and those obtained by patients treated with placebo. Recent primary clinical trials not yet part of the selected meta-analyses were not included. In the first search, only meta-analyses on one of the following medications were included: (1) naltrexone, (2) acamprosate, (3) nalmefene, (4) disulfiram, and (5) GHB. In the second search, only meta-analyses on one of the following medications approved for AWS treatment were included: (1) benzodiazepines, (2) anticonvulsants, and (3) GHB.

Assessment of the Methodological Quality of Included Reviews

The quality of the included reviews was not evaluated, as it was assured by selecting meta-analyses.

Data Extraction and Management

From each selected meta-analysis, the following information was collected: (1) number of randomised controlled trials (RCTs) evaluated; (2) number of patients recruited by these RCTs; (3) number of RCTs in which only male patients were recruited; (4) number of RCTs in which the sex of patients was not indicated; (5) number of RCTs in which female and male patients were recruited; (6) number of RCTs in which only female patients were recruited; (7) medication doses administered (when this information was not specified by the meta-analysis, it was obtained from the original article on the RCT); and (8) levels of medication efficacy assigned by the meta-analysis, regardless of patient sex. From this information, the following data were calculated: (1) the rate of female patients among patients for whom sex was known; (2) the highest and lowest doses used in any RCTs.

Sufficient Number of Female Patients Recruited for RCTs

Considering that the lifetime prevalence of AD is twice as high in men as in women [35], female patients should constitute approximately one-third of the sample of patients recruited in studies evaluating the efficacy of medications for this disorder (33% of patients).

Assessment of Efficacy

For each medication (or class of medications), the efficacy, regardless of the sex of the patient, evaluated by the selected meta-analysis was expressed in levels (table 1) [52–54]. When a meta-analysis showed superiority of a medication to placebo, level A1 was assigned; when a meta-analysis did not show superiority of a medication to placebo, level C was assigned. The efficacy of each medication in female patients was assigned according to the criteria provided in table 1, considering the source of the evidence and possible negative results.

Results

The first search for meta-analyses of medications approved for AD treatment identified 79 articles. Among these, 75 were excluded (see online suppl. references;

Table 1. Levels of efficacy

Level	Source of the evidence	If negative RCTs do exist
A1	One meta-analysis shows superiority to placebo (with a narrow confidence interval in at least 3 RCTs, at least one of which was large)	They have already been evaluated by the meta-analysis
A2	At least 2 positive RCTs show superiority to placebo (with a narrow confidence interval in at least 1 large RCT)	They are outweighed by: (1) a meta-analysis on all available studies showing non-inferiority to an established comparator treatment, or (2) at least 2 more positive studies showing superiority to placebo
B	One or more RCTs shows superiority to placebo	They are outweighed by: (1) a meta-analysis of all available studies showing non-inferiority to an established comparator treatment, or (2) at least 1 more positive study showing superiority to placebo
C	Inconsistent evidence from any number of RCTs	They are not outweighed by positive RCTs

This table summarises how the level of efficacy was established, considering the source of the evidence and possible negative results. RCTs = Randomised, controlled trials based on a double-blind, parallel-group design. Large = Number of patients recruited ≥ 100 subjects.

for all online suppl. material, see www.karger.com/doi/10.1159/000433579) and 4 were selected [55–58] (table 2). Another article was added after a manual search [59]. One meta-analysis specifically investigated the efficacy of acamprosate in AD women [57]. Reasons for exclusion of meta-analyses are listed in online supplementary table S1. Information collected from the selected meta-analyses is summarised in table 2.

Briefly, the meta-analysis selected for disulfiram evaluated the results obtained by 11 RCTs in which 1,521 patients were recruited and did not find a significant effect of this medication on abstinence, regardless of patient sex [59]. Accordingly, the level C of efficacy was assigned to this medication (table 2). The rates of women recruited in these 11 RCTs are shown by table 3. Globally, (a) 7 RCTs recruited only male patients ($n = 1,133$ men), (b) 1 study did not indicate the gender of subjects ($n = 39$ patients), whereas (c) 3 RCTs recruited both male and female patients (92 women in a total sample of 349 patients (26.4%)). Among the 1,482 patients for whom the sex was known, 92 were women (6.2%). Only 3 RCTs compared disulfiram to placebo, and the rate of women recruited in these RCTs was too low (9 women in a sample of 759 patients (1.2%)) to allow a gender analysis (tables 2 and 3; fig. 1). The dose of disulfiram ranged from 100 mg per day to 800 mg twice a week [59]. Only one study included in the meta-analysis adjusted the daily dose of disulfiram according to body weight [60]. In this study, the dose of disulfiram was 100 or 200 mg once a day, or 400 mg twice

a week, but it was not specified whether women received lower doses of disulfiram than men did [60].

The meta-analysis selected for acamprosate evaluated the results obtained by 24 RCTs and found that this medication significantly reduced the risk of any drinking after detoxification (14% lower risk), and increased the cumulative duration of abstinence (3 additional days a month) [56]. According to these results, the level A1 of efficacy for AD treatment was assigned to acamprosate, regardless of sex (table 2). The rates of women recruited in these 24 RCTs are shown by table 4. Globally, (a) 2 RCTs recruited only male patients ($n = 85$ men), whereas (b) the other 22 RCTs recruited both female and male patients (1,326 women in a sample of 6,062 patients (21.9%)). All the RCTs compared acamprosate to placebo. Among the total sample of patients ($n = 6,147$ patients), 1,326 were women (21.9%). The rate of women recruited for RCTs evaluating the efficacy of acamprosate was close to the real frequency of female patients with AD and allowed a gender analysis (tables 2 and 4; fig. 1). Specifically, the second meta-analysis selected found no sex differences in all the outcomes evaluated [57]. According to these results, the level A1 of efficacy for AD treatment was assigned to acamprosate for AD female patients (table 2). The daily dose of acamprosate ranged from 1,332 to 3,000 mg; in most studies, the dose was adjusted according to body weight (1,332 mg for body weight < 60 kg; 1,998 mg for ≥ 60 kg) [56]. It was not specified whether women received lower doses of acamprosate than men did.

Table 2. Information collected by selected meta-analyses on medications approved for the treatment of alcohol dependence

Medication	Disulfiram	Acamprosate	Naltrexone	Nalmefene	GHB
Selected meta-analyses	Jørgensen et al., 2011 [59]	Rösner et al., 2010 [56]	Rösner et al., 2010 [55]	Rösner et al., 2010 [55]	Leone et al., 2010 [58]
<i>Characteristics of RCTs evaluated by the selected meta-analyses</i>					
Total number, n	11	24	47	3	7
Total patients recruited in these RCTs, n	1,521	6,147	6,437	396	345
RCTs in which only male patients were recruited, n	7	2	10	0	0
RCTs in which the sex of patients was not indicated, n	1	0	1	0	1
RCTs in which male and female patients were recruited, n	3	22	35	3	6
RCTs in which only female patients were recruited, n	0	0	1	0	0
Patients for whom sex was known, n	1,482	6,147	6,437	396	305
Women, n	92	1,326	1,479	117	74
Women, % of patients for whom sex was known	6.2	21.6	23.0	29.5	24.3
<i>Characteristics of RCTs evaluated by the selected meta-analyses in which medications were compared to placebo</i>					
Total number, n	3	24	46	3	2
Total patients recruited in these RCTs, n	759	6,147	6,380	396	88
Women, n	9	1,326	1,468	117	28
Women, % of patients for whom sex was known	1.2	21.9	23.0	29.5	31.8
Lower dose used by some RCTs	orally, 100 mg, once a day	orally, 333 mg, 3 times a day	orally, 25 mg, once a day; i.m., 150 mg, every 4 weeks	orally, 5 mg, once a day	orally, 50 mg/kg, divided into 6 daily administrations
Higher dose used by some RCTs	orally, 800 mg, twice a week	orally, 1,500 mg, twice a day	orally, 100 mg, once a day; i.m., 400 mg, every 4 weeks	orally, 80 mg, 2 times a day	orally, 150 mg/kg, divided into 3 daily administrations
Level of efficacy regardless of patient sex	C	A1	A1	C	C
Level of efficacy in female patients	?	A1	not clear	?	?

This table summarises information collected by selected meta-analyses on the efficacy of medications approved for the treatment of alcohol dependence. i.m. = Intramuscularly. Levels of efficacy range from A1 (the best) to C (the worst).

Fig. 1. Rates of male and female patients recruited in randomised, placebo-controlled trials conducted to evaluate the efficacy of AD medications.

Table 3. Number of female patients recruited in the RCTs evaluated by the meta-analysis entitled ‘The efficacy of disulfiram for the treatment of alcohol use disorder’ by Jørgensen et al., 2011 [59]

n	Study	Women		Total patients, n
		n	%	
1	De Sousa and De Sousa, 2004	0	0.0	100
2	De Sousa and De Sousa, 2005	0	0.0	100
3	De Sousa and De Sousa, 2008	0	0.0	100
4	De Sousa et al., 2008	0	0.0	58
5	Fuller and Roth, 1979	0	0.0	128
6	Fuller et al., 1986	0	0.0	605
7	Laaksonen et al., 2008 [60]	71	29.2	243
8	Nava et al., 2006	12	15.0	80
9	Niederhofer and Staffen, 2003	9	34.6	26
10	Tonnesen et al., 1999	0	0.0	42
11	Ulrichsen et al., 2010	n.a.	n.a.	39

n.a. = Data not available. In bold: studies in which disulfiram was compared to placebo. References are listed in online supplementary references.

The meta-analysis selected for naltrexone revealed that both oral and injectable long-acting formulations of this medication are superior to placebo primarily in reducing the risk of heavy drinking [55]. This meta-analysis evaluated the results of 50 RCTs: (a) 43 RCTs, in which patients received the oral formulation of naltrexone, (b) 4 RCTs in which patients received the injectable long-acting formulation of naltrexone, and (c) 3 RCTs in which patients received nalmefene (see below). The rates of

women recruited in the 50 RCTs evaluated by this meta-analysis for naltrexone are shown by table 5. Naltrexone was administered at fixed doses, regardless of body weight [55]. The daily dose of oral naltrexone ranged from 25 to 150 mg; most trials used 50 mg per day. Injectable naltrexone was administered at 4-week intervals at doses between 150 and 400 mg. According to the results obtained by the meta-analysis selected, the level A1 of efficacy for AD treatment was assigned to naltrexone, regardless of sex (table 2). Among the 47 RCTs for naltrexone (including 6,437 patients), globally, (a) 1 study did not indicate the number and gender of patients recruited, (b) 10 RCTs recruited only male patients ($n = 721$), (c) 35 RCTs recruited both male and female patients (1,376 women in a sample of 5,613 subjects (24.5%)), and, interestingly, (d) 1 recruited only female patients ($n = 103$). Among the 6,437 patients for whom the sex was known, 1,479 were women (23.0%). Forty-six RCTs compared naltrexone to placebo recruiting 1,468 women, in a sample of 6,380 patients (23.0%). The rate of women recruited for evaluating the efficacy of naltrexone may allow comparison of results between female and male patients. However, this meta-analysis did not conduct a gender analysis [55]. Moreover, the majority of the studies evaluated by the meta-analysis did not report the results obtained by female patients in detail, while the few studies in which this information was reported found contrasting results. Namely, the RCT in which only female patients were recruited failed to demonstrate a significant effect of naltrexone [61]. In this RCT, naltrexone did not improve drinking outcomes, although naltrexone delayed the on-

Table 4. Number of female patients recruited in the RCTs evaluated by the meta-analysis entitled ‘acamprosate for alcohol dependence’ by Rösner et al., 2010 [56]

n	Study	Women		Total patients, n	n	Study	Women		Total patients, n
		n	%				n	%	
1	Anton et al., 2006	187	30.6	612	14	Morley et al., 2006	35	30.2	116
2	Baltieri and Andrade, 2004	0	0.0	75	15	Namkoong et al., 2003	6	4.2	142
3	Barrias et al., 1997	24	7.9	302	16	Niederhofer and Staffen, 2003	9	34.6	26
4	Besson et al., 1998	22	20.0	110	17	Paille et al., 1995	108	20.1	538
5	Borg, 2003	0	0.0	10	18	Pelc et al., 1992	32	31.4	102
6	Chick et al., 2000	96	16.5	581	19	Pelc et al., 1997	28	14.9	188
7	Geerlings et al., 1997	63	24.0	262	20	Poldrugo F, 1997	67	27.2	246
8	Gual and Leheret, 2001	59	20.5	288	21	Roussaux et al., 1996	38	29.9	127
9	Kiefer et al., 2003	23	28.8	80	22	Sass et al., 1996	61	22.4	272
10	Ladewig et al., 1993	14	23.0	61	23	Tempesta et al., 2000	57	17.3	330
11	Lhuintre et al., 1985	8	11.4	70	24	Whitworth et al., 1996	95	21.2	448
12	Lhuintre et al., 1990	103	18.1	569					
13	Mason et al., 2006	191	32.3	592					

References are listed in online supplementary references.

Table 5. Number of female patients recruited in the RCTs evaluated by the meta-analysis entitled ‘opioid antagonists for alcohol dependence’ by Rösner et al., 2010 [55]

n	Study	Women		Total patients, n	n	Study	Women		Total patients, n
		n	%				n	%	
1	Ahmadi and Ahmadi, 2002	0	0.0	116	28	Lee et al., 2001	0	0.0	53
2	Anton et al., 1999	39	29.0	131	29	<i>Martinotti et al., 2008</i>	11	19.3	57
3	Anton et al., 2004 [68]	76	28.1	270	30	Mason et al., 1994 [66]	6	28.6	21
4	Anton et al., 2005	39	24.4	160	31	Mason et al., 1999 [67]	35	33.3	105
5	Anton et al., 2006 [65]	194	31.4	618	32	Monterosso et al., 2001	50	27.3	183
6	Auriacombe et al., 2000	n.a.	n.a.	n.a.	33	Monti et al., 2001	31	24.2	128
7	Ballidin et al., 2003	18	15.3	118	34	Morley et al., 2006	37	32.5	114
8	Baltieri et al., 2008	0	0.0	155	35	Morris et al., 2001	0	0.0	111
9	Brown et al., 2009	21	48.8	43	36	O'Malley et al., 1992	27	26.0	104
10	Chick et al., 2000	44	25.1	175	37	O'Malley et al., 2007 [61]	103	100.0	103
11	de Goes and Castro, 2004	13	18.3	71	38	O'Malley et al., 2008	25	36.8	68
12	Galarza et al., 1997	0	0.0	20	39	Oslin et al., 1997	0	0.0	44
13	Garbutt et al., 2005 [63]	201	32.2	624	40	Oslin, 2005	15	20.3	74
14	Gastpar et al., 2002	47	27.5	171	41	Oslin et al., 2008	65	27.1	240
15	Guardia et al., 2002	51	25.2	202	42	Petrakis et al., 2004	0	0.0	31
16	Heinala et al., 2001	35	28.9	121	43	Petrakis et al., 2005	3	2.4	123
17	Hersh et al., 1998	5	7.8	64	44	Pettinati et al., 2008a	29	27.2	106
18	Huang et al., 2005	0	0.0	40	45	Pettinati et al., 2008b [62]	48	29.3	164
19	Johnson et al., 2000	5	25.0	20	46	Schmitz et al., 2004	13	16.3	80
20	Johnson et al., 2004	8	26.7	30	47	Schmitz et al., 2009	10	11.5	87
21	Kiefer et al., 2003	42	26.3	160	48	Volpicelli et al., 1992	0	0.0	70
22	Killeen et al., 2004	37	42.5	87	49	Volpicelli et al., 1997	22	22.7	97
23	Kranzler et al., 1998	5	25.0	20	50	Ziolkowski, 2000	0	0.0	81
24	Kranzler et al., 2000	28	22.6	124					
25	Kranzler et al., 2004	110	34.9	315					
26	Krystal et al., 2001	15	2.4	627					
27	Latt et al., 2002	33	30.8	107					

n.a. = Data not available. In bold: studies for nalmefene. In italic: studies in which naltrexone was not compared to placebo. References are listed in online supplementary references.

Table 6. Number of female patients recruited in the RCTs evaluated by the meta-analysis entitled ‘Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses’ by Leone et al., 2010 [58]

n	Study	Women		Total patients, n
		n	%	
1	<i>Addolorato et al., 1999 [72]</i>	9	15.0	60
2	<i>Caputo et al., 2003</i>	8	22.9	35
3	<i>Caputo et al., 2007</i>	12	21.8	55
4	<i>Ceccanti et al., 1996</i>	0	0.0	42
5	Di Bello et al., 1995	4	23.5	17
6	<i>Elsing et al., 1996</i>	3	14.3	21
7	<i>Ferri et al., 1991</i>	n.a.	n.a.	40
8	Gallimberti et al., 1989	7	30.4	23
9	Gallimberti et al., 1992	24	33.8	71
10	<i>Nava et al., 2006</i>	12	15.0	80
11	<i>Nava et al., 2007 [74]</i>	n.a.	n.a.	42
12	<i>Nimmerichter et al., 2002</i>	9	9.2	98
13	<i>Stella et al., 2008</i>	14	29.8	47

n.a. = Data not available; In bold: studies in which GHB was compared to placebo. In italic: studies in which GHB was administered to reduce the severity of AWS. References are listed in online supplementary references.

set of subsequent drinking days among women who lapsed. This RCT also found a higher proportion of adverse effects among women treated with naltrexone (77%) than among those who received placebo (52%). Another RCT evaluated the efficacy of a higher dose of naltrexone compared to the typical one (150 mg instead of 50 mg per day) in 164 patients (48 women) with co-occurring cocaine and AD [62]. The results showed that men treated with naltrexone had reductions in cocaine and alcohol use and drug severity, whereas women did not benefit from this treatment. In fact, women who received naltrexone used more cocaine and had higher rates of drinking than women treated with placebo. Another RCT found that administration of injectable formulations of naltrexone yielded significant results in men (423 patients) but not in women (201 patients) [63]. In the latter RCT, women were more likely to report nausea than men. Conversely, a post-hoc analysis of another RCT evaluated by the meta-analysis (160 patients; 42 women) found that AD women treated with 50 mg of naltrexone per day abstained from alcohol for a longer period than AD men did [64]. Finally, the COMBINE study found that naltrexone induced similar benefits in both men and women [65]. According to these results, it is not clear if women respond differently to naltrexone (tables 2 and 5).

The meta-analysis selected for nalmefene evaluated the results obtained by 3 RCTs and found no significant differences between patients who received this medication and those who received placebo [55]. Accordingly, the level C of efficacy was assigned to this medication, regardless of patient sex (table 2). Globally, the 3 RCTs recruited 117 women in a total sample of 396 subjects (29.5%), and all RCTs compared nalmefene to placebo (table 5). The rate of women recruited for RCTs evaluating the efficacy of nalmefene was close to the real frequency of female patients with AD. However, the meta-analysis did not conduct a gender analysis, and the studies did not report the results obtained by female patients in detail [55, 66–68]. According to these results, it is not clear if women may respond differently to nalmefene. The doses of nalmefene ranged from 5 to 80 mg [55].

The meta-analysis selected for GHB found that patients who received this medication achieved better results than patients who received placebo in treatment of both AD and AWS [58]. This meta-analysis evaluated the results obtained by 7 RCTs (including 345 patients) in which GHB was administered to reduce the risk of relapses, and 6 RCTs (including 286 patients) in which GHB was administered to reduce the severity of AWS. The rates of women recruited in these 13 RCTs are shown by table 6. Globally, among the 7 RCTs for the prevention of relapses (a) 1 study did not indicate the gender of patients (n = 40), whereas (b) the other 6 RCTs recruited both male and female patients for a total of 74 women in a sample of 305 patients (24.3%). Among the 305 patients for whom the sex was known, 74 were women (24.3%). Only 2 RCTs compared GHB to placebo (28 women in a sample 88 subjects (31.8%)). Among the 6 RCTs for AWS treatment (a) 2 studies did not indicate the gender of patients (n = 63), (b) 1 RCT recruited only male patients (n = 42), whereas (c) 3 RCTs recruited both male and female patients for a total of 25 women in a sample of 181 patients (13.8%). Among the 223 patients for whom the sex was known, 25 were women (11.2%). Only 1 RCT compared GHB to placebo (7 women in a sample of 23 patients (30.4%)). Considering the low number of patients recruited by RCTs, the level C of efficacy was assigned to GHB both for AD and AWS, regardless of sex (tables 2 and 7). The daily dose of GHB was always adjusted according to body weight (50 mg/kg body weight, divided into 3 daily doses) [58]. It was not specified whether women received lower doses of GHB than men did.

Globally, the 4 meta-analyses selected reviewed 92 RCTs for AD treatment, in which almost 15,000 patients were recruited (table 2). Among these 92 RCTs, 19 (approximately 21%) recruited only male patients, 3 studies

Table 7. Information collected by selected meta-analyses on medications approved for the treatment of alcohol withdrawal syndrome

Medication	Benzodiazepines	Anticonvulsants	GHB
Selected meta-analyses	Amato et al., 2010 [69]	Minozzi et al., 2010 [70]	Leone et al., 2010 [58]
<i>Characteristics of the RCTs evaluated by the selected meta-analyses</i>			
Total number of RCTs evaluated, n	65	58	6
Total patients recruited in these RCTs, n	4,612	4,218	286
RCTs in which only male patients were recruited, n	21	11	1
RCTs in which the sex of patients was not indicated, n	9	8	2
RCTs in which male and female patients were recruited, n	35	39	3
RCTs in which only female patients were recruited, n	0	0	0
Patients for whom sex was known, n	4,025	3,619	223
Women, n	414	460	25
Women, % of patients for whom sex was known	10.3	12.7	11.2
<i>Characteristics of the studies evaluated by the selected meta-analyses in which medications were compared to placebo</i>			
Total number of these RCTs, n	12	17	1
Total patients recruited in these RCTs, n	1,301	1,602	23
Women, n	42	182	7
Women, % of patients for whom sex was known	3.2	12.6	30.4
Level of efficacy regardless of patient sex	A1	C	C
Levels of efficacy in female patients	?	?	?

This table summarizes information collected by selected meta-analyses on the efficacy of medications approved for the treatment of alcohol withdrawal syndrome. Levels of efficacy range from A1 (the best) to C (the worst).

(3%) did not specify the sex of patients, 1 RCT recruited only female patients, and the other 69 RCTs (75%) recruited both female and male patients. The rate of women (among patients of whom sex was known) recruited by the RCTs in which the efficacy of medications was compared to that of placebo varied from 1.2% for disulfiram to 31.8% for GHB. None of the RCTs evaluated by selected meta-analyses reported the use of different doses of medications for female patients.

The second search for meta-analyses for AWS medications identified 21 articles: of these, 17 were excluded (see online suppl. references) and 4 were selected [58, 69–71]. A meta-analysis investigated the efficacy of GHB for the treatment of both AD and AWS [58]. Finally, 1 article was an overview of meta-analyses that compared the efficacy of different AWS medications [71]. Reasons for exclusion of meta-analyses are listed in online supplementary table S2. Information collected from the selected meta-analyses is summarised in table 7.

The meta-analysis selected for benzodiazepines evaluated the results obtained by 65 RCTs, in which 4,612 patients were included, and demonstrated a significant effect of this class of drugs compared to placebo in treatment of AWS [69]. Accordingly, the level A1 of efficacy was as-

signed to benzodiazepines, regardless of patient sex. The rates of women recruited in these 65 RCTs are shown by table 8. Globally, (a) 21 RCTs recruited only men (n = 1,726), (b) 9 studies did not indicate the gender of patients (n = 587 patients), and (c) 35 RCTs recruited both male and female patients (414 women in a sample of 2,249 subjects (18.4%)). Among the 4,025 patients for whom the sex was known, 414 were women (10.3%). Twelve RCTs compared benzodiazepines to placebo (table 8). Among them, (a) 7 RCTs recruited only male patients (n = 1,035 patients), (b) 1 study did not indicate the gender of subjects (n = 91 patients), and (c) 4 RCTs recruited both male and female patients (42 women in a sample of 175 subjects (24%)). Among the 1,210 patients for whom the sex was known, 42 were women (3.5%). In the evaluation of the efficacy of benzodiazepines compared to that of placebo, the meta-analysis included only 3 of these 12 RCTs: among them, 1 recruited only male patients (n = 537 patients), and the other 2 recruited 13 women and 78 men. Globally, these 3 RCTs recruited 13 women in a sample of 628 patients (equal to 2.1%). The low number of women recruited in these RCTs did not allow the evaluation of possible gender differences in the response to these medications (fig. 2; tables 7 and 8). Among all 65 RCTs evaluated by the meta-analysis, only 3

Table 8. Number of female patients recruited in the RCTs evaluated by the meta-analysis entitled ‘benzodiazepines for alcohol withdrawal’ by Amato et al., 2010 [69]

n	Study	Women		Total patients, n	n	Study	Women		Total patients, n
		n	%				n	%	
1	Addolorato et al., 1999 [72]	9	15.0	60	37	Malcolm et al., 2007	25	24.8	101
2	Addolorato et al., 2006 [73]	5	13.5	37	38	Martin, 1975	12	30.0	40
3	Adinoff, 1994	0	0.0	25	39	McGrath, 1975	n.a.	n.a.	100
4	Ansoms et al., 1991	18	33.3	54	40	McLendon and Fabre, 1980	0	0.0	65
5	Anton et al., 1997	0	0.0	49	41	Mendels et al., 1985	4	4.3	92
6	Bailly et al., 1992	0	0.0	28	42	Mielke et al., 1976	n.a.	n.a.	91
7	Baumgartner and Rowen, 1987	0	0.0	61	43	Miller and McCurdy, 1984	1	1.8	55
8	Baumgartner and Rowen, 1991	0	0.0	50	44	Mukherjee, 1983	n.a.	n.a.	40
9	Borg et al., 1986	0	0.0	45	45	Naranjo et al., 1983	6	14.6	41
10	Brown et al., 1972	n.a.	n.a.	18	46	Nava et al., 2007 [74]	10	23.8	42
11	Burroughs et al., 1985a	17	38.6	44	47	O’Brien et al., 1983	11	21.2	52
12	Burroughs et al., 1985b	10	37.0	27	48	Overall et al., 1973	n.a.	n.a.	147
13	Choi et al., 2005	4	7.7	52	49	Palestine and Alatorre, 1976	8	16.3	49
14	Daepfen et al., 2002	27	23.1	117	50	Pena-Ramos, 1977	n.a.	n.a.	70
15	Day et al., 2004	9	39.1	23	51	Pena-Ramos and Hornberger, 1979	6	17.6	34
16	Dion et al., 1968	0	0.0	45	52	Radouco-Thomas et al., 1989	0	0.0	67
17	Favre et al., 2005	12	13.5	89	53	Ritson and Chick, 1986	12	30.0	40
18	Funderburk et al., 1978	0	0.0	18	54	Runion and Fowler, 1978	n.a.	n.a.	50
19	Gillman and Lichtigfeld, 2004	n.a.	n.a.	51	55	Saitz et al., 1994	1	1.0	101
20	Gillmer, 1973	9	25.7	35	56	Saletu et al., 1983	0	0.0	42
21	Golbert et al., 1967	0	0.0	49	57	Sellers et al., 1977	0	0.0	30
22	Jauhar et al., 2000	n.a.	n.a.	20	58	Sellers et al., 1983	7	14.0	50
23	Kaim et al., 1969	0	0.0	537	59	Solomon et al., 1983	0	0.0	50
24	Kaim and Klett, 1972	0	0.0	202	60	Spies et al., 1996	10	6.3	159
25	Kalyoncu et al., 1996	0	0.0	83	61	Spies et al., 2003	8	18.2	44
26	Kolin and Linet, 1981	21	42.9	49	62	Stuppaeck et al., 1992	11	18.3	60
27	Kramp and Rafaelsen, 1978	10	11.0	91	63	Tubridy, 1988	31	34.4	90
28	Krupitsky et al., 2007	0	0.0	127	64	Wilson and Vulcano, 1985	30	30.0	100
29	Kumar et al., 2009	0	0.0	100	65	Worner, 1994	0	0.0	37
30	Lapierre et al., 1983	7	17.5	40	n.a. = Data not available. In bold: studies in which a BDZ was compared to placebo. In italic: studies analysed by the meta-analysis for the evaluation of the efficacy of benzodiazepines compared to placebo. References are listed in online supplementary references.				
31	Lenzenhuber et al., 1999	5	11.9	42					
32	Lepola et al., 1984	7	11.7	60					
33	Longo et al., 2002	8	50.0	16					
34	Lucht et al., 2003	9	7.1	127					
35	Malcolm et al., 1989	0	0.0	66					
36	Malcolm et al., 2002	34	25.0	136					

studies adjusted benzodiazepine doses according to body weight [72–74]. In these studies, a daily oral dose of diazepam of 0.5–0.75 mg/kg body weight was administered for 6 days; then the dose was tapered off by 25% daily until day 10 in 139 patients, comprising 24 women. However, information on female patients was not provided.

The meta-analysis selected for anticonvulsants evaluated the results obtained by 58 RCTs, including 4,218 patients, and failed to demonstrate a significant effect of anticonvulsants compared to placebo in treatment of AWS [70]. Accordingly, the level C of efficacy was assigned to

anticonvulsants, regardless of patient sex. The rates of women recruited in these 58 RCTs are shown by table 9. Globally, (a) 11 RCTs recruited only men (n = 905), (b) 8 studies did not indicate the gender of patients (n = 599 patients), and (c) 39 RCTs recruited both male and female patients (460 women in a sample of 2,714 subjects (16.9%)). Among the 3,619 patients for whom the sex was known, 460 were women (12.7%). Seventeen RCTs compared anticonvulsants to placebo; among them, (a) 4 RCTs recruited only male patients (n = 489 patients), (b) 1 study did not indicate the gender of subjects (n = 157 patients), and (c)

Fig. 2. Rates of male and female patients recruited in randomised, placebo-controlled trials conducted to evaluate the efficacy of AWS medications.

12 RCTs recruited both male and female patients (182 women in a sample of 956 subjects (19.0%)). Among the 1,445 patients for whom the sex was known, 182 were women (12.6%). In the evaluation of the efficacy of anticonvulsants compared to that of placebo, the meta-analysis included only 9 of these 17 RCTs. These 9 RCTs recruited 933 patients, including 106 women (13.7%). The majority of the studies evaluated by the meta-analysis did not report the results obtained by female patients in details. Moreover, among these RCTs, some recruited a number of women too small to investigate possible gender differences (fig. 2; tables 7 and 9). According to these results, it is not clear if women may respond differently to anticonvulsants.

Globally, table 7 shows that, the 3 selected meta-analyses reviewed 129 studies for AWS medications, in which more than 9,000 subjects were recruited. Thirty-three out of 129 studies (approximately 26%) recruited only male patients, 19 studies (15%) did not specify the sex of patients, no study recruited only female patients, and the other 77 studies (60%) recruited both female and male patients. The rate of women (among patients of whom sex was known) recruited by the studies in which the efficacy of medications was compared to that of placebo varied from 3.2% for benzodiazepines to 30.4% for GHB. None of the selected meta-analyses reported the use of different doses of medications for female patients.

Discussion

The results of this study showed that the rates of women recruited by studies evaluating the efficacy of disulfiram (1%) for AD treatment and of benzodiazepines (3%)

and anticonvulsants (13%) for AWS treatment were too low to establish possible sex differences in the response to these medications (fig. 1 and 2). The rate of women recruited for GHB was higher (32%), but the total number of patients was too small (88 subjects) to reach any significant conclusion regarding its efficacy for the treatment of both AD and AWS. Finally, the rates of women recruited for acamprosate (22%), naltrexone (23%), and nalmefene (30%) for AD treatment were sufficient to permit gender analysis, but the results of these comparisons are contrasting and not conclusive.

Acamprosate was the only medication that could achieve the best level of efficacy for AD treatment in female patients [56, 57]. However, in the COMBINE study, acamprosate failed to reduce alcohol consumption, regardless of patient sex [65]. Although these negative results were already evaluated in the selected meta-analysis [56], they deserve further explanation because of the large number of patients recruited [65]. Moreover, a gender analysis (not included in the meta-analysis we selected) of the results obtained by the COMBINE study specifically showed that acamprosate failed to reduce alcohol consumption in women as well as in men [75].

Naltrexone achieved the best level of efficacy regardless of the sex of patients, but it is not clear if women respond differently to this medication. Indeed, among the studies included in the selected meta-analysis, some found that naltrexone is not effective in female patients [61] or is more effective in men than in women [62, 63], whereas others found that naltrexone is more effective in women than in men [64]. The gender analysis on the results obtained by the COMBINE study found that naltrexone induced similar benefits in both men and wom-

Table 9. Number of female patients recruited in the RCTs evaluated by the meta-analysis entitled ‘anticonvulsants for alcohol withdrawal’ by Minozzi et al., 2010 [70]

n	Studies	Women		Total patients, n	n	Studies	Women		Total patients, n
		n	%				n	%	
1	Agricola et al., 1982	7	11.7	60	33	Malcolm et al., 2002	34	25.0	136
2	Aldredge et al., 1989	5	5.6	90	34	Malcolm et al., 2007	25	24.8	101
3	Ballidin and Bokstrom, 1986	n.a.	n.a.	38	35	Manhem et al., 1985	5	25.0	20
4	Bjorkqvist et al., 1976	0	0.0	105	36	Mariani et al., 2006	8	29.6	27
5	Blanchard, 1985	9	23.7	38	37	McGrath, 1975	n.a.	n.a.	100
6	Bonnet et al., 2003	18	29.5	61	38	Murphy et al., 1983	17	25.0	68
7	Bonnet et al., 2007	n.a.	n.a.	n.a.	39	Myrick et al., 2000	n.a.	n.a.	11
8	Borg et al., 1986	0	0.0	45	40	Nimmerrichter et al., 2002	9	9.2	98
9	Burroughs et al., 1985a	17	38.6	44	41	Radouco-Thomas et al., 1989	0	0.0	67
10	Burroughs et al., 1985b	10	37.0	27	42	Rathlev et al., 1994	4	4.0	100
11	Chance, 1991	0	0.0	55	43	Reoux et al., 2001	1	2.8	36
12	Choi et al., 2005	4	7.7	52	44	Ritola and Malinen, 1981	0	0.0	68
13	Croissant et al., 2009	10	17.9	56	45	Robinson et al., 1989	6	18.8	32
14	Dencker et al., 1978	4	6.3	63	46	Rosenthal et al., 1998	6	14.3	42
15	Elsing et al., 1996	3	14.3	21	47	Rothstein, 1973	n.a.	n.a.	200
16	Elsing et al., 2009	4	15.4	26	48	Sampliner and Iber, 1974	n.a.	n.a.	157
17	Flygenring et al., 1984	7	9.7	72	49	Santo Domingo Carrasco et al., 1985	0	0.0	38
18	Gann et al., 2004	5	25.0	20	50	Schik et al., 2005	5	17.2	29
19	Glatt et al., 1966	44	45.4	97	51	Seifert et al., 2004	9	5.7	159
20	Golbert et al., 1967	0	0.0	49	52	Spies et al., 1996	10	6.3	159
21	Kaim and Klett, 1972	0	0.0	202	53	Stanhope, 1989	48	15.8	304
22	Kalyoncu et al., 1996	0	0.0	83	54	Stuppaeck et al., 1992	11	18.3	60
23	Koethe et al., 2007	10	20.0	50	55	Stuppaeck et al., 1998	n.a.	n.a.	38
24	Koppi et al., 1987	1	5.0	20	56	Teijeiro, 1975	n.a.	n.a.	55
25	Kramp and Rafaelsen, 1978	10	11.0	91	57	Thompson et al., 1975	8	23.5	34
26	Krupitsky et al., 2007	0	0.0	127	58	Tubridy, 1988	31	34.4	90
27	Lambie et al., 1980	4	8.3	48	<p>n.a. = Data not available. In bold: studies in which anticonvulsants were compared to placebo. In italic: Studies analysed by the meta-analysis for the evaluation of the efficacy of anticonvulsants compared to placebo. References are listed in online supplementary references.</p>				
28	Lapierre et al., 1983	7	17.5	40					
29	Longo et al., 2002	8	50.0	16					
30	Lucht et al., 2003	9	7.1	127					
31	Madden et al., 1969	27	27.0	100					
32	Malcolm et al., 1989	0	0.0	66					

en, as well as another study not included in the selected meta-analysis [75, 76]. It is important to note that in the COMBINE study, patients treated with naltrexone achieved better results than patients treated with placebo, while the results obtained did not differ between patients treated with acamprosate and patients treated with placebo [65]. Globally women reported more adverse effects than men with naltrexone treatment [61, 63].

The lack of information on the results obtained by female patients recruited by primary trials of the selected meta-analysis for nalmefene did not allow the possibility of conducting a gender-analysis [55]. Subsequent multicentre RCTs (not included in the meta-analysis we selected) – in which a total of 1,322 AD patients (394 women) were re-

cruited – found that nalmefene significantly reduced the number of heavy drinking days compared to placebo, with the same efficacy in both sexes [77, 78]. This number of patients was three times higher than that in the RCTs evaluated by the meta-analysis we selected. Considering the results obtained by these recent studies, nalmefene may achieve the best level of efficacy both in female and in male AD patients. Nevertheless, the efficacy of nalmefene has recently been severely criticised [79]. It was calculated that nalmefene reduced alcohol consumption by approximately 1–2 units of alcohol per day in people who consumed an average of 13.5 units per day. The magnitude of this effect raises the question whether statistically significant benefits may be marginal in clinical practice [80].

Theoretically, disulfiram could act differently in the two sexes. Indeed, one study (not included in the meta-analysis we selected) found that disulfiram was effective in men with cocaine and AD but not in women with the same disorders [81]. The use of disulfiram for the treatment of cocaine dependence is motivated by a mechanism of action other than ALDH inhibition. In details, the primary metabolite of disulfiram, S-methyl N,N-diethyldithiocarbamate sulfoxide, chelates copper and inhibits the function of enzymes that require copper as a cofactor [82]. One of these enzymes is dopamine β -hydroxylase (D β H), which converts dopamine to noradrenaline in the final step of noradrenaline synthesis in noradrenergic neurons [83]. Through D β H inhibition, it has been found that disulfiram depletes noradrenaline and increases dopamine concentrations in rodents and humans, a mechanism proposed to explain the efficacy of disulfiram for cocaine dependence [83]. The sex difference in the response to disulfiram observed in patients with cocaine and AD may be due to the sex differences in D β H activity, as oestrogens and oral contraceptives stimulate the activity of this enzyme [84, 85]. Accordingly, in women, the inhibition of D β H activity due to disulfiram administration may be attenuated by the stimulating effect of D β H activity induced by oestrogens and/or oral contraceptives. Another study, not included in the meta-analysis we selected, recently found an inverse relationship between the efficacy of disulfiram and D β H activity in patients with cocaine dependence [86].

Sex differences have already been described for benzodiazepines in studies conducted for reasons other than AWS treatment, and not included in the meta-analysis we selected. These studies observed that women metabolise diazepam faster than men do [87, 88]. This difference may be because diazepam is metabolised by the cytochrome enzymes CYP3A4 and CYP2C19, and CYP3A4 is more highly expressed in women than in men [21]. It is therefore possible that women and men may require different doses of benzodiazepines for AWS treatment, as already observed for zolpidem [26].

Women appear to be at higher risk than men to develop brain damage following chronic alcohol consumption [89, 90]. For instance, it has been found that AD women have smaller gray and white matter volumes and greater CSF volumes than healthy women, and that these differences are considerably larger than those found between alcoholic and healthy men, despite the fact that AD women have consumed large amounts of alcohol for fewer years than AD men [91]. The higher vulnerability to the neurotoxic effects of alcohol, and the subsequent increased severity of brain damage in AD women compared to AD men, might

constitute a further cause of possible gender differences in response to AD medications. However, the complete lack of information on female patients does not allow the possibility of investigating the possible differences and potential explanations in response to pharmacotherapy.

In addition, the selected meta-analyses did not report the use of different doses of medications for male and female patients. The doses of some medications (e.g. acamprosate and GHB) were adjusted according to body weight. As women usually have a lower body weight than men, it is possible that female patients received lower doses of these medications than male patients did. However, it was not specified.

Finally, the specific hormonal phases of women life (e.g. pregnancy) were not considered, even if many medications for AD and AWS belonged to FDA class C pregnancy risk [92]. Conversely, female patients should receive doses adjusted according to body weight, at least at the start of treatment and female AD patients of child-bearing age should also be tested for pregnancy before starting pharmacological treatment.

In conclusion, women receive medications for treatment of AD and/or AWS for which efficacy has been demonstrated in studies in which men were more largely represented. The scarce enrolment of women strongly suggests that it is time to perform further studies to evaluate the efficacy and safety of AD and/or AWS medications in women considering different subgroups of the female population, such as adolescents, adults, and the elderly, to reveal gender differences in response to these medications and improve the quality of medical assistance for AD women. It is important to bear in mind that the majority of subjects with AD never receive treatment [35, 93]. Women are more likely than men to meet numerous barriers to accessing treatment, and pregnant women are less likely to receive AD therapy than non-pregnant women [94, 95]. Improving knowledge of the efficacy and safety of medications for treating AD and/or AWS may contribute to the amelioration of the quality of medical assistance for AD women and increase the number of female patients who seek and receive medical treatment for this disorder.

Disclosure Statement

None declared. This study was partially supported by a grant from the Regione Sardegna 'Progetti di farmacovigilanza attiva, finanziabili attraverso i fondi fv 2008/09'. We are grateful to the Major of Osilo and all Municipal Hall for the laboratory space that they dedicated to the National Laboratory in Gender Medicine of INBB.

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