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ORIGINAL ARTICLE

Prescribing practice and off-label use of psychotropic medications in post-acute brain injury rehabilitation centres: A cross-sectional survey

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Abstract

Objective: Guidance on pharmacotherapy of neurobehavioural sequelae post-acquired brain injury (ABI) is limited. Clinicians face the choice of prescribing off-label. This survey assesses prescribing practice and off-label use of psychotropic medications in Italian brain injury rehabilitation centres and factors associated with atypical antipsychotics use.

Materials and methods: Centres were identified through the roster of the Italian Society for Rehabilitation Medicine. Information was collected through a structured questionnaire. This study calculated the prevalence of centres reporting to use off-label individual medications and unconditional logistic regression Odds Ratio (OR), with 95% confidence interval (95% CI) of atypical antipsychotics use.

Results: Psychotropic medications were commonly used. More than 50% of the 35 centres (participation ratio 87.5%) reported to use off-label selected antipsychotics, mostly for agitation (90.5%) and behavioural disturbances (19.0%), and antidepressants, mostly for insomnia (37.5%) and pain (25.0%). Atypical antipsychotic use was directly associated with age <40 years (OR = 2.68; 95% CI = 1.25–5.76), recent ABI (1.74; 0.74–4.09), not with reported off-label use (0.98; 0.44–2.18).

Conclusion: In clinical practice, the effectiveness and safety of medications, in particular off-label, should be systematically monitored. Studies are needed to improve the quality of evidence guiding pharmacotherapy and to evaluate effectiveness and safety of off-label prescribing.

Keywords

Acquired brain injuries, antidepressants, anti-epileptic agents, antipsychotics, off-label, pharmacoepidemiology, prescribing, prevalence, psychotropic medications, survey

History

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Introduction

During post-acute rehabilitation, patients with acquired brain injury (ABI), traumatic and non-traumatic, may suffer neurobehavioural sequelae [1–4] requiring treatment with psychotropic medications. The quantity and quality of evidence guiding pharmacotherapy of neurobehavioural sequelae of ABI is limited. Recent systematic reviews reported supporting evidence of efficacy of methylphenidate, donepezil and dopamine enhancing agents to improve cognition [5, 6], of beta-blockers on aggression [7] and methylphenidate on behaviour (anger/aggression, psychosocial functioning) [5] after traumatic brain injury (TBI). Serotoninergic antidepressants and sertraline had the strongest evidence of efficacy on depression following TBI [8, 9] and a positive effect of methylphenidate has also been reported [10]. SSRIs proved to be effective on post-stroke depression [11]. Paroxetine and buspirone may be effective in reducing anxiety symptoms in stroke patients with co-morbid anxiety and depression [12]. For most treatments, however, the available evidence is insufficient to promulgate practice standards or guidelines and only treatment options (lowest level of recommendation) are currently available [5–9, 13–15].

Therefore, clinicians rely on clinical experience and on treatment options. Moreover, they often face the choice of prescribing off-label.

In several contexts of clinical practice, it is not uncommon to use a medication outside the indications, dose range and patient population approved by regulatory agencies after the scrutiny of pre-clinical and clinical data has confirmed its efficacy and safety [16]. Off-label use of medications raises complex issues [16–21]. Little is known about the prevalence of off-label prescribing in the post-acute rehabilitation of persons with ABI.

A survey was performed to assess the prescribing practice of psychotropic medications in Italian tertiary brain injury rehabilitation centres providing post-acute rehabilitation to inpatients who suffered a severe traumatic or non-traumatic

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brain injury. Objectives of this study were to assess (a) the prevalence of use of psychotropic medications; (b) the prevalence of the off-label use of psychotropic medications; and (c) the factors associated with the use of atypical antipsychotics.

Materials and methods

Study design

This study is a 1-day cross-sectional survey conducted in tertiary centres for post-acute brain injury rehabilitation in Italy. The survey had a centre-level and a patient-level part. The units under study were: (a) in the centre-level part, all the tertiary centres for post-acute brain injury rehabilitation in Italy; and (b) in the patient-level part, all the patients with ABI, following a traumatic or non-traumatic cause, receiving post-acute rehabilitation and hospitalized in the participating centres at the day of the survey. The centres were identified through the roster of the Italian Society for Physical and Rehabilitation Medicine (Società Italiana di Medicina Fisica e Riabilitazione, SIMFER).

Data collection

An invitation e-mail was sent to the medical director of each identified centre. A structured questionnaire and a guide with definitions and instructions were sent to participating centres. At each centre, a designated rehabilitation physician compiled the questionnaire, which encompassed a centre-level and a patient-level part. The centre-level part inquired on facility characteristics, including the number of beds and of inpatients at the time of the survey and prescribing practice. The questionnaire listed 108 psychotropic medications commonly used in the post-acute rehabilitation of persons with ABI and identified by means of a systematic review of the literature (list of medications displayed in Supplemental electronic Table e1). For each of the listed psychotropic medications, the following information was collected: use (yes/no), off-label prescription with reference to the Italian formulary (yes/no) and indication/s (a free text answer without limitations to the number of indications to be reported). In addition, the respondents could report up to 15 additional psychotropic medications, not included in the list. The survey questions are provided in Supplemental electronic Table e2.

The patient-level part of the questionnaire collected, for each included patient, demographic and clinical characteristics, such as gender and age, the Rancho Level of Cognitive Functioning Scale (LCF) score [http://www.rancho.org/Research_RanchoLevels.aspx, last accessed on July 1, 2012] at admission and time since the occurrence of ABI. For each patient a copy of the anonymized medication chart was obtained. The information on the medication used on one single day (the day before the survey) was extracted from the medication chart.

The survey was conducted on 15 September 2012. Centres with a high number of inpatients could collect data over 2 or more consecutive days. A form was sent to non-participating centres to collect information on reasons for not partaking in the survey and on facility characteristics.

Questionnaire delivery, quality controls and data input

Compiled questionnaires were delivered to the study co-ordination centre by mail or e-mail. Upon delivery, compiled questionnaires were inspected for the completeness and consistency of the recorded information. Any omission, error or inconsistent data was checked through immediate contact with the compiling physician and corrected as appropriate. The medications were then classified using the Anatomical Therapeutic Chemical (ATC) classification system codes. The data were recorded into an electronic database using an entry form created specifically for this study. For the input of selected variables, a range of allowable values was established. Further quality control of the data included the identification of missing and out-of-range values, tests for logical data relationships and generation of output for review. Any inconsistency was investigated by reviewing the recorded data, re-examining the questionnaire or through contact with the compiling physician and corrected as appropriate.

Statistical analysis

Descriptive statistics were calculated to characterize the centres. Continuous variables, such as number of beds and of inpatients, were categorized using the quartiles as cut-off values. For each medication, this study calculated the prevalence of centres (a) reporting its use, by dividing the number of centres reporting its use by the total number of participating centres; and (b) reporting its off-label use, by dividing the number of centres reporting its use off-label by the total number of centres reporting to use that medication. For each therapeutic class, the frequency of off-label indications was calculated by dividing the number of centres reporting the individual indication by the number of centres reporting to use off-label at least one medication in the same therapeutic class.

The Odds Ratio (OR), with 95% confidence interval (95%CI), of receiving an atypical antipsychotic agent was calculated by means of multivariate unconditional logistic regression. This analysis was performed on patient-level data and was, therefore, restricted to the 31 centres providing patient-level data. Before building the multivariate model, all variables (reported off-label use of atypical antipsychotics at the centre, yes/no; age; sex; number of weeks since ABI; LCF score; geographical area; number of beds) were evaluated by univariate logistic regression. The variables that explained the variability or modified the regression coefficient estimators were retained in the final model for other covariates.

Statistical analysis was performed using SAS© statistical package 9.2 (SAS Institute Inc., Cary, NC).

Ethics committee review

The study protocol was reviewed by the Ethics Committee at the University Hospital of Udine and at participating centres.

Results

A total of 40 centres were identified and 35 (87.5%) agreed to participate, 31 (77.5%) providing patient-level data (Figure 1). About two-thirds of the participating centres were located in northern Italy, half had 15 or more beds,

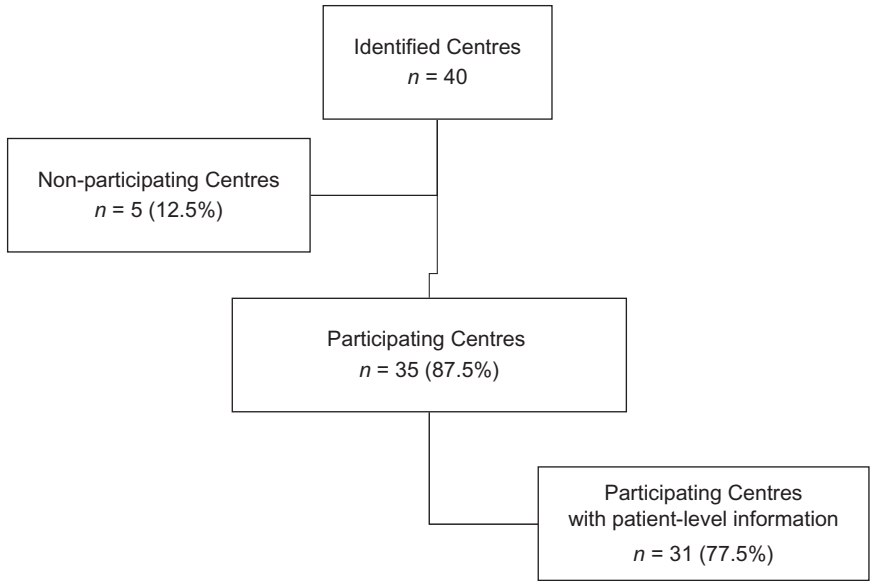

Figure 1. Flow diagram describing the inclusion of Centres for Post-acute Brain Injury Rehabilitation in the survey.

Table I. Characteristics of participating centres.

	n (*n* = 35)	%
Geographic area		
North East	13	37.1
North West	10	28.6
North – sub-total	23	65.7
Centre	6	17.1
South and Islands	6	17.1
Number of beds for patients with ABI		
<8	8	22.9
8–14	9	25.7
15–29	9	25.7
≥30	9	25.7
Minimum–maximum	4–67	
Number of inpatients with ABI		
<6	8	22.9
6–11	6	17.1
12–22	12	34.3
≥23	9	25.7
Minimum–maximum	2–65	

ranging from 4–67, and 60% had 12 or more inpatients at the time of the survey, ranging from 2–65 (Table I).

The prevalence of centres reporting to use and to use off-label individual medications is displayed in Table II. The most used analgesic was tramadol, by 88.6% of the centres, followed by codeine and oxycodone (57.1%). All the centres reported to use levetiracetam, but only one (2.9%) to use it off-label. The second most used antiepileptic was valproate (91.4%), followed by carbamazepine and benzodiazepines (82.9%).

The most used antipsychotics were the atypical agents quetiapine (97%) and olanzapine (83%). More than 50% of the centres reported to use off-label these medications and risperidone, while the prevalence was lower for typical antipsychotics, ranging from 9.5% ($n = 2$) for promazine to 42.9% ($n = 3$) for prometazine.

The most used antidepressants were citalopram (91.4%), sertraline (85.7%) and venlafaxine (74.3%). The antidepressants most used off-label were trazodone, by 57.9% of the centres, amitryptiline (54.5%) and mirtazapine (53.3%).

Bromocriptine was reported to be used off-label by 54.5% of the centres, amantadine by 41.9% and levodopa–benserazide by 35.7%. Table III displays the results for additional medications not included in the list. Of note, eight (22.9%) centres reported the use of beta blocking agents.

The indications for off-label use are displayed in Table IV. Antiepileptics were prescribed for a wide range of indications, including paroxysmal autonomic instability, depression, psychomotor agitation and disturbances such as myoclonus, muscle hypertonia and essential tremor. Three centres reported to use antiepileptics for depression. Psychomotor agitation (90.5%) was the main indication for antipsychotics, followed by behavioural disturbances (19.0%). Insomnia and sleep disturbances (37.5%, $n = 9$), were the main indications for antidepressants, followed by pain (25.0%, $n = 6$), sialorrhea (20.8%, $n = 5$) and psychomotor agitation or neurostimulation (16.7%). Neurostimulation was the main off-label indication for psychostimulants, dopaminergics and anti-dementia drugs.

Among the inpatients of the 31 centres providing patient-level data, the Odds Ratio (OR) of receiving an atypical antipsychotic agent was directly associated with age <40 years, recent (≤11 weeks) ABI and LCF score 4 (confused–agitated) and inversely associated with LCF score 1–2 (none or generalized response) (Table V). When the model was adjusted simultaneously for age, sex, LCF score, time since ABI and geographical location, inpatients of centres reporting atypical antipsychotics off-label use were not at increased risk of receiving these agents (OR = 0.98; 95% CI = 0.44–2.18) compared to inpatients of centres reporting no off-label use.

Discussion

This survey found that psychotropic medications were commonly used in Italian tertiary centres for post-acute brain injury rehabilitation. More than 90% of the centres reported to use levetiracetam, quetiapine, valproate and citalopram. More than 50% of centres reported to use off-label the atypical antipsychotics quetiapine, olanzapine and risperidone and the antidepressants trazodone and amitryptiline. Fewer centres

Table II. Prevalence of centres reporting the use and the off-label use of psychotropic medications[a] by therapeutic class.

		Centres reporting use		Centres reporting off-label use	
Therapeutic class (ATC)	Medication	*n*	%	*n*	%
Analgesics (N02)	tramadol	31	88.6	0	—
	oxycodone	20	57.1	1	5.0
	codeine	20	57.1	0	—
	morphine	14	40.0	1	7.1
	buprenorphine	13	37.1	1	7.7
	methadone	4	11.4	2	50.0
	paracetamol	35	100.0	0	—
Antiepileptics (N03)	levetiracetam	35	100.0	1	2.9
	valproate	32	91.4	3	9.4
	carbamazepine	29	82.9	3	10.3
	benzodiazepines	29	82.9	3	10.3
	oxcarbazepine	27	77.1	2	7.4
	phenytoin	26	74.3	0	—
	pregabalin	25	71.4	1	4.0
	phenobarbital	24	68.6	0	—
	gabapentin	17	48.6	2	11.8
	lamotrigine	16	45.7	0	—
	topiramate	14	40.0	0	—
	tizanidine	14	40.0	2	14.3
	dantrolene	8	22.9	0	—
	zonisamide	3	8.6	0	—
	thiocolchicoside	3	8.6	0	—
	vigabatrin	2	5.7	0	—
	ethosuximide	1	2.9	1	100.0
Antipsychotics (N05A)					
Typical	haloperidol	24	68.6	6	25.0
	promazine	21	60.0	2	9.5
	chlorpromazine	16	45.7	0	—
	promethazine	7	20.0	3	42.9
Atypical	quetiapine	34	97.1	18	52.9
	olanzapine	29	82.9	15	51.7
	risperidone	18	51.4	10	55.6
	clozapine	8	22.9	3	37.5
	sulpiride	6	17.1	3	50.0
	aripiprazole	4	11.4	2	50.0
Anxiolytics, hypnotics and sedatives (N05B, N05C)	lorazepam	29	82.9	1	3.5
	clonazepam	28	80.0	5	17.9
	zolpidem	27	77.1	6	22.2
	alprazolam	26	74.3	0	—
	diazepam	26	74.3	2	7.7
	bromazepam	20	57.1	0	—
	triazolam	17	48.6	1	5.9
	melatonin agonists	8	22.9	1	12.5
	lormetazepam	7	20.0	1	14.3
	flurazepam	4	11.4	0	—
	others[b]	5	14.5	0	—
Antidepressants (N06A)	citalopram	32	91.4	1	3.1
	sertraline	30	85.7	3	10.0
	venlafaxine	26	74.3	4	15.4
	paroxetine	24	68.6	1	4.2
	escitalopram	24	68.6	1	4.2
	duloxetine	23	65.7	1	4.3
	amitriptyline	22	62.9	12	54.5
	trazodone	19	54.3	11	57.9
	mirtazapine	15	42.9	8	53.3
	fluoxetine	15	42.9	2	13.3
	reboxetine	7	20.0	1	14.3
	clomipramine	4	11.4	1	25.0
	lithium	4	11.4	0	—
	fluvoxamine	3	8.6	1	33.3
	imipramine	1	2.9	0	—
Psychostimulants, dopaminergics and anti-dementia drugs (N06B, N06D, N04B)	amantadine	31	88.6	13	41.9
	L-dopa/benserazide	28	80.0	10	35.7
	L-dopa/carbidopa	26	74.3	7	26.9
	bromocriptine	11	31.4	6	54.5
	donepezil	5	14.3	1	20.0

(*continued*)

Therapeutic class (ATC)	Medication	Centres reporting use		Centres reporting off-label use	
		n	%	*n*	%
	memantine	4	11.4	0	—
	rivastigmine	4	11.4	1	25.0
	methyilphenidate	3	8.6	0	—
	modafinil	1	2.9	0	—
	galantamine	1	2.9	0	—

[a]Results for psychotropic medications included in the questionnaire list. The complete list of the 108 psychotropic medications assessed in the questionnaire is available in Supplemental electronic Table 1.
[b]This category includes temazepam, chlordiazepoxide, vigabatrin, buspirone and zaleplon, each used by 1 centre.

Table III. Prevalence of centres reporting the use of additional psychotropic medications.[a]

Medication	ATC	Centres reporting use	
		n	%
beta blocking agents[b]	C07A	8	22.9
clotiapine	N05AH06	3	8.6
L deprenyl	N04BD01	1	2.9
agomelatine	N06AX22	1	2.9
amisulpride	N05AL05	1	2.9
biperiden	N04	1	2.9
clonidine	C02AC01	1	2.9
lacosamide	N03AX18	1	2.9
levomepromazine	N05AA02	1	2.9
acetylcarnitine	N06BX12	1	2.9
oxycodone and naloxone	N02AA55	1	2.9
oxcarbazepine	N03AF02	1	2.9
piracetam	N06BX03	1	2.9
pramipexole	N04BC05	1	2.9
tetrabenazine	N07XX06	1	2.9
trihexyphenidyl	N04AA01	1	2.9
valpromide	N03AG02	1	2.9
zuclopenthixol	N05AF05	1	2.9

[a]Results for additional psychotropic medications not included in the questionnaire list and reported by respondents.
[b]atenolol, $n = 1$; propranolol, $n = 7$.

reported to use off-label typical antipsychotics than atypical ones. Off-label prescribing is not uncommon in several contexts of clinical practice and it raises complex issues [16–21]. The absence of approval for a specific indication or group of patients does not necessarily mean that the medication use is inappropriate for that indication or population. No request to expand the labelling may have been submitted to the regulatory agency, even in the presence of additional supporting evidence [21]. Off-label prescribing may provide a treatment for patients with an orphan disease, prompting access to therapeutic options based on new emerging evidence or new options when approved treatments have failed [22]. On the other hand, off-label prescribing involves the extrapolation of evidence on both effectiveness and safety to an indication not assessed in development trials or to an unstudied population [23]. Therefore, it raises concern, in particular when occurring without scientific evidence on efficacy and safety [17].

In this study, psychomotor agitation was the main off-label indication for atypical antipsychotic agents. Consistently, a previous survey in Italian rehabilitation centres [24] found that atypical antipsychotics were the most used medication for agitation, followed by antiepileptics, typical antipsychotics, benzodiazepines and antidepressants. A recent study found that lorazepam and methotrimeprazine were the most common agitation medications on an 'as needed' basis, while methotrimeprazine and quetiapine were the most used in long-standing treatments [25].

In this survey, the other agitation medications were antidepressants and antiepileptics. The questionnaire list did not include beta blocking agents, reported as additional medications by eight centres.

In clinical practice, antipsychotics and benzodiazepines are commonly used as first line treatment for acute agitation and aggressive behaviour [26]. Atypical antipsychotics are preferred to typical agents for their lower cognitive and motor adverse effects [8, 26]. The strongest evidence of efficacy, however, has been found for beta-blocking agents and methylphenidate [5, 7, 13]. The evidence of efficacy of atypical antipsychotic medications used off-label in other patient populations has been reviewed. This evidence is restricted to a few indications: aripiprazole, olanzapine and risperidone were associated with small but statistically significant benefits for the treatment of agitation and behavioural symptoms in dementia [27].

A retrospective audit conducted in a neurorehabilitation unit for patients with ABI found that the assessment for agitation was not consistently performed to support pharmacological treatment decisions, not to monitor the effectiveness of treatment. Moreover, the results of assessments did not correlate well with pharmacological management [25].

It was found that SSRIs and, in particular, sertraline were the most used antidepressants, consistently with the results of a survey on rehabilitation specialists in the Netherland and the UK [28]. SSRIs [9, 29] and sertraline [7, 9] have been recommended as first choice agents for treating depression in patients with brain injury. In this study, selected antidepressants, such as amitriptyline, trazodone and mirtazapine, were used off-label. The main non-licensed indications were insomnia and sleep disturbances, followed by pain and sialorrhea. Several agents and therapeutic classes were used for neurostimulation, including psychostimulants, antidementia medications, anxiolytics, hypnotics and sedatives, antiepileptics and antidepressants. No firm evidence exists to support any pharmacological intervention for neurofacilitation or neurostimulation [8, 30].

This study found that age <40 years, recent (≤11 weeks) ABI and LCF score 4 are associated with an increased probability of receiving atypical antipsychotics. Agitated and aggressive behaviour, the main off-label indication of antipsychotics in this study, may characterize patients with

Table IV. Number and distribution of reported off-label indications, by therapeutic class.

Therapeutic class	Indication	Centres reporting the off-label indication	
		n	%
Antiepileptics (N03)	paroxysmal autonomic instability	5	38.5
	depression	3	23.1
	psychomotor agitation	2	15.4
	pain	2	15.4
	myoclonus	2	15.4
	muscle hypertonia	2	15.4
	other[a]	9	69.2
	total[b]	13	100.0
Antipsychotics (N05A)	psychomotor agitation	19	90.5
	behavioural disturbance	4	19.0
	depression	2	9.5
	other[c]	6	28.6
	total[b]	21	100.0
Anxiolytics, hypnotics and sedatives (N05B, N05C)	neurostimulation	4	40.0
	muscle hypertonia	2	20.0
	other[d]	7	70.0
	total[b]	10	100.0
Antidepressants (N06A)	insomnia and sleep disturbances	9	37.5
	pain	6	25.0
	sialorrhoea	5	20.8
	psychomotor agitation	4	16.7
	neurostimulation	4	16.7
	inappetence	2	8.3
	dyskinesia	2	8.3
	other[e]	11	45.8
	total[b]	24	100.0
Psychostimulants, anti-dementia drugs (N06B, N06D, N04B)	neurostimulation	13	81.3
	paroxysmal autonomic instability	2	12.5
	other[f]	2	12.5
	total[b]	16	100.0

[a]Includes essential tremor, behavioural disturbance, migraine, infectious fever, seizures, anxiety, neurostimulation, paresthesia, hiccup.
[b]The totals are the number of centres reporting the use off-label of at least one medication of the individual therapeutic class. The totals do not sum up to the total number of indications because more than one indication could be written.
[c]Includes anxiety, inertia, insomnia, frontal lobe syndrome, vertiginous syndrome, hiccup.
[d]Includes pain, paroxysmal autonomic instability, inertia, insomnia and sleep disturbances, anxiety, psychomotor agitation, aggressive behaviour.
[e]Includes compulsive behaviour, emotional incontinence, inertia, anorexia, muscle hypertonia, paroxysmal autonomic instability, paresthesia, psychosis, anxiety, hiccup, tremor.
[f]Includes psychomotor agitation, central fever.

Table V. Odds ratio (OR) and 95% confidence interval (95% CI) of receiving an atypical antipsychotic medication.

	Non-users ($n = 420$) *n* (%)	Users ($n = 54$) *n* (%)	Univariate			Age-adjusted			Multivariate[c]		
			OR	95% CI		OR	95% CI		OR	95% CI	
Center[a] reported off-label prescribing											
No[b]	99 (23.6)	11 (20.4)	1.00	—	—	1.00	—	—	1.00	—	—
Yes	321 (76.4)	43 (79.6)	1.21	0.60	2.43	1.19	0.59	2.41	0.98	0.44	2.18
Age class (years)											
≤39[b]	104 (24.8)	23 (42.6)	2.43	1.20	4.95				2.68	1.25	5.76
40–59	162 (38.6)	17 (31.5)	1.15	0.55	2.42	—	—	—	1.31	0.61	2.85
≥60	154 (36.7)	14 (25.9)	1.00	—	—	—	—	—	1.00	—	—
Sex											
Men[b]	265 (63.1)	34 (63.0)	1.00	—	—	1.00	—	—	1.00	—	—
Women	155 (36.9)	20 (37.0)	1.01	0.60	1.81	1.08	0.59	1.95	1.17	0.62	2.20
LCF score											
1–2 No or generalized response	155 (36.9)	5 (9.3)	0.21	0.06	0.78	0.19	0.05	0.71	0.20	0.05	0.76
3 Localized	76 (18.1)	13 (24.1)	1.13	0.37	3.42	1.14	0.37	3.48	1.20	0.39	3.74
4 Confused–agitated	38 (9.1)	14 (25.9)	2.43	0.79	7.47	2.08	0.66	6.51	2.25	0.69	7.35

(*continued*)

	Non-users ($n = 420$) n (%)	Users ($n = 54$) n (%)	Univariate OR	Univariate 95% CI		Age-adjusted OR	Age-adjusted 95% CI		Multivariate[c] OR	Multivariate[c] 95% CI	
5 Confused, inappropriate, non-agitated	75 (17.9)	13 (24.1)	1.14	0.38	3.47	1.15	0.37	3.53	1.17	0.38	3.63
6 Confused–appropriate	43 (10.2)	4 (7.4)	0.61	0.15	2.47	0.55	0.14	2.26	0.60	0.14	2.47
7–8 Automatic/purposeful and Appropriate[b]	33 (7.9)	5 (9.3)	1.00	—	—	1.00	—	—	1.00	—	—
Time since ABI (weeks)											
≤11[b]	110 (26.2)	22 (40.7)	2.08	0.94	4.60	2.12	0.95	4.74	1.74	0.74	4.09
12–18.5	95 (22.6)	11 (20.4)	1.20	0.49	2.96	1.34	0.54	3.34	1.10	0.42	2.90
18.5–32	111 (26.4)	11 (20.4)	1.03	0.42	2.53	1.11	0.45	2.74	0.99	0.39	2.52
>32	104 (24.8)	10 (18.5)	1.00	—	—	1.00	—	—	1.00	—	—
Geographical area											
Centre[b]	95 (22.62)	14 (25.9)	1.00	—	—	1.00	—	—	1.00	—	—
North-East	113 (26.9)	12 (22.2)	0.72	0.32	1.63	0.68	0.30	1.55	0.67	0.27	1.67
North-West	99 (23.6)	12 (22.2)	0.82	0.36	1.87	0.90	0.39	2.06	0.96	0.40	2.29
South and Islands	113 (26.9)	16 (29.6)	0.96	0.45	2.07	1.00	0.46	2.16	1.17	0.51	2.68

[a]This analysis is restricted to the 31 centres providing patient-level data.
[b]Reference category.
[c]The unconditional logistic regression model included terms for: off-label prescribing of atypical antipsychotics at the centre, age class (≤39 years; 40–59 years; ≥60 years), sex, LCF score, number of weeks since ABI (<11; 11–<18.5; 18.5–32; >32), geographical area (North; Centre; South and Islands).

LCF score 4 and have been positively associated with younger age [31, 32]. The results suggest that these symptoms may be more frequent in the first 3 months after ABI, although the course and timing of recovery has a high inter-patient variability.

Limitations

This survey was conducted in Italian rehabilitation centres and the generalizability of results may be limited. Several factors, including national regulation and drug marketing strategies, affect prescribing practices.

The non-participating centres did not provide any information. One cannot, therefore, evaluate reasons for not participating nor the differences from the participating centres.

This study assessed prescribing practices of psychotropic medication through a physician-compiled questionnaire. Although the compiling physicians were rehabilitation specialist aware of their centre prescribing practice, errors in reporting cannot be ruled out.

The questionnaire sought information about additional psychotropic medications not included in the list. It is, therefore, likely that few, if any, psychotropic medications used in the current practice of the participating centres have been missed.

Conclusions

This survey showed that off-label use of psychotropic medications, in particular selected antipsychotics and antidepressants, is not uncommon in the current clinical practice of ABI rehabilitation centres. Competent, effective and safe off-label prescribing requires high awareness about its scientific validity and medical evidence. Careful and systematic monitoring of the effectiveness and safety of medications, in particular when prescribed off-label, is highly recommended in patients with ABI.

Well designed studies are needed to improve the quality of evidence guiding pharmacological treatments of neurobehavioural sequelae of ABI and to evaluate the risks and benefits of off-label prescribing.

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Declaration of interest

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Good Pharmacoepidemiology Practice: The study adhered to the Guidelines for Good Pharmacoepidemiology Practices (GPP) (International Society for Pharmacoepidemiology, 2008). STROBE (http://www.strobe-statement.org) was used as a guideline for the reporting of observational studies.

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