Anxiety and benzodiazepines. A Delphi method-based survey of knowledge on their pharmacology and clinical use

Ansia e benzodiazepine. Il metodo Delphi basato sulle conoscenze della loro farmacologia e del loro uso clinico

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Summary

Objectives

To evaluate the knowledge of specialists on the pharmacological properties and clinical use of benzodiazepines (BDZs) in anxiety.

Methods

A 16-item online questionnaire, produced using the Delphi method, was submitted to a panel of 300 psychiatrists and neurologists.

Results

The specialists showed poor knowledge regarding the pharmacokinetic and pharmacodynamic principles of BDZs, but good knowledge on the mechanisms of interactions of these drugs and their co-administration in polytherapy. Patients receiving prolonged treatment with BDZs can develop "psychological attachment" to the drug. The phase of tapering down the dose of BDZ that is easiest for patients is the initial, intermediate or final phase, but not an undetermined phase. The optimal withdrawal strategy should take 2-4, 4-6 or 8-12 weeks. All patients are at risk of using BDZs poorly, and the doctor must "educate" the patient on correct administration of BDZs. It is prudent to advise patients to not use BDZs during pregnancy and lactation. The ideal pharmacokinetic profile of a BDZ in elderly subjects is one with a short half-life either without active metabolites or with one or more active metabolites, or an intermediate half-life with no active metabolites. Lorazepam has the best risk/benefit ratio for "acute" use in psychomotor agitation in cases of dementia. Treatment with BDZs should be withdrawn gradually when the symptoms requiring treatment disappear, with the awareness that it can be re-introduced if needed. The specialists indicated an even shorter treatment time than the those reported in the prescribing information for BDZs data sheets.

Conclusions

This shows that the use of BDZs is empirical and based only poorly on clinical and pharmacological knowledge about these compounds.

Key words

Anxiety • Benzodiazepines • Delphi method

Introduction

Benzodiazepines (BDZs) are the most commonly-prescribed class of drugs worldwide due to their anxiolytic, hypnotic, sedative, muscle relaxant and anticonvulsant effects [1 2].

BDZs act by potentiating the gamma-aminobutyric acid (GABA) pathway through binding to the GABA-A receptor, increasing permeability to chloride ions [3]. Once bound to the receptor, BDZs act as positive allosteric modifiers, altering the spatial conformation of the protein complex and increasing the receptor's affinity for GABA [4] and the frequency of channel opening. In this way, BDZs have an inhibitory effect on the central nervous system at the level of the limbic system, the reticular formation of the brain stem and the cerebral cortex [5].

The pharmacokinetic properties of BDZs, and in particular their absorption and metabolism, influence their clinical applicability, since they determine the speed of onset and duration of pharmacological effects [6]. In addition to the chemical characteristics of these drugs, another important factor that influences their absorption is the route of administration [7].

The oral route of administration is most commonly used in the treatment of anxiety, since BDZs administered orally are almost completely absorbed in the gastrointestinal tract, although there are differences in terms of speed of onset. Other factors can also influence the rate of absorption when the drugs are administered orally, and, for example, concomitant administration of anticholinergic drugs can slow gastric emptying. A valid alternative to oral

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administration is a rectal route, which ensures faster absorption than an intramuscular route, while intravenous administration is reserved for emergency treatment of epilepsy (diazepam) or for use in the setting of anaesthesiology (lorazepam and midazolam) since they have an immediate effect when given intravenously [8]. The intramuscular route of administration, characterized by slower and less complete absorption, is used less frequently.
Once in the circulation, 97-99% of BDZs binds to albumin at the BDZs binding site, which ensures a large distribution [6 9]. The duration of the pharmacological effect of BDZs following the administration of a single dose depends on the rate and degree of tissue distribution, hepatic metabolism and the presence of active metabolites [8].
BDZs are metabolised in the liver and excreted in urine [6]. On the basis of their metabolism, the BDZs are divided into those with a long half-life (> 48 h), an intermediate half-life (24-48 h), a short half-life (< 24 h) and a very short half-life (1-7 h). This differentiation has enabled compounds to be classified into those with a predominant anxiolytic and/or sedative effect, as indicated in the British National Formulary [10]. Age, smoking, comorbid conditions and multiple treatments influence the pharmacokinetic parameters of BDZs and the choice of these drugs in various patients.
BDZs are very well tolerated, despite the fact that their chronic use is associated with tolerance, dependence and symptoms of abstinence. The efficacy of BDZs at relieving symptoms of anxiety is well established and has been repeatedly confirmed since their earliest use in clinical practice [11]. Nevertheless, there is a body of contradictory, out-of-date and often only anecdotal literature which hampers the correct and homogeneous use of BDZs in daily clinical practice in the different medical disciplines in which they are commonly used.
The aim of this study was to evaluate, using the Delphi method, the degree of knowledge that a group of psychiatrists and neurologists had about the pharmacological properties and clinical use of BDZs in anxiety.

Materials and methods

Using the Delphi method, an on-line questionnaire consisting of 16 items was prepared and submitted to a group of 300 psychiatrists and neurologists who answered the questions in an anonymous manner. Each item could be answered with a score from 1 to 5 (although not all questions received an answer from all participants). Scores 1 and 2 indicated some degree of disagreement, while scores 3, 4 and 5 indicated progressive levels of agreement. The Delphi technique considers the presence of a positive consensus when > 66% of those interviewed give a score of 3, 4 or 5, while a negative consensus was defined by > 66% of the responses scored as 1 or 2.

The Delphi technique is a widely used and accepted method for gathering data from respondents within their domain of expertise. The technique is designed as a group communication process that aims to achieve a convergence of opinion on a specific real-world issue.
This technique is designed as a group communication process that aims at conducting detailed examinations and discussions of a specific issue for the purpose of goal setting, policy investigation, or predicting the occurrence of future events; while common surveys try to identify "what is," the Delphi technique attempts to address "what could/should be".
The Delphi technique is well suited as a means and method for consensus-building by using a series of questionnaires to collect data from a group of selected subjects; it employs multiple iterations so that this feedback process allows and encourages Delphi participants to reassess their initial judgments about the information provided in previous iterations.
From a practical point of view, the Delphi method consists of a collection of forecasts, operational decisions, or a questionnaire that focuses on a very specific problem recommended by experts in order to achieve, through successive approximations, a "consensus" decision. To achieve this goal, the experts who ignore each other and together act distant, are consulted individually on the same questions; these questions are gathered and their degree of reliability depends on the percentage of consent obtained. The questions with less "consensual" agreement go through a second collection of opinions that implies plenary discussion of the experts interviewed.
This original technique has been adapted and transformed with new applications. Among the best known is its use in the medical world to reach a "Consensus" that is very often found in scientific journals.
The questionnaire was developed by a panel of experts who formulated the questions and possible answers according to different topics and clinical situations.

Results

Pharmacodynamics of BDZs

Effect on the limbic system

The specialists interviewed agreed that the BDZs that act on the limbic system are: lorazepam (88% of those interviewed), oxazepam (85%), bromazepam (88%), triazolam (83%) and clonazepam (90%). Furthermore, there was positive consensus that all the abovementioned BDZs act on the limbic system (79%) (Tab. I).

Hypnotic effects

The specialists interviewed agreed that the BDZs with the

TABLE I.
Responses to the question on whether a given BDZ acts on the limbic system. *Risposte al quesito se una data BDZ agisce sul sistema limbico.*

	1	2	3	4	5	Tot.
Lorazepam	11	34	111	30	187	**373**
	12%		88%			**100%**
Oxazepam	40	17	227	60	29	**373**
	15%		85%			**100%**
Bromazepam	11	32	230	41	59	**373**
	12%		88%			**100%**
Triazolam	16	48	146	30	133	**373**
	17%		83%			**100%**
Clonazepam	11	28	153	108	73	**373**
	10%		90%			**100%**
All the above	62	16	24	48	223	**373**
	21%		79%			**100%**

greatest hypnotic effect are: flurazepam (96% of those interviewed), triazolam (92%), nitrazepam (73%), diazepam (74%) and lorazepam (80%). There was no consensus on the statement that aprazolam is a BDZ with a major hypnotic effect (Tab. II).

Pharmacokinetics of the BDZs

Half-life

The specialists indicated that brotizolam (68%), chlordesmethyldiazepam (94%) and lorazepam (75%) have the longest half-lives. A consensus was not reached considering alprazolam, oxazepam and triazolam are the BDZs with the longest half-lives (Tab. III).

Metabolism

The specialists interviewed agreed that alprazolam (74%), oxazepam (74%) and lorazepam (67%) are not metabolised by CYP450. Consensus was not reached on the statement that bromazepam, prazepam and diazepam are not metabolised by CYP450 (Tab. IV).

TABLE II.
Responses to the question on whether a given BDZ has a hypnotic effect. *Risposte al quesito se una data BDZ ha un effetto ipnotico.*

	1	2	3	4	5	Tot.
Flurazepam	12	3	66	35	257	**373**
	4%		96%			**100%**
Triazolam	22	9	60	44	238	**373**
	8%		92%			**100%**
Nitrazepam	31	68	26	216	32	**373**
	27%		73%			**100%**
Alprazolam	40	192	40	76	25	**373**
	62%		38%			**100%**
Diazepam	55	43	208	29	38	**373**
	26%		74%			**100%**
Lorazepam	46	30	217	55	25	**373**
	20%		80%			**100%**

TABLE III.
Responses to the question on whether a given BDZ has a long half-life. *Risposte al quesito se una data BDZ ha una lunga emivita.*

	1	2	3	4	5	Tot.
Alprazolam	37	195	37	70	34	**373**
	62%		38%			**100%**
Brotizolam	86	34	199	41	13	**373**
	32%		68%			**100%**
Chlordesmethyldiazepam	6	16	61	109	181	**373**
	6%		94%			**100%**
Lorazepam	70	24	212	46	21	**373**
	25%		75%			**100%**
Oxazepam	76	101	140	36	20	**373**
	47%		53%			**100%**
Triazolam	202	19	65	50	37	**373**
	59%		41%			**100%**

Pharmacological interactions of BDZs

Interactions with alprazolam

There was positive consensus regarding the statement that the dose of alprazolam should be reduced in the case of concomitant administration of fluvoxamine (86% of those interviewed), ketoconazole (87%) or erythromycin (68%).

In contrast, 70% stated that the dose of alprazolam did not need to be decreased in the case of concomitant administration of escitalopram.

Finally, consensus was not reached on the need to reduce the daily dose of alprazolam in the case of concomitant administration of fluoxetine or pravastatin (Tab. V).

Toxicity

The specialists considered that the toxicity of BDZs increases in the case of concomitant administration of amitriptyline (87%), alcohol (100%), phenobarbital (94%) or cetirizine (80%).

There was no consensus on the statement that toxicity increases in the case of concomitant administration of pregabalin or theophylline (Tab. VI).

TABLE IV.
Responses to the question on whether a given BDZ is metabolised by CYP450. *Risposte al quesito se una data BDZ è metabolizzata dal CYP450.*

	1	2	3	4	5	Tot.
Alprazolam	53	41	80	141	45	**360**
	26%		74%			**100%**
Bromazepam	36	89	140	63	32	**360**
	35%		65%			**100%**
Prazepam	70	57	188	39	6	**360**
	35%		65%			**100%**
Oxazepam	40	54	138	25	103	**360**
	26%		74%			**100%**
Lorazepam	61	57	182	41	19	**360**
	33%		67%			**100%**
Diazepam	66	76	188	24	6	**360**
	39%		61%			**100%**

TABLE V.
Responses to the question on which drugs alprazolam interacts with. *Risposte al quesito su con quali farmaci interagisce alprazolam.*

	1	2	3	4	5	Tot.
Fluvoxamine	36	15	97	147	65	**360**
	14%		86%			**100%**
Fluoxetine	40	147	81	45	47	**360**
	52%		48%			**100%**
Ketoconazole	14	38	18	163	127	**360**
	14%		87%			**100%**
Pravastatin	36	191	26	81	26	**360**
	63%		37%			**100%**
Escitalopram	44	207	22	65	22	**360**
	70%		30%			**100%**
Erythromycin	35	80	151	43	51	**360**
	32%		68%			**100%**

Dependence on BDZs: the size of the problem

Most of the specialists interviewed (89%) agreed in considering that the problem of dependence (in particular on BDZs) can be summarised as a complex syndrome with somatic and/or psychological manifestations, caused by the prolonged assumption of some compounds, such as BDZs, which have a strong psychoactive potential. Furthermore, 82% of those interviewed considered that patients receiving prolonged treatment with BDZs develop a "psychological attachment" to the substance, which is rarely identified as a real, true dependence. Thus, deciding to stop BZDs and succeed in doing so, without having troublesome symptoms, is particularly complicated.
Considering the problem of dependence, consensus was not reached on the following statements:

- a condition of functional addiction is possible, essentially due to problems of receptor sensitivity;
- it seems possible to exclude that phenomena of metabolic addiction develop due to increased activity of liver enzymes;
- a true picture of dependence, characterized by a compulsive search for the substance, rapid development

TABLE VI.
Responses to the question on which substances increase the toxicity of BDZs when taken concomitantly. *Risposte al quesito su quali sostanze incrementino la tossicità delle BDZ se assunte in concomitanza.*

	1	2	3	4	5	Tot.
Amitriptyline	8	39	97	156	60	**360**
	13%		87%			**100%**
Alcohol	1	0	22	78	259	**360**
	0%		100%			**100%**
Phenobarbital	5	16	40	51	248	**360**
	6%		94%			**100%**
Cetirizine	27	45	139	118	31	**360**
	20%		80%			**100%**
Pregabalin	34	205	15	68	38	**360**
	66%		34%			**100%**
Theophylline	67	148	79	38	28	**360**
	59%		41%			**100%**

of tolerance, and the need for progressively increasing doses to obtain the same benefit, has almost never been found with BDZs;
- the risk of developing a real, true dependence on BDZs is defined as very low by various authors who have reviewed international literature (Tab. VII).

The strategy of preventing BDZs withdrawal syndrome

The most easily tolerated stage of tapering of BDZs

The specialists interviewed stated that the stage of gradual reduction of the dose of BDZs that is easiest to tolerate for patients is, without difference, the initial (76%), intermediate (76%) or final (80%) stage.

The group interviewed reached a negative consensus (76%), considering the statement that the easiest phase to reduce the dose of BDZs is undetermined.

Finally, consensus was not reached on the items according to which the phase of reduction that is easiest to tolerate is, indifferently, the initial, intermediate or final one, and that the phase is determined by somatic comorbidity (Tab. VIII).

Optimal duration of a BDZs withdrawal strategy

The participants in the survey agreed in stating that, for most patients, the optimal duration of a withdrawal strategy is 2-4 weeks (70% of those interviewed), 4-6 weeks (76%), or 8-12 weeks (82%). Thus, the overall evaluation does not appear to discriminate between different clinical practices. However, a more detailed analysis of the responses, considering the numbers agreeing on each of the proposed options, did reveal some differences. For the responses "2-4 weeks" and "4-6 weeks", the sum of scores 4 and 5 (strongest agreement) was high (174 and 249 respondents, respectively), while for "8-12 weeks" more participants chose score 3 (216 respondents), half way on the scale between negative and positive consensus. There was agreement (74%) that the withdrawal strategy should not last 20-40 weeks, whereas agreement was not reached on the options 12-16 weeks and 16-20 weeks (Tab. IX).

The psychological profile associated with excessive use of BDZs

With regards to the psychological profile associated with excessive use of BDZs, the specialists interviewed agreed on the following points:
- all patients are constantly at risk of using BDZs poorly (80%);
- not all patients are at risk of using BDZs poorly (78%);
- it is the duty of the doctor to identity, each time, spe-

TABLE VII.
Responses to statements on dependence on BDZs. *Risposte alle affermazioni sulla dipendenza da BDZ.*

	1	2	3	4	5	Tot.
Dependence on a substance is a complex syndrome with somatic and/or psychological manifestations, caused by the prolonged assumption of some compounds, such as BDZs, which have a strong psychoactive potential	26	14	30	27	259	**356**
	11%		89%			**100%**
A condition of functional addiction is possible, essentially due to problems of receptor sensitivity	47	117	111	45	36	**356**
	46%		54%			**100%**
It is known that patients receiving prolonged treatment with BDZs can develop a "psychological attachment" to the substance, which is rarely identified as a real, true addiction, so deciding to stop taking them and succeed doing so, without having troublesome symptoms, is particularly complicated	47	17	18	231	43	**356**
	18%		82%			**100%**
It seems possible to exclude that phenomena of metabolic addiction develop due to increased activity of liver enzymes	19	193	24	84	36	**356**
	60%		40%			**100%**
A true picture of dependence, characteriszed by a compulsive search for the substance, rapid development of tolerance, and the need for progressively increasing doses to obtain the same benefit, has almost never been found with BDZs	90	123	70	50	23	**356**
	60%		40%			**100%**
The risk of developing a real, true dependence on BDZs is defined as very low by various authors who have reviewed international literature	67	143	92	75	29	**356**
	59%		41%			**100%**

TABLE VIII.
Responses to statements on the most easily tolerated phase of tapering BDZs. *Risposte alle affermazioni sulla fase di riduzione graduale delle BZD più facilmente tollerata.*

	1	2	3	4	5	Tot.
Initial phase	66	18	43	23	206	**356**
	24%		76%			**100%**
Intermediate phase	43	43	81	180	9	**356**
	24%		76%			**100%**
Final phase	32	39	28	32	225	**356**
	20%		80%			**100%**
Indifferently considering the initial, intermediate, or final phases	128	23	122	46	37	**356**
	42%		58%			**100%**
Undetermined	238	33	47	25	13	**356**
	76%		24%			**100%**
Determined by somatic comorbidity	47	145	82	49	33	**356**
	54%		46%			**100%**

cific characteristics of the patient and "educate" him or her on the correct use of BDZs (96%);
- patients who use BDZs poorly have specific characteristics (84%);
- the risk of using BDZs poorly is increased mainly in patients who have already shown dependence on other substances and/or addiction to alcohol (92%);
- patients with a tendency to use BDZs incorrectly have three characteristic features: (i) intake of a dose four times higher than the recommended one, (ii) maintenance of treatment for more than 12 months, (iii) history of concomitant intake of alcohol or other drugs (90%) (Tab. X).

Clinical risks of BDZs during pregnancy and breastfeeding

The majority of the specialists who participated in the survey agreed on the following statements concerning the use of BDZs during pregnancy and breastfeeding:
- definitive data on the teratogenic potential of BDZs

TABLE IX.
Responses to statements on the optimal duration of a BDZs withdrawal strategy. *Risposte alle affermazioni sulla durata ottimale di una strategia di sospensione da BDZ.*

	1	2	3	4	5	Tot.
2-4 weeks	57	50	75	125	49	**356**
	30%		70%			**100%**
4-6 weeks	40	44	23	231	18	**356**
	24%		76%			**100%**
8-12 weeks	21	43	216	40	36	**356**
	18%		82%			**100%**
12-16 weeks	9	183	68	42	54	**356**
	54%		46%			**100%**
16-20 weeks	45	146	49	92	24	**356**
	54%		46%			**100%**
20-40 weeks	51	213	24	50	18	**356**
	74%		26%			**100%**

TABLE X.
Responses to statements on the psychological profile of patients misusing BDZs. *Risposte alle affermazioni sul profilo psicologico dei pazienti che abusano di BDZ.*

	1	2	3	4	5	Tot.
All patients are constantly at risk of using BDZs poorly	28	43	30	156	95	**352**
	20%		80%			**100%**
Not all patients are at risk of using BDZs poorly	40	38	81	35	158	**352**
	22%		78%			**100%**
It is the duty of the doctor to identity, every time, specific characteristics of the patient and "educate" him or her on the correct use of BDZs	11	3	50	42	246	**352**
	4%		96%			**100%**
Patients who use BDZs poorly have specific characteristics	11	45	144	96	56	**352**
	16%		84%			**100%**
The risk of using BDZs poorly increases mainly in patients who have already shown dependence on other substances and/or addiction to alcohol	21	8	26	54	243	**352**
	8%		92%			**100%**
Patients with a tendency to use BDZs incorrectly have three characteristic features: (i) intake of a dose 4 times higher than the recommended one, (ii) maintenance of treatment for more than 12 months, (iii) history of contemporaneous intake of alcohol or other drugs	16	19	51	32	234	**352**
	10%		90%			**100%**

are lacking despite the fact that these drugs have been on the market for more than 30 years (82%);
- some data in the literature suggest that malformations (cleft lip and palate) can occur in association with prolonged use of BDZs, but do not seem to be significant, given the methodological weaknesses involved in the observations (86%);
- it seems prudent to not use BDZs during pregnancy, and in particular during the first trimester (100%);
- BDZs cross the placental barrier and affect the foetus; it has been seen that the foetal heart rate is altered by the administration of diazepam given to alleviate labour pain (92%);
- diazepam passes freely into breast milk: since neonates are particularly sensitive to the toxic and paradoxical effects of the drugs, great care must be taken to avoid phenomena of sedation because the infant could develop problems with suction and, therefore, interfere with normal body growth (96%).

In contrast, a consensus was not reached on the statement that BDZs must not be taken during pregnancy (Tab. XI).

The risk-benefit ratio of BDZs in the elderly

Pharmacokinetics of the ideal BDZs for the elderly patient

According to the specialists interviewed, the ideal BDZ for elderly patients should have the following pharmacokinetic profile: a short half-life and no active metabolites (92% of those interviewed), a short half-life and one or more active metabolites (74%), or an intermediate half-life and no active metabolites (79%).

The participants in the survey agreed in considering that a BDZ with an intermediate half-life and one or more active metabolites (75%), a long half-with no active metabolites (84%) or a long half-life with one or more active metabolites (88%) was not ideal for elderly patients (Tab. XII).

The BDZ which, administered intramuscularly, has the best risk/benefit ratio for "acute" use in psychomotor agitation in dementia

Most specialists interviewed (72%) considered that lorazepam is the BDZ that, administered intramuscularly, has the highest risk/benefit ratio for "acute" use in psychomotor agitation in dementia.

Consensus was not reached on diazepam, chlordiazepoxide, chlordesmethyldiazepam, midazolam or any other BDZs available for intramuscular injection (Tab. XIII).

General principles of the management of duration of treatment with BDZs

Management of the duration of treatment with BDZs

With regards to the management of the duration of treatment with BDZs, the specialists who participated in the survey responded that the following aspects should be taken into consideration:
- since anxiety is a state of sufferance that is often episodic and related to transient conditions, it is a good

TABLE XI.
Responses to statements on the clinical risks of taking BDZs during pregnancy and breastfeeding. *Risposte alle affermazioni sui rischi clinici nell'assumere BDZ durante la gravidanza e l'allattamento.*

	1	2	3	4	5	Tot.
BDZs must not be taken during pregnancy	45	132	20	47	108	**352**
	50%		50%			**100%**
Although BDZs have been on the market for more than 30 years, definitive data on their teratogenic potential are lacking	19	44	218	40	31	**352**
	18%		82%			**100%**
Some data in the literature suggest that malformations (cleft lip and palate) can occur in association with prolonged use of BDZs, but do not seem to be significant given the methodological weaknesses involved in the observations	9	40	224	34	45	**352**
	14%		86%			**100%**
It seems prudent to not use BDZs during pregnancy, and in particular during the first trimester	0	1	60	44	247	**352**
	0%		100%			**100%**
BDZs cross the placental barrier and affect the foetus; it has been seen that the foetal heart rate is altered by the administration of diazepam given to alleviate labour pain	6	21	25	220	80	**352**
	8%		92%			**100%**
Diazepam passes freely into breast milk: since neonates are particularly sensitive to the toxic and paradoxical effects of the drugs, great care must be taken to avoid phenomena of sedation because a sleepy baby could develop problems with suction and, therefore, interfere with normal body growth	8	6	35	221	82	**352**
	4%		96%			**100%**

idea to withdraw treatment (gradually in all cases) as soon as the anxiety disappears, with the awareness that the treatment can be re-introduced if needed again (83%);
- it is sometimes useful to warn the patient that dependence (mainly psychological) on the drug can develop and it is not, therefore, clinically useful to continue treatment indefinitely because it could then become difficult to stop (96%);
- a precautionary approach should be adopted for patients who can exploit it best and should not be used indiscriminately (79%);

TABLE XII.
Responses to statements on the pharmacokinetic profile of the ideal BDZ for elderly patients. *Risposte alle affermazioni sul profilo farmacocinetico della BDZ ideale per i pazienti anziani.*

	1	2	3	4	5	Tot.
Short half-life, no active metabolites	17	12	43	23	257	**352**
	8%		92%			**100%**
Short half-life, one or more active metabolites	66	25	82	142	37	**352**
	26%		74%			**100%**
Intermediate half-life, no active metabolites	40	34	49	207	22	**352**
	21%		79%			**100%**
Intermediate half-life, one or more active metabolites	45	219	24	43	21	**352**
	75%		25%			**100%**
Long half-life, no active metabolites	52	244	12	34	10	**352**
	84%		16%			**100%**
Long half-life, one or more active metabolites	236	74	13	13	16	**352**
	88%		12%			**100%**

TABLE XIII.
Responses to statements on the BDZs which, administered intramuscularly, have the highest risk/benefit ratio for "acute" use in psychomotor agitation in dementia. *Risposte alle affermazioni sulle BDZ che, somministrate per via intramuscolare, hanno il miglior rapporto rischio/beneficio per l'impiego "acuto" nell'agitazione psicomotoria.*

	1	2	3	4	5	Tot.
Diazepam	71	149	70	38	20	**348**
	63%		37%			**100%**
Chlordiazepoxide	35	192	37	33	51	**348**
	65%		35%			**100%**
Lorazepam	54	44	26	35	189	**348**
	28%		72%			**100%**
Chlordesmethyldiazepam	46	117	33	36	56	**348**
	47%		53%			**100%**
Midazolam	46	180	33	33	56	**348**
	65%		35%			**100%**
Any other BDZ available for intramuscular injection	216	12	36	27	57	**348**
	66%		34%			**100%**

- psychological strategies of strong reassurance and progressive «exposure» to some anxiety-inducing stimuli should be used to give the patient a conscious comfort of working towards symptomatic improvement, but also towards psychological growth supported by the drug (85%);
- it is important to use a personalized and extremely flexible dose and check that the patient does not increase the prescribed dose on his or her own initiative (96%).

In contrast, consensus was not reached on the option that a patient should be informed at the start of the treatment that the therapy cannot be continued for too long, and that it must follow rules that should be established in advance (Tab. XIV).

Treatment times reported in the product data sheets

With regards to the treatment times reported in the product data sheets for BDZs, the specialists interviewed reached a positive consensus on the following statements:

- 2 weeks for insomnia and 4-6 weeks for anxiety disorders (74%);
- 4 weeks for insomnia and 4-6 weeks for anxiety disorders (79%);
- 4 weeks for insomnia and 8-12 weeks for anxiety disorders (90%);
- 8 weeks for insomnia and 8-12 weeks for anxiety disorders (67%).

However, 68% of those interviewed did not agree that the times reported in the product data sheets are 10 weeks for insomnia and 20-24 weeks for anxiety disorders.

Finally, consensus was not reached on the option that the times reported in the BDZs data sheets are 6 weeks for insomnia and 18-20 weeks for anxiety disorders (Tab. XV).

Variables related to the treatment times reported in the data sheets

The participants in the survey agreed in stating that the duration of treatment with BDZs must take into account the clinical response (98%), severity of the anxiety (94%), whether triggering factors are still present (94%), the patient's personality (94%), psychoactive drug history (92%) and patient preference (75%) (Tab. XVI).

Discussion and conclusions

This study was designed to evaluate the level of knowledge on the use of BDZs in a group of psychiatrists and neurologists.

With regards to the pharmacodynamics of the drugs, specialists were asked which of the following BDZs, lorazepam, oxazepam, bromazepam, triazolam, or clonazepam, has an effect on the limbic system and which out of flurazepam, triazolam, nitrazepam, alprazolam, diazepam and lorazepam has a hypnotic effect. The specialists agreed that all the BDZs indicated have an effect on the limbic system, whereas they did not consider that alprazolam to have hypnotic effects. This is partially in agreement with the data from the literature. On this subject, Nelson and Chouinard [12] documented that lorazepam, oxazepam and bromazepam have a marked effect

TABLE XIV.
Responses to statements on the management of duration of treatment with BDZs. *Risposte alle affermazioni sulla gestione della durata del trattamento con BDZ.*

	1	2	3	4	5	Tot.
The patient should know from at start of treatment that the therapy cannot be continued for too long, but that it must follow rules that should be established in advance	1	16	26	37	268	**348**
	49%		51%			**100%**
Since anxiety is a state of sufferance that is often episodic and related to transient conditions, it is a good idea to withdraw treatment (gradually in all cases) as soon anxiety disappears, with the awareness that the treatment can be re-introduced if needed again	39	21	8	233	47	**348**
	17%		83%			**100%**
It is sometimes useful to warn the patient that dependence (mainly psychological) on the drug can develop and it is not, therefore, clinically useful to continue treatment indefinitely because it could become difficult to stop	8	6	56	232	46	**348**
	4%		96%			**100%**
A precautionary approach should be adopted for patients who can exploit it best and should not be used indiscriminately	20	54	25	89	160	**348**
	21%		79%			**100%**
Psychological strategies of strong reassurance and progressive «exposure» to some anxiety-inducing stimuli should be used to give the patient the conscious comfort working towards a symptomatic improvement, but also towards psychological growth supported by the drug	20	33	15	211	69	**348**
	15%		85%			**100%**
It is important to use a personalized and extremely flexible dose and ensure that the patient does not increase the prescribed dose on his or her initiative	7	7	12	64	258	**348**
	4%		96%			**100%**

on the limbic system, explaining their anxiolytic action. In contrast, triazolam acts predominantly on the brain stem, which justifies its hypnotic property and its suitability for short-term treatment of insomnia. Clonazepam acts mainly on the reticular formation, the midbrain and the cerebral cortex, and is thus more indicated for the treatment of epilepsy in adults and for the treatment of focal seizures [12].

TABLE XV.
Responses to statements on the duration of BDZs treatment indicated in the product data sheets. *Risposte alle affermazioni sulla durata del trattamento con le BDZ indicata nelle schede tecniche di prodotto.*

	1	2	3	4	5	Tot.
2 weeks for insomnia and 4-6 weeks for anxiety disorders	57	33	16	46	196	**348**
	26%		74%			**100%**
4 weeks for insomnia and 4-6 weeks for anxiety disorders	53	20	207	44	24	**348**
	21%		79%			**100%**
4 weeks for insomnia and 8-12 weeks for anxiety disorders	16	19	207	45	61	**348**
	10%		90%			**100%**
6 weeks for insomnia and 18-20 weeks for anxiety disorders	19	186	13	57	73	**348**
	59%		41%			**100%**
8 weeks for insomnia and 8-12 weeks for anxiety disorders	91	25	111	92	29	**348**
	33%		67%			**100%**
10 weeks for insomnia and 20-24 weeks for anxiety disorders	153	85	22	64	24	**348**
	68%		41%			**100%**

TABLE XVI.
Responses to statements on whether certain variables should be taken into consideration when determining the duration of treatment with BDZs. *Risposte alle affermazioni sul fatto che alcune variabili dovrebbero essere tenute in considerazione nel determinare la durata del trattamento con BDZ.*

	1	2	3	4	5	Tot.
Clinical response	7	0	21	67	253	**348**
	2%		98%			**100%**
Severity of the anxiety state	7	14	19	225	83	**348**
	6%		94%			**100%**
Persistence of triggering factors	7	14	36	98	193	**348**
	6%		94%			**100%**
Patient's personality	7	14	38	101	188	**348**
	6%		94%			**100%**
Psychoactive drug history	8	20	30	101	189	**348**
	8%		92%			**100%**
Patient preference	66	20	193	24	45	**348**
	25%		75%			**100%**

Concerning the pharmacokinetics of BDZs, the specialists indicated that those with a longer half-life are brotizolam, chlordesmethyldiazepam and lorazepam, compared to alprazolam, oxazepam and triazolam, which were identified as BDZs with a shorter half-life. Considering the half-life of these drugs, the only BDZ with a long half-life is chlordesmethyldiazepam (50-140 hours), while lorazepam (10-20 hours) and brotizolam (3-5 hours) have a short and ultrashort half-life, respectively. The participants correctly indicated that alprazolam (6-12 hours), oxazepam (5-24 hours) and triazolam (2-5 hours) do not have a long half-life.

Alprazolam, oxazepam and lorazepam were identified by specialists as BDZs that are not metabolised by cytochrome P450 (CYP450), in contrast to bromazepam, prazepam and diazepam. However, alprazolam and prazepam are in fact metabolised by CYP450 and in particular by CYP3A4, while diazepam is metabolised by CYP3A4 and CYP2C19. In contrast, oxazepam and lorazepam are metabolised by glucuronyl-transferase, while the route of metabolism of chlordiazepoxide has not yet been determined.

Adverse drug reactions and drug-drug interactions are responsible for increased health costs and admissions to hospital [13-15]. Thus, early recognition of the adverse drug reactions and correct prescriptions could improve adherence with pharmacological treatments and reduce health costs. For this reason, the participants in the study were asked which drugs interact with BDZs. The specialists correctly indicated that the toxicity of BDZs increases in the case of concomitant administration of amitriptyline, alcohol and phenobarbital, but not in the case of concomitant administration of pregabalin or theophylline. However, 80% of those interviewed considered that there could be interaction between cetirizine and BDZs. Griffin et al. reported interactions between BDZs and inducers or inhibitors of CYP3A4, and between BDZs and substances that depress the respiratory system, such as antidepressants, barbiturates and alcohol [16]. Although cetirizine is able to induce sedation [17], no cases of interactions between cetirizine and BDZs have been reported to date. Alprazolam is metabolised by CYP3A4 [16], as correctly indicated by the specialists participating in the survey, and fluvoxamine, ketoconazole and erythromycin, which are inhibitors of CYP3A4, are able to increase the plasma concentrations of alprazolam, while escitalopram, fluoxetine and pravastatin do not interact with alprazolam.

With regards to the problem of dependence on BDZs, the specialists reached a consensus on only two of the six items proposed. They consider that this problem can be summarised as a complex syndrome with somatic and/or psychological manifestations, caused by the prolonged assumption of these drugs, which have a strong psychoactive potential. Furthermore, patients receiving prolonged treatment with BDZs can develop a "psychological attachment" to the substance, which is rarely identified as a real, true dependence, and therefore it is decisions to interrupt its administration and to succeed in doing so without having troublesome symptoms, are particularly complicated.

According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), depend-

ence on BDZs is characterized by biological features, such as the onset of tolerance and rebound symptoms at drug withdrawal and/or an abstinence syndrome, and by psychosocial features, such as a persistent desire for the substance (craving), interrupted, reduced, or compromised social and working activities, and continued use of the substance despite the presence of psychophysical disorders and complications contraindicating its use [18].

Laux and Puryear evaluated numerous series and identified three types of dependence on BDZs: (i) primary high-dose, when the dose used is more than five times higher than the therapeutic dose, (ii) primary low-dose, when the dose taken is a therapeutic one, and (iii) secondary, related to abuse of several drugs, in particular in association with dependence on alcohol [19].

It was recently seen that individuals who become dependent on BDZs have particular psychological and situational characteristics. Examining the psychological profile of 120 subjects, 60 patients with a diagnosis of dependence on BDZs and an equally-sized control group formed of past users of BDZs who had not developed dependence, it was found that dependence on these drugs was associated with higher levels of neuroticism and introversion and with a prevalence of emotional rather than task-based mechanisms for coping with stressful situations [20]. Furthermore, significant correlations were found between dependence and negative or traumatic experiences before the treatment or prior to inadequate therapy with BDZs (e.g., use without medical prescription). The psychological and situational factors that were identified could, therefore, be considered as potential risk factors for addiction to BDZs. Greater awareness among specialists of the various risk factors for dependence could lead to improved strategies for managing treatment [20]. Concerning the problem of dependence on BDZs, it is important to emphasize that a consensus was not reached on the options related to: the establishment of a state of functional addiction; the absence of phenomena of metabolic addiction; the lack of a real picture of addiction understood as craving for the substance, the rapid development of tolerance and the need for progressively increasing doses to obtain the same effect; and the almost total absence of a real physical dependence on BDZs. These results suggest scarce information and/or experience of this clinical aspect of the use of BDZs among the specialists interviewed.

With regards to strategies to prevent BDZ withdrawal syndrome, the specialists who were asked to reply to two questions. The first concerned the phase of gradual dose reduction of the BDZs that is easiest for patients to tolerate. There was a positive consensus on each of the options: the initial, intermediate, or final phase. Thus, the overall evaluation did not seem to discriminate between different clinical periods. Further analysis of the responses, examining the number of responses to each option, did however reveal some differences. The sums of participants choosing scores 4 and 5 (maximum agreement) for the "initial phase" and "final phase" were high, whereas most of the scores for the "intermediate phase" were 4 (n = 180) and 3 (n = 81), indicating a globally weaker consensus and showing, ultimately, stronger belief in the idea that patients tolerate the initial and final phases of BDZ withdrawal better than the intermediate one. There did not, however, seem to be clear information and/or experience about this clinical aspect among the participants of the survey. The interruption of treatment with BDZs or an abrupt reduction in dose after 4-6 weeks of continuous intake can lead to the development of both psychological and physical withdrawal symptoms in about 15-30% of patients [21]. The most common symptoms are insomnia, agitation, anxiety, altered perception, dysphoria and gastrointestinal disturbances. More rarely, severe reactions may occur, such as *petit mal* or *grand mal* seizures, coma and psychotic states. The symptoms of BDZ withdrawal can usually be avoided or controlled by gradual reduction in the dose of the drug in order to allow re-adaptation of the GABA-A receptors and to minimise the rebound effect [8 22 23]. In a broad review of the use of BDZs in clinical practice, it was reported that the early phases of treatment withdrawal are usually easier to tolerate than the subsequent or final stages, so the specialist must remain alert to the possible development of withdrawal symptoms, particularly when continuing the tapering-down process [10].

With regards to the second question about the optimal duration of the withdrawal of BDZs, the overall evaluation of the specialists interviewed, on which a consensus was reached, did not discriminate between the three different periods proposed (2-4 weeks; 4-6 weeks; 8-12 weeks). Re-analysis of the results, examining the scores for each option, did show some differences. In particular, for "2-4 weeks" and "4-6 weeks" the sum of number of scores 4 and 5 (strongest agreement) was higher (174 and 249, respectively), while for the option "8-12 weeks" essentially equal numbers of specialists disagreed (scores 1 and 2) or strongly agreed (scores 4 and 5), with most choosing score 3. Some authors have highlighted the lack of data supporting an optimal strategy for the duration of the withdrawal phase of BDZs, which still remains undetermined. It is generally recommended that the tapering down takes place over a period of 8-12 weeks and is completed within 6 months [24 25]. The importance of flexibility in the administration of BDZs during the withdrawal phase, with personalised management, should be emphasized. This is also true with regards to the duration of treatment and the possible slowing of the tapering in the case that withdrawal symptoms are too distressing [26].

Concerning identification of a psychological profile asso-

ciated with excessive use of BDZs, the specialists agreed on all the items proposed. It is worth commenting on the first two points, "All patients are constantly exposed to the risk of using BDZs poorly" - "Not all patients are at risk of using BDZs poorly", since the overall evaluation on which a consensus was reached appears to be contradictory with regards to the specific content of the items themselves, which are in contrast. This seems to reflect an underlying ambivalence that the specialists have concerning treatment with BDZs, particularly with regards to the potential risk of their inappropriate use. Even a deeper analysis of the responses, considering the degree of consensus on the two options, does not help much in resolving this ambivalence. The number of participants who chose scores 4 or 5 (strongest agreement) for the item "All patients are constantly exposed to the risk of using BDZs poorly" was 251, while that for the item "Not all patients are at risk of using BDZs poorly" was 193.

The excessive use of BDZs, in terms of dose and/or duration, includes the phenomena of over-prescription and habitual self-medication under the "control" or, better still, with the complicity of the physician, in a doctor-patient relationship in which the responsibilities seem to be broadly shared [27 28]. Furthermore, a substantial proportion of BDZs are obtained without a medical prescription [29].

There are numerous reasons why overuse of BDZs has been increasing in recent years, and all are related to the positive, general characteristics of these drugs: (i) risk/benefit ratio strongly in favour of the latter; (ii) good tolerability even in the long-term; (iii) few contraindications; (iv) little toxicity even in the elderly and patients with chronic diseases; (v) easy to manage and/or can be associated with other drugs; (vi) low cost. These qualities have contributed to the large-scale use of BDZs with underestimation and poor prediction of the phenomena resulting from their overuse: misuse and abuse/dependence [27 28].

Misuse is the use of a drug that is mistaken, incorrect or inappropriate considering its indications, dose, duration or methods of treatment for the subject and/or circumstances. It is a characteristic feature of patients predisposed to abuse/dependence, who generally take doses more than four times higher than the recommended ones, are under treatment for more than 12 months and have a positive history of associated use of alcohol or other psychoactive drugs [30]. Furthermore, an increasing number of people with problems of alcohol dependency are misusing BDZs, since the association of these two substances increases the sensation of inebriation [10 31]. These literature data are in agreement with the last two items proposed, over which very high percentages of specialists participating in the survey (92% and 90%, respectively) reached a positive consensus and which concerned the excessive use of these drugs in patients dependent on alcohol and other substances and in subjects who, besides being dependent, take doses more than four times higher than recommended and who have been receiving therapy for more than 12 months. On the basis of these results it can be stated that the specialists interviewed have a good knowledge on the psychological profile of the subjects most at risk of incorrect use of BDZs. This knowledge is fundamental for correct management of the treatment, minimising the risk of both dependence and an abstinence syndrome on withdrawal of the drug.

Considering the possible clinical risks related to taking the drug during pregnancy or breastfeeding, the specialists reached a consensus on five of the six items proposed, whereas they did not reach a consensus on the statement that BDZs must not be taken during pregnancy (first item). The lack of consensus on this point deserves some comment, particularly if compared with the opinion about the prudence of not advising the use of BDZs during pregnancy, especially during the first trimester (fourth item). There was 100% agreement over this item and the sum of the respondents giving a score of 4 or 5 (strongest agreement) to this item was 291. Although the two items do not express the same concept – the former, in particular, reveals uncertainty about an "all or nothing" approach to prescribing BDZs in pregnancy, while the latter reflects an opinion on the "non-utility" of using the drugs – it does appear that there is some ambivalence underlying the two responses.

With regards to the problem of the teratogenic potential of BDZs, the specialists' opinions are more or less in agreement with the data in the literature. In fact, some authors have found significant associations between the use of BDZs in the first trimester of pregnancy and the development of specific (cleft lip and palate) or major (pulmonary, cardiac, renal and skeletal) malformations and dysmorphic phenomena (epicanthus, high-arched palate, webbed neck, wide-spaced nipples), whereas these findings were not confirmed by subsequent studies, thus preventing a definitive conclusion on the teratogenic risk of this class of psychoactive drugs [32 35]. Two meta-analyses [36 37] evaluated the relationship between the assumption of BDZs in the first trimester and the development of congenital anomalies. Despite the evident methodological problems of the various studies considered (heterogeneity and size of the groups studied, type of BDZs used, method of classifying the malformations, exposure to other potentially teratogenic drugs, bias in collection of information related to recall), both meta-analyses showed significant increases in specific malformations such as cleft lip and cleft palate in case-control studies. These increases were not, however, significant when only the cohort studies were analysed [37]. Enato et al. recently updated the meta-analysis by Dolovich et al. [37] including another three cohort studies: they did not find any association between the use of BDZs in pregnancy and the risk

of teratogenesis [38]. Another study compared the use of different BDZs during pregnancy, demonstrating that diazepam and chlordiazepoxide have a good safety profile, unlike clonazepam, alprazolam and lorazepam, which were associated with a high risk of teratogenesis when used in pregnancy [39]. These results suggest that the safety profile of each BDZ is important when choosing a drug to prescribe in the early stages of pregnancy [40]. The administration of BDZs during labour and particularly during the last stage of gestation is associated with symptoms of overdose in the neonate, such as sedation, flaccidity, difficulty in sucking, cyanosis, periods of apnoea and defects in thermoregulation. Furthermore, neonates of mothers who were taking BDZs on a chronic basis were found to develop symptoms resembling those occurring in abstinence, such as tremors, hypertonia, hyperreflexia, diarrhoea, vomiting and tachypnoea [41]. Only a few studies have tried to evaluate the long-term consequences of BDZs use. With the exception of the study by Viggedal et al. [42] which showed a delay in mental development up to 18 months of age in babies exposed in utero to BDZs, neurobehavioural abnormalities or impaired intelligence have not been reported [41 43].

The evaluation of the risk of exposure to BDZs during breastfeeding is based exclusively on the analysis of some case-reports. The available studies have shown that BDZs are excreted in breast milk, but at fairly low concentrations. The possibility of toxic effects would, therefore, be higher in premature babies or neonates exposed to higher concentrations during pregnancy or at the time of delivery [44]. The most thoroughly studied BDZs are clonazepam, diazepam and temazepam. Regarding clonazepam, there is a report of some episodes of apnoea, which resolved completely 10 months after birth (neurological development normal after 5 months) in a baby exposed both during pregnancy and while being breastfed [45]. These symptoms were not subsequently found in a second case of a baby whose mother was receiving treatment with clonazepam and phenytoin during both pregnancy and lactation [46]. Contrasting data have also been reported on the toxic effects (cyanosis, apnoea, hypotonia and jaundice) in neonates being breastfed by mothers treated with diazepam [47-49].

In conclusion, treating pregnant women with psychoactive drugs is a complex therapeutic problem [50]. On the one hand it is essential to consider the possible risks to the foetus due to exposure to the drugs, on the other the potential consequences of not treating a serious mental disorder that develops or worsens during pregnancy must be taken into account [50]. The choice of treating a mother affected by mental disorders with psychoactive drugs during puerperium is fairly similar and must, therefore, be based on an evaluation of the individual risk-benefit ratio that breastfeeding involves [50]. Collaboration between the doctor (whether psychiatrist, paediatrician or gynaecologist) and the patient is essential, in that the former is responsible for choosing the most appropriate treatment, and the latter for promptly recognizing the appearance of any adverse effects in the baby [50].

Discussion about the risk-benefit ratio of using BDZs in the elderly is very relevant both because of the progressive ageing of the population and because the elderly tend to have a low level of education and concomitant physical disorders, constitute the subpopulation in which the consumption of these drugs is highest, together with women [51]. The pharmacokinetic characteristics of BDZs of primary importance in the treatment of the elderly are plasma half-life ($T_{½}$) and type of metabolism, and in particular the presence of metabolic pathways involving or not hydroxylation and any formation of active metabolites [52]. Concerning the volume of distribution, for BDZs, as for other lipid-soluble drugs, an increase in the ratio between body mass and muscle tissue, together with a reduction in body mass and total body water, causes an increase in the volume of distribution and, therefore, a decrease in the elimination rate. Furthermore, if the plasma concentration decreases because of dilution in peripheral tissues, a smaller proportion of the drug reaches the central nervous system and the pharmacological effects may be attenuated. Ageing is accompanied by a reduction in plasma albumin, which can lead to an increase in the unbound fraction of drugs and, therefore, an increase in their pharmacological effects. In elderly subjects there is also a significant reduction in the metabolic capacity of the hepatic oxidative system, through which many psychoactive drugs are metabolised, whereas the glucuronic conjugation pathways do not show obvious age-related differences. Finally, the elimination of drugs can be affected in the elderly as a result of possible reductions in renal blood flow, glomerular filtration and tubule function. Alterations in metabolic processes in the liver and kidney can contribute to a significant increase in the plasma steady-state level and prolong the elimination half-life of the various compounds [52].

Considering the ideal pharmacokinetic profile of a BDZ for elderly subjects, most of the specialists interviewed considered that the BDZs should have a short half-life, either without active metabolites or with one or more active metabolites, or an intermediate half-life and no active metabolites. This opinion seems to be essentially correct, considering that ageing is characterized by the above-described pharmacokinetic alterations, which increase the bioavailability of BDZs. One exception is alprazolam, since the volume of distribution of this drug, for reasons that have not been clarified, decreases slightly in elderly males and remains unchanged in elderly females, with the advantage that the duration of effect of this drug is closer to that in young adults [53]. Furthermore,

the pharmacokinetic parameters of various compounds can be altered by the presence of somatic disorders and/or by interaction with other drugs, which it is nowadays highly likely that an elderly person will be taking [54]. A short/intermediate half-life and as simple a metabolism as possible are, therefore, desirable pharmacological characteristics for BDZs being used in a geriatric setting, and the specialists essentially reached a positive consensus on these concepts. It should be noted that the specialists strongly disagreed that BDZs with a long half-life are suitable for use in the elderly. This opinion is clearly supported by the literature, which shows a higher probability of drug accumulation in the elderly and, therefore, of side effects, especially psychomotor and cognitive, independently of the doses used. In BDZs with a short half-life, such effects are only evident when high doses are used [55 56]. Finally, Hemmelgarn et al. reported a significant increase in road traffic accidents in the elderly in association with the use of BDZs with a long half-life, but not in those with a short half-life [57].

Short-term use of intramuscular BDZs is indicated in the pharmacological management of behavioural and psychological symptoms of dementia (BPSD) in cases of severe, acute agitation [58]. With regards to the question on which BDZs has the highest risk/benefit ratio when given intramuscularly for "acute" use in psychomotor agitation of dementia, the specialists reached consensus on indicating lorazepam. This opinion is supported by pharmacological and clinical data in the literature as well as by the main guidelines, which propose lorazepam as a drug of first choice in the treatment of anxiety since it is the only BZD with constant, complete and fast absorption by an intramuscular route, unlike compounds such as diazepam and chlordiazepoxide, which are less water soluble [59-61]. Furthermore, as already shown, lorazepam has a particularly favourable pharmacokinetic profile even in frail elderly subjects because it has a single metabolic step, glucuronidation, which does not give rise to active metabolites, and it does not tend to accumulate in the body.

Finally, the specialists who participated in the survey were asked to give their opinion on the main principles to consider when deciding the duration of treatment with BDZs. Most of specialists believed that, since anxiety is transient state, when the symptoms disappear it is wise to interrupt treatment gradually, with the knowledge that it can be re-introduced if it is needed again and that sometimes it can be useful to explain to the patient that dependence (mainly psychological) can develop in the case of prolonged use of these drugs.

On this subject, according to the latest guidelines from the National Institute of Clinical Excellence (NICE) on the treatment of anxiety (including panic attacks, with or with agoraphobia, and generalised anxiety disorder), in the setting of general medicine, BDZs should be used in adults for only brief periods, and no longer than 2-4 weeks. The long-term interventions supported by clinical evidence include cognitive-behavioural psychotherapy, treatment with antidepressants, or self-help therapy [62]. However, given the broad margin of therapeutic safety, the limited occurrence of serious adverse events and the low probability of creating physical dependence [63], long-term treatment with BDZs can be observed [64], and has been reported to be more common in women and in subjects concomitantly using other psychotropic drugs [65].

NICE recommends that treatment with combinations of drugs should only be prescribed by doctors with experience in the psychological and pharmacological treatment of anxiety disorders, and who should discuss the possible advantages and disadvantages of the treatments proposed with the patient [62].

Given their characteristics, BDZs are predominantly symptomatic drugs, acting on the effects and not the causes of the anxiety. This concept, which must be explained carefully and thoroughly when prescribing a BDZ, is essential in order to determine the risk-benefit ratio for treatment of any form of anxiety. In fact, the need for pharmacological treatment can only be evaluated and discussed with the patient in this context.

Despite the evidence of good clinical effects [66-68], the opinion that BDZs were among the safest drugs in the pharmacopeia began to weaken in the 1970s with the first descriptions of cases of abuse and dependence, although these reports, ever more frequent and well documented, failed to limit the prescription and widespread use of these drugs [29].

Concerning the problem of dependence, a first distinction should be made between patients who need chronic treatment with anxiolytics (patients with disabling chronic anxiety, possibly concomitant with organic or psychiatric pathologies) and patients who, on the other hand, although having suffered in the past from manifestations of anxiety or insomnia, have continued to take the BDZs repeatedly. In the former group of patients, consideration can be given to replacing BDZs with other drugs with an anxiolytic effect or directing the patient towards non-pharmacological treatment, while the aim in the latter group must be withdrawal of the treatment. Appreciating that treatment with BDZs, even following chronic usage, can be stopped is a key point in the correct management of the problem by both the physician (e.g. when discussing the reason for continued treatment with a patient on the occasion of a request for a repeat prescription) and the patient (who must be informed of this possibility). It can be sufficient to send a letter advising progressive reduction of BDZs to patients who are found to be chronic users to obtain substantial results [69 70]. Indeed, since various strategies have equal efficacy, simply tackling the problem in some way decreases the prescription rate [71].

In any case, the patient should be encouraged to report any need to increase the dose to maintain the same clinical effects and, also during consultations for other reasons, a search should be made for signs and symptoms suggestive of a dependence syndrome.
The opinions of the specialists interviewed were mainly in agreement with published data regarding the patients' involvement in some aspects of pharmacological treatment with BDZs. However, it is important to point out that a consensus was not reached on whether patients should be informed at the start of treatment that this cannot be continued in the long-term and that precise rules must be followed, suggesting that the specialists lacked clear information and/or experience on this clinical aspect.
The specialists who participated in the survey correctly considered that personalised and extremely flexible dosing must be used when establishing treatment, and that it must be ensured that the patient does not increase the dose on his or her own initiative. The specialists also agreed that the duration of treatment with BDZs must take into account clinical response, severity of the anxiety state, continued presence of triggering factors, patient's personality, psychotropic drug history, and patient preferences.
In this regard, given the variety of compounds within the pharmacological class of BDZs, the specific treatment can be tailored to meet the needs of an individual patient [10]. The evidence that has accumulated in the first 50 years of the clinical use of these drugs enables reasonably precise indications on the appropriate use of BDZs, optimising the ratio between efficacy and tolerability [10]. In fact, respecting some general principles, such as using the minimum effective dose, personalising the treatment in relation to the particular features of the underlying psychopathological picture (e.g., an intermittent treatment in forms of resistant insomnia and anxiety) and the pharmacological properties of the compound taken, as well as gradual withdrawal of the treatment [64], undoubtedly facilitate the use of this class of drugs in the treatment of anxiety disorders [8].
With regards to the question of duration of treatment reported in the BDZs data sheets, the overall evaluation of the responses to the four items on which a consensus was reached did not seem to make a net distinction between the presented options, which are based on regulatory factors. However, a closer analysis of the responses, considering the degree of agreement on each of the proposed options, did reveal some qualitative differences: for the option "2 weeks for insomnia and 4-6 weeks for anxiety disorders", 242 participants selected a score of 4 or 5 (strongest agreement); for the option "4 weeks for insomnia and 4-6 weeks for anxiety disorders" the sum of the participants choosing score 3 or 4 (not maximum agreement) was 251; and for the option "4 weeks for insomnia and 8-12 weeks for anxiety disorders" 252 people chose score 3 or 4 (not maximum agreement). Thus, there was stronger agreement on the fact that the treatment durations indicated in the BDZs data sheets are 2 weeks for insomnia and 4-6 weeks for anxiety disorders. In fact, the data sheets for BDZs on the Italian market report "normal" treatment durations as 4 weeks for insomnia and 8-12 weeks for anxiety disorders, including the period of gradual withdrawal. On the other hand, it is common belief that BDZs are normally used for longer periods than indicated in the respective data-sheets. It can be hypothesised that those interviewed, aware of not prescribing these drugs in perfect adherence with their indications, paradoxically indicated an even shorter time than the real one.
In conclusion, from an analysis of the data it can be stated that although not all specialists were fully aware of the pharmacokinetic and pharmacodynamics characteristics of the BDZs, those interviewed did know the fundamental safety features of these drugs, perhaps due to their experience in clinical practice. As far as the clinical use of BDZs is concerned, specialists showed limited information and/or experience regarding some aspects of dependence on BDZs and on withdrawing treatment. For the remaining clinical aspects, overall, the participants showed a certain competence, in this case, too, probably derived from their clinical experience.

Conflict of Interest
Claudio Vampini has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Angelini, Astra Zeneca, Bristol Myers Squibb, Lilly, Lundbeck, Pfizer, Otsuka, Sanofi, Servier.
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