The EURO-FORTA (Fit fOR The Aged) List Version 2: Consensus Validation of a Clinical Tool for Improved Pharmacotherapy in Older Adults

Drugs & Aging

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The F O R T A List
"Fit for The Aged"
Expert Consensus Validation
Spain

F O R T A [5]			
A	B	C	D

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Disclaimer

Please keep in mind that the FORTA Concept was conceived and developed in Germany. While building on an international foundation of medical evidence and experience for the medications listed, including already existing "negative lists" and classification systems, this FORTA List primarily reflects prescribing tendencies in Spain. The FORTA labels themselves, being evidence-based, may possibly be subject to change during the course of further consensus evaluation procedures, depending on the state of evidence and clinical experience for a given substance[5]. Meanwhile, the FORTA principle has been validated in a randomized clinical trial (VALFORTA) showing a large improvement of medication quality and amelioration of clinical parameters[6].

With the goal of creating a user-friendly clinical tool, a summary of relevant comments is given directly in the FORTA List, drawing on the Delphi experts' extensive clinical experience. This is however by no means comprehensive and does not necessarily refer to specific evidence or sources. Therefore, the authors' selection of suggestions, comments and warnings may be subjective[5]. 'No comment' reflects the absence of noteworthy or relevant words of information or caution within the context of the expert evaluation. All information herein is believed to be true and accurate. Neither the authors nor the University of Heidelberg or affiliated institutions, as the publishers of this list, can accept legal responsibility for any errors or omissions made in the contents of this list[5].

We welcome all comments and criticism which may contribute to the quality, safety and usability of the FORTA List in daily clinical practice.

The FORTA Concept: expert panel for the FORTA classification system

FORTA Expert Review Panel

The following 4 colleagues, representing Spain, provided their expertise for purposes of evaluating the proposed FORTA List. They received no honoraria in connection with this project. All panel members contributed actively to the development of the content of the FORTA List.

Expert Panel Members and their affiliations

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F O R T A – Physician's guide[1,2,5,7]

1. **FORTA is evidence-based + real-life-oriented (factors such as compliance issues, age-dependent tolerance and frequency of relative contraindications are considered).**

2. **Classifications are indication (or diagnosis)-dependent: a medication can receive different FORTA classifications based on differing indications.**

3. **Contraindications <u>always</u> take precedence over the FORTA-classification (for example, even Class A medications may not be given if allergies are present).**

4. **FORTA is designed to be a quick and user-friendly clinical tool to aid in the pharmacotherapy of older patients[*]. The system is <u>not</u> intended to take the place of individual therapeutic considerations or decisions. As with any simplified model, it <u>does</u> allow for exceptions.**

F O R T A – Classification System A-D[1,2,3,4,7]

Class A	Class B	Class C	Class D
= Indispensable drug, clear-cut benefit in terms of efficacy/safety ratio proven in elderly patients for a given indication	= Drugs with proven or obvious efficacy in the elderly, but limited extent of effect and/or safety concerns	= Drugs with questionable efficacy/safety profiles in the elderly which should be avoided or omitted in the presence of too many drugs, absence of benefits or emerging side effects; explore alternatives	= Avoid if at all possible in the elderly, omit first and use alternative substances

* FORTA aims at older patients, has been validated primarily for patients 65 years of age or older with significant comorbidities (3 or more diagnoses and drugs) and should be used in all patients 80 years of age or older will. These target groups are mostly defined as geriatric patients.

The F O R T A List[3,4,5]
Delphi Expert Consensus Validation

F	O	R	T	A
A	B	C		D

Classification of the most frequently used long-term medications†
for the pharmacotherapy of older patients
by indication/diagnosis, ranked according to FORTA classification
Newly proposed drugs are mentioned under the respective diagnosis and marked by *; they are listed in greater detail in the second part.

(† long-term defined as > 4 weeks. Please note that the distinction between acute/chronic may not always be clear-cut; exceptions are noted)

ARTERIAL HYPERTENSION Substance/Group	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Renin-Angiotensin system inhibitors ACE inhibitors	A	4	1.000	1.0; 1	
Angiotensin receptor antagonists	A	4	1.000	1.0; 1	
Long-acting calcium antagonists, dihydropyridine type, for example amlodipine	A	4	1.000	1.0; 1	
Betablockers except atenolol	C	4	0.875	2.8; 3	
Atenolol	D	4	0.875	3.8; 4	
Diuretics except indapamid	B	3	0.833	1.7; 2	
Indapamid	A	4	1.000	1.0; 1	
Alpha blockers	C	4	1.000	3.0; 3	
Spironolactone	C	4	1.000	3.0; 3	
Moxonidine	C	3	1.000	3.0; 3	
Aliskiren	C	4	1.000	3.0; 3	
Urapidil	C	3	1.000	3.0; 3	
Clonidine	D	3	1.000	4.0; 4	

Substance/Group	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Minoxidil	D	3	1.000	4.0; 4	
Calcium antagonists, verapamil type	D	4	1.000	4.0; 4	
Hydralazine	C	4	1.000	3.0; 3	
CARDIAC INSUFFICIENCY					
Renin-angiotensin system inhibitors					
ACE inhibitors	A	4	1.000	1.0; 1	
Angiotensin receptor antagonists	A	4	1.000	1.0; 1	
Betablockers (metoprolol, carvedilol, bisoprolol)	A	4	1.000	1.0; 1	
Diuretics	A	4	1.000	1.0; 1	
Gliflozins (SGLT2 inhibitors) only those substances which have been approved for this indication (dapgliflozine)	B	4	0.875	2.3; 2	
Spironolactone	B	4	1.000	2.0; 2	
Digitalis preparations	C	4	0.875	2.8; 3	
Ivabradine	C	4	1.000	3.0; 3	
Iron substitution in patients with iron deficiency	A	4	1.000	1.0; 1	

ACUTE CORONARY SYNDROME	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/Group					
Renin-Angiotensin-System-Blocker: ACE-Hemmer	A	4	1.000	1.0; 1	
Acetylsalicylic acid	A	4	1.000	1.0; 1	
Unfractionated heparin and low molecular weight heparin	A	4	1.000	1.0; 1	
Frequency-lowering betablockers, e.g. metoprolol or bisoprolol	A	4	1.000	1.0; 1	
Atorvastatin	A	4	1.000	1.0; 1	
Nitroglycerin spray, single use, acute as on-demand medication	A	4	1.000	1.0; 1	
Clopidogrel, prasugrel	B	4	1.000	2.0; 2	
	A for stent	2	1.000	1.0; 1	
Thrombolytics, especially rTPA (recombinant tissue-type plasminogen activator)	B	4	1.000	2.0; 2	
Nitrates, long-term	C	4	1.000	3.0; 3	
Gp IIb/IIIa antagonists (glycoprotein 2b/3a inhibitors)	C	4	1.000	3.0; 3	
Ivabradine	C	4	1.000	3.0; 3	

CHRONIC THERAPY FOLLOWING MYOCARDIAL INFARCTION	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
Renin angiotensin system blockers ACE Inhibitors	A	4	1.000	1.0; 1	
Acetylsalicylic acid (100 mg/d)	A	4	1.000	1.0; 1	
Frequency-lowering beta blockers up to 3 years	A	4	1.000	1.0; 1	
Frequency-lowering beta blockers longer than 3 years	C	4	1.000	3.0; 3	
Nitroglycerin spray, single use as on-demand medication	A	4	1.000	1.0; 1	
Influenza vaccination (inactivated subunit vaccines)/pneumococcal immunizations	See vaccinations				
Statins	A B for very old (>85 years) patients	4 4	1.000 1.000	1.0; 1 2.0; 2	
Clopidogrel (12 months after acute coronary	A with aspirin intolerance	4	1.000	1.0; 1	

syndrome)					
Nitrates, long-term	C	4	0.875	2.8; 3	
Fibrates	C	4	1.000	3.0; 3	
Ezetimibe	C	4	1.000	3.0; 3	
Amiodarone	C	4	1.000	3.0; 3	
All other class-I-III antiarrhythmic agents	D	4	1.000	4.0; 4	
Dihydropyridine antagonists (if no hypertension)	D	4	1.000	4.0; 4	
Niacin	D	4	1.000	4.0; 4	

STROKE	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/Group					
Acetylsalicylic acid	A	4	1.000	1.0; 1	
Atorvastatin	A	4	0.875	1.3; 1	
rTPA (recombinant tissue-type plasminogen activator); only for emergency use	A	4	1.000	1.0; 1	
Simvastatin	A	4	0.875	1.3; 1	
Anticoagulants including new oral anticoagulants	A	4	1.000	1.0; 1	
Clopidogrel	A	4	1.000	1.0; 1	
Dipyridamole plus	B	4	0.875	2.3; 2	

acetylsalicylic acid					
Ticlopidine	D	3	1.000	4.0; 4	

ATRIAL FIBRILLATION	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
Frequency-lowering betablockers	A	4	1.000	1.0; 1	
Digoxin	B	4	1.000	2.0; 2	
New Oral Anticoagulants (NOACs)	B	4 (R1) 4 (R2)	0.750(R1) 0.875(R2)	1.5; -(R1) 1.8; 2(R2)	**Note:** Substantial evidence from large Clinical trials supporting the benefit with a good ratio risk/benefit
Except dabigatran	C	2	1.000	3.0; 3	
Oral anticoagulation by vitamin-K-antagonists (e.g. phenprocoumon, warfarin)	B	4	0.875	1.8; 2	
Alternative: low molecular weight heparin	C	4	0.875	3.3; 3	
Digitoxin	C	3	1.000	3.0; 3	
Diltiazem, verapamil	C	4	1.000	3.0; 3	
Class III antiarrhythmic	C	4	1.000	3.0; 3	

agent amiodarone					
All other class I or III antiarrhythmic agents	**D**	4	1.000	4.0; 4	
Acetylsalicylic acid (100 mg/d)	**(C)** **D**	3(R1) 4(R2)	0.667(R1) 0.625(R2)	3.7; 4(R1) 3.8; 4(R2)	**Note:** Much lower benefit than anticoagulants, generally a marker of wrong assessment of patient risk in complex older patients; It is not indicated for atrial fibrillation and it is not considered an alternative to be used in either circumstance in patients with atrial fibrillation. Benefit/risk relationship unfavorable.
Class III antiarrhythmic agent dronedarone	**D**	4	1.000	4.0; 4	

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
Inhalative long-acting parasympatholytic agents	A	4	1.000	1.0; 1	
Systemic glucocorticoids, acute, short-term use in cases of exacerbation	A	4	1.000	1.0; 1	
Antibiotics (acute) in cases of exacerbation, after calculated selection and, if necessary, according to antibiogram	A	4	1.000	1.0; 1	
Long-term administration of oxygen	A	4	1.000	1.0; 1	
Annual influenza immunizations	See vaccinations				
Pneumococcal immunizations for persons ≥ 65 years	See vaccinations				
Inhalative beta 2 mimetic agents	B	4	1.000	2.0; 2	
Inhalative glucocorticoids	C	4	0.875	2.8; 3	
Theophylline	D	4	1.000	4.0; 4	
Mucolytic agents, e,g,	C	4	1.000	3.00; 3	

	FORTA Class	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
acetyl cysteine, bromhexine					
Roflumilast	**C**	4	0.875	3.3; 3	
Systemic glucocorticoids, chronic use	**D**	4	1.000	4.0; 4	
Antitussives: opioid A., e.g. codein; non-opioid A., e.g. butamirate	**D**	4	1.000	4.0; 4	
Benzodiazepines	**D**	4	1.000	4.0; 4	

OSTEOPOROSIS	**FORTA Class** (original FORTA class in parenteses if different from consensus results)	**Nr. of raters**	**Consensus coefficient, Round 1 (cutoff 0.800)**	**Expert ratings on a numerical scale: A=1, B=2, C=3, D=4** **Mean; Mode**	**Selection of pertinent comments given by participating experts during the consensus procedure**
Substance/Group					
Calcium and vitamin D supplements (as prophylaxis for persons ≥ 65 years)	**A**	4	0.875	1.3; 1	
Parenteral bisphosphonates (e.g. ibandronate, IV every 3 months)	**B**	4	1.000	2.0; 2	
Raloxifene for women	**B**	4	0.875	2.3; 2	
Denosumab	**B**	4	1.000	2.0; 2	
Bisphosphonates, oral	**B**	4	0.875	1.8; 2	
Teriparatide	**C**	4	0.875	2.8; 3	
Alfacalcidol	**C**	3	1.000	3.0; 3	
Parathormone	**C**	3	1.000	3.0; 3	
Strontium ranelate	**D**	4	1.000	4.0; 4	
Nandrolone decanoate	**D**	3	1.000	4.0; 4	
Fluoride	**D**	3	1.000	4.0; 4	
Hormone replacement	**D**	4	1.000	4.0; 4	

therapy (HRT): estrogen, except for perimenopausal)					
Calcitonin	D	4	1.000	4.0; 4	

TYPE II DIABETES MELLITUS	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
DPP4 (Dipeptidylpeptidase) Inhibitors	A	4	1.000	1.00; 1	
Insulin and insulin analogs (if absolutely necessary)	(B) A	4 (R1) 4 (R2)	0.625(R1) 0.500(R2)	1.3; 1(R1) 1.0; 1(R2)	**Note:** When needed, it is not possible to substitute it. Although there is a risk for hypos, mainly in some subpopulations of older people, the benefits are really big when insulin is needed; Clear benefit in terms of efficacy/safety ratio, proven in elderly patients; I consider insulin is first line treatment over any other drug
Metformin	A	4	0.875	1.3; 1	
GLP1 (Glucagon-Like Peptide-1) analogs	B	4	1.000	2.0; 2	
Acarbose	(B) C	4(R1) 4(R2)	0.750(R1) 0.625(R2)	2.5; -(R1) 2.8; 3(R2)	**Note:** Effect size very small, side effects leading to drug cessation are quite frequent; Secondary effects are very frequent and disturbing, leading many times to the removal of the treatment
3rd generation sulfonylureas (for example, glimepiride)	C	4	0.875	3.3; 3	
Glinides (for example, nateglinide)	C	4	1.000	3.0; 3	
PPAR-γ Ligands		4	1.000	3.0; 3	

	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	
(Peroxisomal Proliferator-Activated Receptor gamma) Pioglitazone	C				
Rosiglitazone	D	3	1.000	4.0; 4	
SGLT-2 inhibitors/Gliflozins	(D) C	4(R1) 4(R2)	0.625(R1) 0.500(R2)	3.3; 3(R1) 3.0; 3(R2)	**Note:** C (B if certain concomitant diseases such as HF or CV)
1st generation sulfonylureas (for example, glibenclamide)	D	4	1.000	4.0; 4	
DEMENTIA	**FORTA Class** (original FORTA class in parentheses if different from consensus results)	**Nr. of raters**	**Consensus coefficient, Round 1 (cutoff 0.800)**	**Expert ratings on a numerical scale: A=1, B=2, C=3, D=4** **Mean; Mode**	**Selection of pertinent comments given by participating experts during the consensus procedure**
Substance/group					
Acetylcholinesterase inhibitors e.g. donepezil, galantamine, rivastigmine (Only if indicated for the present stage of the disease)	B	4	0.875	1.8; 2	
Memantine	C	4	0.875	2.8; 3	
Ginkgo biloba	D	4	1.000	4.0; 4	
Statins	D	4	1.000	4.0; 4	
Selegiline	D	4	1.000	4.0; 4	
Nimodipine	D	4	1.000	4.0; 4	

	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Ergoline derivatives	D	4	1.000	4.0; 4	
Piracetam	D	4	1.000	4.0; 4	
Pyritinol	D	4	1.000	4.0; 4	
Antioxidants: Vitamin E, selenium, vitamin C	D	4	1.000	4.0; 4	
Phytotherapeutic agents, e.g. ginseng	D	4	1.000	4.0; 4	
Hormone preparations, e.g. DHEA (Dehydroepiandrosterone), testosterone	D	4	1.000	4.0; 4	
Antiphlogistics, e.g. indomethacin	D	4	1.000	4.0; 4	
Desferrioxamine	D	4	1.000	4.0; 4	
BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
DEPRESSION					
Substance/group					
SSRI (Selective Serotonin Reuptake Inhibitors) Citalopram/escitalopram, sertraline, fluoxetine in the usual dosages	C	4	1.000	3.0; 3	
Mirtazapine (15-45mg/d)	C	4	1.000	3.0; 3	
SNRI (Serotonin-Noradrenalin-Reuptake-Inhibitors) Venlafaxine, duloxetine	C	4	1.000	3.0; 3	

	FORTA Class	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	
Trazodone	C	4	1.000	3.0; 3	
Reboxetine	C	4	1.000	3.0; 3	
Tricyclic antidepressants	D	4	1.000	4.0; 4	
Agomelatine	D	4	1.000	4.0; 4	
BPSD: PARANOIA, HALLUCINATION	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
Risperidone (initially 0,5-1 mg/d)	C	4	1.000	3.0; 3	
Melperone (25-150mg/d)	C	1	1.000	3.0; 3	
Quetiapine (25-200 mg/d)	C	4	1.000	3.0; 3	
Aripiprazole (2-15 mg/d)	D	4	1.000	4.0; 4	
Clozapine (10-50 mg/d)	D	4	1.000	4.0; 4	
Haloperidol (initially 0.5 mg/d, max. 3 mg/d)	(C) D	4 (R1) 4 (R2)	0.750 (R1) 0.750 (R2)	3.5; - (R1) 3.5; - (R2)	**Note:** Unclear effect in older subjects with BDSP (only used as control arm, Cochrane review negative), side effects unacceptable; More side effects
Olanzapine	D	4	1.000	4.0; 4	
BPSD: RESTLESSNESS, AGITATION, (AGGRESSIVENESS)	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of	Consensus coefficient, Round 1 (cutoff	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4	Selection of pertinent comments given by participating experts during the consensus procedure

		raters	0.800)	Mean; Mode	
Substance/group					
Trazodone (50-200 mg/d)	**C**	4	1.000	3.0; 3	
Risperidone (initiallly 0,5-1 mg/d, Maximum 3 mg/d)	**C**	4	1.000	3.0; 3	
Quetiapine (25-200 mg/d)	**C**	4	1.000	3.0; 3	
Melperone (25-150 mg/d)	**C**	1	1.000	3.0; 3	
Pipamperone (20-120 mg/d)	**D**	2	1.000	4.0; 4	
Citalopram (10-30mg)	**C**	4	1.000	3.0; 3	
Clomethiazole (5-15 mg/d)	**D**	4	1.000	4.0; 4	
Chlorpromazine (40 mg/ml)	**(C)** **D**	4 (R1) 4 (R2)	0.750(R1) 0.500(R2)	3.50; -(R1) 4.0; 4(R2)	**Note:** No evidence at all, harms well known; More side effects
BPSD: SLEEP DISORDERS	**FORTA Class (original FORTA class in parentheses if different from consensus results)**	**Nr. of raters**	**Consensus coefficient, Round 1 (cutoff 0.800)**	**Expert ratings on a numerical scale: A=1, B=2, C=3, D=4** **Mean; Mode**	**Selection of pertinent comments given by participating experts during the consensus procedure**
Substance/group					
Slow-release melatonin (2-4 mg)	**C**	4	1.000	3.0; 3	
Tetracyclic antidepressant Mirtazapine (15-30mg)	**C**	4	1.000	3.0; 3	
Tricyclic antidepressant	**(C)**	4(R1)	0.750(R1)	3.5; -(R1)	**Note:** Anticholinergic side effects, interacts with pro-cholinergic

	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Doxepine (25-50 mg)	D	4(R2)	0.750(R2)	3.5; -(R2)	treatments of dementia; Avoid, if possible, in the elderly
Zopiclone (3,75-7,5 mg)	C	4	1.000	3.0; 3	
Trazodone (50-200 mg/d)	B	4	0.875	2.3; 2	
Clomethiazole (192-384 mg/d)	C	3	1.000	3.0; 3	
DEPRESSION Prophylaxis and therapy for patients with moderate to major depression					
Substance/group					
SSRIs (Selective Serotonin Reuptake Inhibitor)		4	1.000	2.0; 2	
Sertraline	B				
Escitalopram	B	4	1.000	2.0; 2	
Citalopram	B	4	1.000	2.0; 2	
Tricyclic antidepressant Nortriptyline	D	4	1.000	4.0; 4	
Tetracyclic antidepressant Mirtazapine	C	4	1.000	3.0; 3	
SNRIs (Serotonin-Noradrenalin Reuptake Inhibitors) Venlafaxine	C	4	1.000	3.0; 3	

Substance/group	FORTA Class	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings: Mean; Mode	Comments
Duloxetine	C	4	1.000	3.0; 3	
Monoamine oxidase A (MAO) inhibitor Moclobemide	D	4	1.000	4.0; 4	
Dopamine and norepinephrine reuptake inhibitor Bupropion	C	4	1.000	3.0; 3	
Vortioxetine	C	4	0.875	3.3; 3	
Quetiapine	(C) D	4 (R1) 4(R2)	0.750 (R1) 0.625(R2)	3.5; - (R1) 3.8; 4(R2)	**Note:** It is an antipsychotic drug.; Lack of efficacy for depression in the elderly
Trazodone	C	4	1.000	3.0; 3	
Olanzapine	C	4	0.875	3.3; 3	
Benzodiazepines: General	D	4	1.000	4.0; 4	
Long-acting,	D	4	1.000	4.0; 4	
Short-acting	D	4	1.000	4.0; 4	
St. John's Wort	D	4	1.000	4.0; 4	
Agomelatine	D	4	1.000	4.0; 4	
Selective noradrenaline re-uptake inhibitor Reboxetine	D	4	0.875	3.8; 4	

BIPOLAR DISORDER	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					

Lithium	B	4	1.000	2.0; 2	
Quetiapine	B	4	1.000	2.0; 2	
Valproic acid	C	4	1.000	3.0; 3	
Lamotrigine	C	4	0.875	3.3; 3	
Carbamazepine	D	4	1.000	4.0; 4	

INSOMNIA / SLEEP DISORDERS	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
Melatonin (slow-release)	B	4	0.875	2.3; 2	

ω1-Benzodiazepine agonists Zolpidem	C	4	1.000	3.0; 3	
Zaleplone	C	3	1.000	3.0; 3	
Non-benzodiazepine hypnotic Zopiclone	C	4	1.000	3.0; 3	
Butyrophenone derivative Pipamperone	C	2	1.000	3.0; 3	
Melperone	C	2	1.000	3.0; 3	
Tetracyclic antidepressant Mirtazapine	C	4	1.000	3.0; 3	
Tricyclic antidepressant Doxepine	D	4	1.000	4.0; 4	
Benzodiazepines, e.g. Oxazepam (medium half-life)	D	4	0.875	3.8; 4	
Triazolam (very short half-life)	D	4	1.000	4.0; 4	
Sigma receptor agonist Opipramole	D	2	1.000	4.0; 4	
Antihistamine Diphenhydramine	D	4	1.000	4.0; 4	
Lorazepam	C	4	1.000	3.0; 3	
Pregabalin (25mg/12h)	(C) D	4(R1) 4(R2)	0.750 (R1) 0.750(R2)	3.5; - (R1) 3.5; -(R2)	**Note:** Not approved by EMA for insomnia, no clinical trials to support, high risk effect profile; Not indicated in Spain for this condition and not used for this indication.

CHRONIC PAIN	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
Paracetamol (acetaminophen)	A	4	1.000	1.0; 1	
Metamizole	B	4	1.000	2.0; 2	
Opioids, e.g. Buprenorphine, oxycodone, hydromorphone	B	4	0.875	2.3; 2	
Primary use of a combination of an agonist and an antagonist, e.g. Tilidine/naloxone	C	1	1.000	3.0; 3	
Oxycodone/naloxone	C	4	1.000	3.0; 3	
Morphine	C	4	1.000	3.0; 3	
SSRI (Selective Serotonin Reuptake Inhibitors) / SNRI (Serotonin-Norepinephrine-Reuptake Inhibitor), e.g. venlafaxine (only if absolutely	C	4	1.000	3.0; 3	

	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
necessary)					
Antiepileptic agents (only for neuropathic pain) **Pregabalin/gabapentin**	**C**	4	0.875	3.3; 3	
Carbamazepine	**D**	4	1.000	4.0; 4	
Tricyclic antidepressant amitriptyline (does not apply to doses up to 10mg per day)	**D**	4	1.000	4.0; 4	
NSAIDs (nonsteroidal anti-inflammatory drugs, for long-term use), e.g. naproxen	**D**	4	0.875	3.8; 4	
Cox-2 inhibitors, e.g. celecoxib	**D**	4	0.875	3.8; 4	
Fentanyl	**(B)** **C**	4 (R1) 4 (R2)	0.750 (R1) 0.750 (R2)	2.5; - (R1) 2.5; - (R2)	**Note:** Difficult to understand why fentanyl better than morphine or tramadol.; Many side effects and interactions with many other drugs
Tramadol	**C**	4	1.000	3.0; 3	
EPILEPSY	**FORTA Class (original FORTA class in parentheses if different from consensus results)**	**Nr. of raters**	**Consensus coefficient, Round 1 (cutoff 0.800)**	**Expert ratings on a numerical scale: A=1, B=2, C=3, D=4** **Mean; Mode**	**Selection of pertinent comments given by participating experts during the consensus procedure**
Substance/group					
Levetiracetam	**B**	4	1.000	2.0; 2	

Lamotrigine	B	4	1.000	2.0; 2	
Gabapentin	B	4	1.000	2.0; 2	
Topiramate	B	4	1.000	2.0; 2	
Lorazepam (emergency use)	B	4	1.000	2.0; 2	
Lorazepam (long-term use)	D	4	1.000	4.0; 4	
Pregabalin	C	4	1.000	3.0; 3	
Oxcarbazepine	C	4	1.000	3.0; 3	
Valproic acid	C	4	0.875	2.8; 3	
Eslicarbazepine	C	3	1.000	3.0; 3	
Lacosamide	C	4	0.875	2.8; 3	
Zonisamide	C	4	1.000	3.0; 3	
Carbamazepine	C	4	0.875	3.3; 3	
Diazepam (emrgency use)	C	4	1.000	3.0; 3	
Diazepam (long-term use)	D	4	1.000	4.0; 4	
Midazolam (emrgency use)	C	4	1.000	3.0; 3	
Midazolam (long-term use)	D	4	1.000	4.0; 4	
Phenytoin	D	4	1.000	4.0; 4	
Phenobarbital	D	4	1.000	4.0; 4	
Ethosuximide	D	4	1.000	4.0; 4	

PARKINSON'S DISEASE	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
L-DOPA	A	4	1.000	1.0; 1	
COMT (Catechol-O-Methyltransferase) Inhibitor Entacapone, opicapon	B	4	1.000	2.0; 2	
Dopamine agonists, e.g. Ropinirole	B	4	1.000	2.0; 2	
Pramipexole	B	4	1.000	2.0; 2	
Piribedil, quinagolide, rotigotine	B	4	1.000	2.0; 2	
MAO-B inhibitors Rasagiline	C	4	1.000	3.0; 3	

	FORTA Class	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	
Selegiline					
	C	4	1.000	3.0; 3	
Bromocriptine, cabergoline	**D**	4	1.000	4.0; 4	
Glutamate antagonists Amantadine	**D**	4	1.000	4.0; 4	
Anticholinergics Biperidene	**D**	4	1.000	4.0; 4	
INCONTINENCE Drug therapy for urge incontinence	**FORTA Class (original FORTA class in parentheses if different from consensus results)**	**Nr. of raters**	**Consensus coefficient, Round 1 (cutoff 0.800)**	**Expert ratings on a numerical scale: A=1, B=2, C=3, D=4** **Mean; Mode**	**Selection of pertinent comments given by participating experts during the consensus procedure**
Substance/group					
Fesoterodine	**B**	4	0.875	2.3; 2	
Tolterodine	**C**	4	0.875	3.3; 3	
Trospium chloride	**C**	4	1.000	3.0; 3	
Extended-release Oxybutynin	**C**	4	1.000	3.0; 3	
Immediate-release Oxybutynin	**D**	4	1.000	4.0; 4	

GASTROINTESTINAL ILLNESSES/ CONCOMITANT THERAPY WITH NSAIDs	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. Of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
Proton pump inhibitors (PPI), only if absolutely necessary	B	4	1.000	2.0; 2	
H$_2$ receptor antagonists	C	4	1.000	3.0; 3	
Metoclopramide	B	4	0.875	2.3; 2	
Domperidone	B	4	1.000	2.0; 2	

Anemia	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
Substitution (iron, vitamin B12, folic acid in cases of deficiency)	A	4	1.000	1.0; 1	
Erythropoetin-stimulating agents (ESA) in patients with renal insufficiency	A	4	1.000	1.0; 1	

| Iron substitution in patients with cardiac insufficiency

With proof of iron deficiency	See cardiac insufficiency				

| Vaccinations | FORTA Class (original FORTA class in parentheses if different from consensus results) | Nr. of raters | Consensus coefficient, Round 1 (cutoff 0.800) | Expert ratings on a numerical scale: A=1, B=2, C=3, D=4

Mean; Mode | Selection of pertinent comments given by participating experts during the consensus procedure |
|---|---|---|---|---|---|
| Substance/group | | | | | |
| Annual influenza immunizations | A | 4 | 1.000 | 1.0; 1 | |
| Pneumococcal immunizations for persons ≥ 65 years | A | 4 | 1.000 | 1.0; 1 | |
| Shingles (Herpes Zoster) Vaccination | A | 3 | 1.000 | 1.0; 1 | |

ONCOLOGICAL DISEASES: SOLID TUMORS	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
INDICATION Substance/group					
BREAST CANCER Adjuvant therapy					
Hormone therapy, e.g. Tamoxifen	B	4	1.000	2.0; 2	
Aromatase inhibitors	B	4	0.875	2.3; 2	
Immunotherapy / "Targeted" therapy Trastuzumab	B	3	1.000	2.0; 2	
Chemotherapy, e.g. CMF (Combination Cyclophosphamide, Methotrexate, 5-Fluorouracil)	C	3	1.000	3.0; 3	
AC/EC Regimen(Anthracycline/ Epirubicin, Cyclophosphamide)	C	3	1.000	3.0; 3	
BREAST CANCER Advanced Stage					
Hormone therapy, e.g. tamoxifen, aromatase	B	4	1.000	2.0; 2	

inhibitors					
Immunotherapy/Targeted Therapy Trastuzumab / lapatinib	B	3	1.000	2.0; 2	
Chemotherapy, e.g. anthracyclins, taxanes	C	3	1.000	3.0; 3	
VEGF (Vascular Endothelial Growth Factor) Inhibition Bevacizumab	D	2	1.000	4.0; 4	
COLORECTAL CARCINOMA Adjuvant Therapy					
FOLFOX Regimen (Folinic acid, Fluorouracil, Oxaliplatin)	C	3	1.000	3.0; 3	
5-Fluorouracil based infusion regimen	C	3	1.000	3.0; 3	
Capecitabine	C	4	1.000	3.0; 3	
COLORECTAL CARCINOMA Advanced stage					
Chemotherapy FOLFOX (Folinic acid, Fluorouracil, Oxaliplatin)	C	3	1.000	3.0; 3	
VEGF (Vascular Endothelial Growth Factor) Inhibition Bevacizumab	C	3	1.000	3.0; 3	
EGFR (Epidermal-Growth-Factor-Receptor) Inhibition Cetuximab	C	3	1.000	3.0; 3	
Panitumumab	C	3	1.000	3.0; 3	
BRONCHIAL CARCINOMA Adjuvant therapy					
Adjuvant chemotherapy (Cisplatin-based)	C	3	1.000	3.0; 3	

BRONCHIAL CARCINOMA Advanced Stage					
Docetaxel	B	3	1.000	2.0; 2	
Vinorelbin	B	3	1.000	2.0; 2	
Primary combination therapy Cisplatin/gemcitabin, or cisplatin/vinorelbin	C	2	1.000	3.0; 3	
GASTRIC CANCER					
ECF Regime (Epirubicin, Cisplatin, 5-Fluorouracil)	B	2	1.000	2.0; 2	
ONCOLOGICAL DISEASES HEMATOLOGICAL NEOPLASIAS	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
INDICATION Substance/group					
MDS (Myelodysplastic syndrome) Azacytidine	B	2	1.000	2.0; 2	
AML (Acute myeloid leukemia) Anthracyclines + cytosine arabinoside (cytarabine)	B	2	1.000	2.0; 2	
CLL (Chronic lymphatic leukemia) Chlorambucil, Fludarabin, Bendamustin	B	2	1.000	2.0; 2	

	FORTA Class	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
CLL Obinutuzumab	B	2	1.000	2.0; 2	
CLL Rituximab	B	3	1.000	2.0; 2	
Multiple myeloma Primary therapy with Prednisolone	B	4	1.000	2.0; 2	
Thalidomide	B	4	1.000	2.0; 2	
Melphalan	B	4	1.000	2.0; 2	
Bortezomib	B	4	1.000	2.0; 2	
Lenalidomide	B	3	1.000	2.0; 2	
CLL Ibrutinib	C	2	1.000	3.0; 3	
CLL Idelalisib	C	2	1.000	3.0; 3	

ONCOLOGICAL SUPPORTIVE THERAPY	FORTA Class (original FORTA class in parentheses if different from consensus results)	Nr. of raters	Consensus coefficient, Round 1 (cutoff 0.800)	Expert ratings on a numerical scale: A=1, B=2, C=3, D=4 Mean; Mode	Selection of pertinent comments given by participating experts during the consensus procedure
Substance/group					
G-CSF (Granulocyte Colony Stimulation Factor)	A	3	1.000	1.0; 1	
Antiemetic agents (e.g. 5-HT receptor inhibitors)	A	4	1.000	1.0; 1	

Erythropoesis Stimulating Agents, ESA	B	3	1.000	2.0; 2	

*This substance or indication was suggested by the participating experts during the course of Round 1 and evaluated by the experts during Round 2, see second table below.

R1= Round 1

R2= Round 2

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SUMMARY OF STATISTICAL METHODS
(The following descriptions of the statistical methods and calculations are based on the first version of the FORTA List[5]. Former definitions and explanations are adopted unchanged.)

Consensus Coefficient[5]

Consensus parameters were generated by calculating the percentage of experts' FORTA ratings (minus abstentions) agreeing with the original FORTA values, both overall and for each item separately (n = 282). The coefficients were then corrected (cons_corr) to weight the degree of deviation between the experts' individual FORTA ratings, expressed in terms of range class, from 0-3 as defined:

- Range = 0: unanimity among all experts (no deviation)**;**
- Range = 1: greatest range only from A to B or B to C, or C to D (neighboring classes), ½ weight**;**
- Range = 2: greatest distance from A to C or B to D, full weight**;**
- Range = 3: greatest distance from A to D, full weight.

Frequency of substances in defined range groups according to degree of consensus

Range	Frequency (n total=282)	%
0	232	82.27
1	50	17.73
2	0	-
3	0	-

Cons_corr coefficients ranged from 0.625 to 1.000 (mean 0.972, median 1.000). Substances falling short of our established cons_corr cutoff of 0.800 underwent re-evaluation in a second round: n=11

Confirmation/determination of FORTA labels[5]

In order to compare the rater-based FORTA labels with the original author-based labels, the labels A, B, C and D were transformed as follows[5]:

A → 1
B → 2
C → 3
D → 4

These numerical "grades" were used for the calculation of arithmetic mean. The mode (=grade appearing most frequently for rated item) is also shown. For the 11 re-evaluated items, grading was performed twice. The rater-based FORTA labels are derived from the arithmetic mean from Round 1, or if re-evaluated, from Round 2. The range for each grade was set at :

If $1 \leq m < 1.5$ → FORTA Class **A**

If $1.5 \leq m < 2.5$ → FORTA Class **B**

If $2.5 \leq m < 3.5$ → FORTA Class **C**

If $m \geq 3.5$ → FORTA Class **D**

m= arithmetic mean based on the grades 1-4

The results of The Delphi Consensus Validation Procedure confirmed the original FORTA labels for 96.5% of all substances (n=282); for 10/282 substances (3.5%), the FORTA labels changed over the course of two rounds. All consensus-based FORTA ratings are listed in bold print**: A B C D**, and the original author-based FORTA ratings are supplied in parentheses: (A) (B) (C) (D).