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DEPRESCRIBING IN DEMENTIA

OBJECTIVE To provide healthcare professionals with a guide for deprescribing anti-dementia drugs (cholinesterase inhibitors and memantine) in patients who may benefit from it. METHODS A multidisciplinary working group was created to perform a literature search on Pubmed and Cochrane for clinical practice guidelines. A set of guidelines for deprescribing anti-dementia drugs were agreed upon and adapted for publication in this Bulletin. RESULTS These guidelines describe the settings where deprescribing cholinesterase inhibitors or memantine should be considered. For that purpose, a deprescribing algorithm and a tapering regimen have been designed for cessation of these medications. A description is provided of the actions to be undertaken if a return of symptoms occurs. The potential adverse effects and interactions of anti-dementia drugs are described and an outline of the precautions to be taken in specific patient subgroups is provided. CONCLUSIONS Deprescribing should be performed in patients with advanced dementia (GDS ≥6), patients who have experienced adverse events or interactions, and patients who do not benefit from the treatment. The lack of consensus as to when and how to deprescribe anti-dementia drugs show the need for a guide to deprescribing anti-dementia drugs. A set of technical and ethical considerations should be taken into account in the prescribing/deprescribing process. Decisions surrounding deprescribing should be conducted as shared decision making with the patients and/or their caregivers ensuring that they are duly informed.

AMAYA ECHEVERRÍA
BELÉN GONZÁLEZ
NURIA GOÑI
ANA ROSA GÓMEZ
On behalf of the Working Group for Deprescription in Dementia of SNS-O

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Introduction

Healthcare should be governed by the ethical principles of beneficence, non-maleficence, autonomy, and justice, with the essential criteria of non-maleficence and justice.[1] In the prescribing/deprescribing process, beneficence is defined by the efficacy, non-maleficence based on the risk for adverse events, autonomy, and respect for patient preferences after having been duly informed, and justice in resource allocation.

In the prescribing/deprescribing process, a balance must be achieved among the indication of the drug, its benefits for the patient considering their clinical situation, the time required to reach the objective, life expectancy, acceptable risks, patient's autonomy to make decisions, goals of care, and economic burden for the global healthcare system.

Deprescribing is defined as the systematic process of identifying and discontinuing potentially inappropriate drugs, with the aim of minimizing polypharmacy and improving patient outcomes.[2] Deprescribing involves discontinuance of medication based on the analysis of its therapeutic goals and risks. This process must be part of the healthcare process and is aimed at restoring the balance lost due to a variety of circumstances (e.g. loss of efficacy, intolerable or unacceptable side effects, change in patient's expectations or preferences, and life expectancy, to name a few).

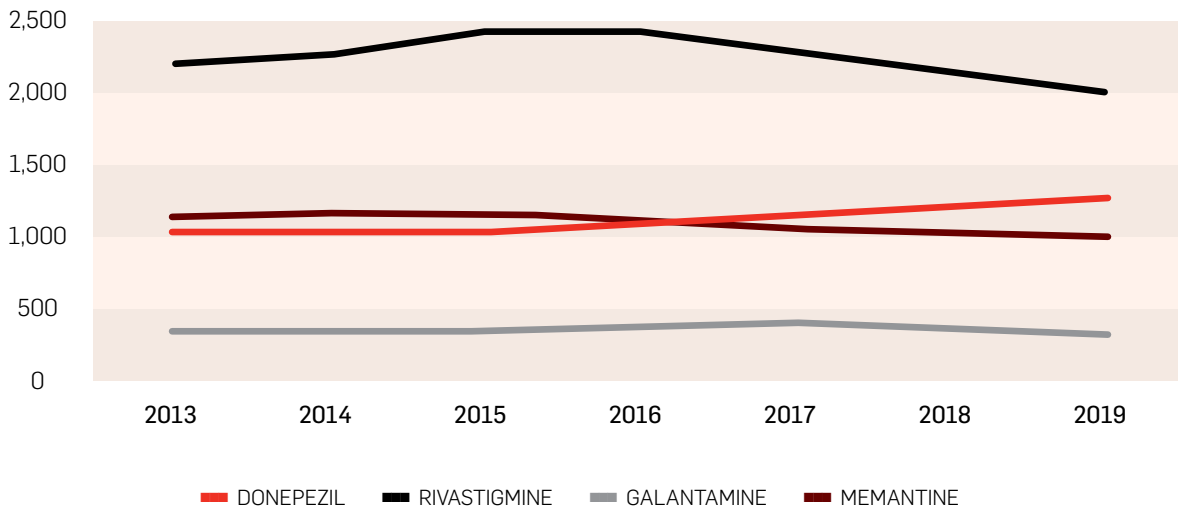
Both, scientific-technical and ethical aspects must be considered throughout the deprescribing process. The clinical needs of the patient may change over time, especially in patients with dementia.

Deprescribing should be considered in the healthcare process, as circumstances may arise that require discontinuation of medication because of a change in the clinical status of the patient that renders the medication no longer necessary or the risks outweigh the benefits.

The prevalence of dementia among adults older than 65 years in Spain is 5-7%.[3] According to the population-based medical database of Navarre (BARDENA), the prevalence of dementia in 2018 was 4.5% in patients older than 65 years. It is expected that prevalence increases with the ageing of the population. The use of acetylcholinesterase inhibitors (AChEIs) and memantine in this age group remained stable in Navarre between 2013 and 2019 (Figure 1), with a mean of 4,762 patients per year, which accounts for 88% of patients with an episode of dementia (P70).

The relevance and course of dementia and the limited effects of drug therapies in the early stages of the disease represent a perfect scenario for considering withdrawal. The approach to dementia and its associated syndromes is of great interest.

Figure 1. Evolution of the number of patients treated with anti-dementia drugs in Navarre between 2013 and 2019.



As mentioned above, the clinical situation of the patient with dementia must be taken into account when deprescribing is considered. The Global Deterioration Scale (GDS) is the most widely-used scale to measure progression of dementia. GDS classifies cognitive decline into seven stages ranging from 1, which indicates a normal cognitive function, to 7, which describes terminal stage. This scale assesses both cognitive decline (assessed by a lower score on cognitive tests) and functional deterioration (assessed by the FAST scale):[4]

GDS 1	->	Absence of cognitive alteration
GDS 2	->	Very mild cognitive impairment
GDS 3	->	Mild cognitive impairment
GDS 4	->	Moderate cognitive impairment
GDS 5	->	Moderately severe cognitive impairment
GDS 6	->	Severe cognitive impairment
GDS 7	->	Very severe cognitive impairment

Statistically significant differences have been documented in the beneficial effects of approved AChEIs[5] on cognitive function, as compared to placebo. However, the clinical relevance of these therapies is unclear.[6] Some studies have revealed that about a third of AChEIs and memantine prescriptions are potentially inappropriate.[7]

This Bulletin is based on the guideline *Deprescripción en pacientes con demencia avanzada (Deprescribing in patients with advanced dementia)* published by the Navarre Health Service - Osasunbidea.[8] The first part of this Bulletin addresses the deprescription of anti-dementia drugs (donepezil, rivastigmine, galantamine) and memantine. The second part of this issue will address deprescribing of other chronic therapies in patients with dementia.

Therapeutic indications of anti-dementia drugs

AChEIs (donepezil, rivastigmine, galantamine) are approved for the treatment of Alzheimer's disease (AD) in patients with a mild to moderate level of cognitive impairment. Rivastigmine is also indicated for the symptomatic treatment of mild to moderate dementia in patients with idiopathic Parkinson's disease.[5] Although approval for this indication has not been granted, it is also used for the treatment of Lewy body dementia (LBD) and mixed-type dementia.[9]

The goal of this prescription is to improve cognitive symptoms, help the patient to maintain the ability to perform activities of daily living (ADLs), and manage neuropsychiatric symptoms. Its benefits are moderate and vary across patients.

The indication of anti-dementia medication should be reviewed on a regular basis

Memantine is indicated for the treatment of moderate to severe AD.[5] Some authors recommend its use in case of intolerance to AChEIs or in combination with other drugs.[10] In contrast, other authors have raised concerns about its little benefit either in monotherapy or in combination with AChEIs.[11] In any case, the clinical relevance of its effects has not been established yet.[11,12]

Evidence on the effectiveness of these drugs is limited[3,11,13,14] and data available have been obtained in studies with a short follow-up period of no more than 1 year. Hence, there is a necessity of reconsidering the appropriateness of this treatment.[3]

This led some countries such as France to stop funding these treatments.[15] The French Health System (Haute Autorité de Santé) states that the clinical relevance of these drugs is insufficient to justify the use of public funds.[16] This decision meets the principle of justice, which requires that resources are equally distributed.

When to deprescribe?

There is no scientific evidence as to when to withdraw these medications. The only certainty is that the treatment must be reviewed on a regular basis[17] to determine whether the indication and benefit-risk balance are still valid.

There is general agreement that decisions about discontinuing drugs must be made on a case-by-case basis and in the following settings:

- Advanced or terminal stage of disease with overall loss of cognitive and/or functional abilities.
- In patients who no longer benefit from the use of this medication.[18]
- Patients or caregivers who do not wish to continue using this medication.
- Intolerable side effects[18] (Table 1). It should be taken into account that the appearance of side effects not identified as such, may lead to a prescribing cascade. E.g. if donepezil is used at night, disturbs sleep, and a benzodiazepine is then prescribed.

- Situations where therapeutic adherence cannot be guaranteed: refusal to take the medication, severe dysphagia, lack of supervision, etc.

- Interactions with concurrent therapies, which may increase the risks associated with anti-dementia drugs (Table 2).

- Comorbidities that cause benefit-risk unbalance such as hepatic insufficiency, severe chronic obstructive pulmonary disease or syncopes, among others (Table 3).

In some circumstances, it is recommended to evaluate the clinical status of the patient to reconsider the suitability of these treatments:

- On a yearly basis in patients with dementia with GDS ≥6.

- In patients who have stopped their anti-dementia medication (e.g. for surgery or hospitalization) and have not experienced a decline.

- When a change occurs in the clinical situation of the patient (which may change diagnosis or prognosis), a new comorbidity appears, or a new lifelong therapy that may cause interactions is prescribed.

- At hospitalization: there is always the need for reconsidering the therapy, and especially in dementia patients, the adequacy of AChEIs or memantine treatment.

- When patients are admitted to a nursing home their medication should be reviewed. Indeed, admission to a nursing home is the result of a worsening in the status of the patient. In case of institutionalization, it is recommended:

  » To individualize decisions and consider: side effects, cognitive and functional status, presence of behavioral disorders, and preferences of the family.

  » To continue treatment in patients who can perform some ADL or social interaction.

Drug discontinuation should be undertaken gradually and on a case-by-case basis

  » For the remainder of patients, the recommendation is to discontinue medication progressively and, in case deterioration unrelated to other events occurs, consider re-initiation.

  » In end-of-life stages, discontinue treatment fot dementia, as it exerts limited (or no) benefits, has side effects, and entail costs.

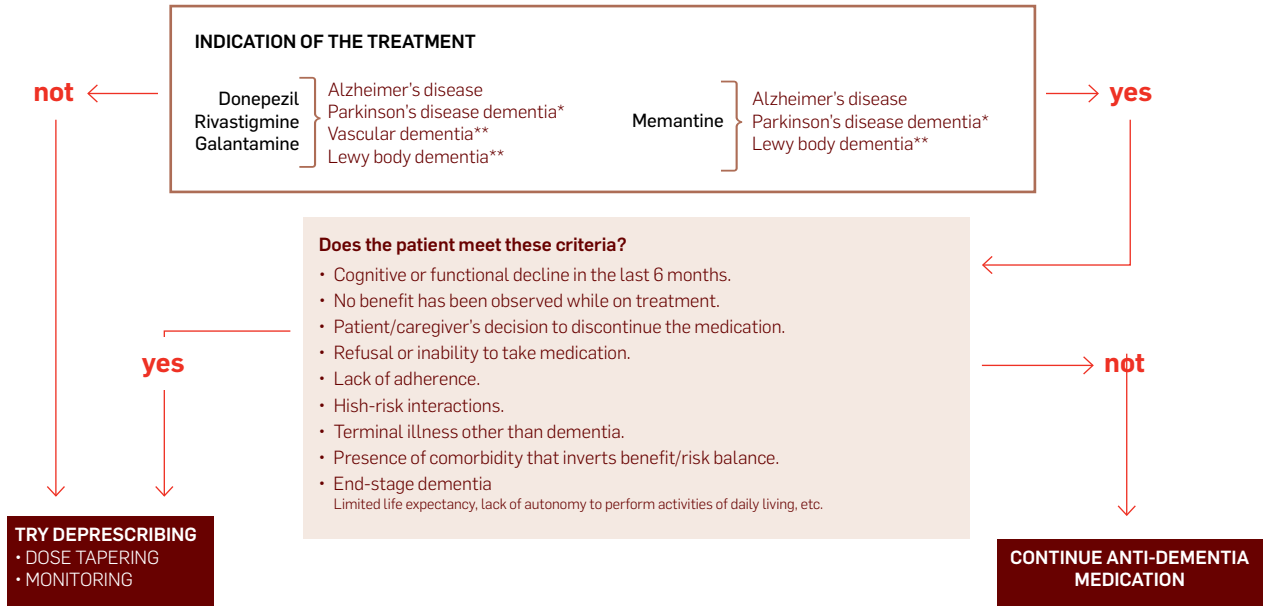
Specially critical situations may arise where appropriate information and communication are essential to facilitate deprescribing in the future:[8]

- On first prescription and in follow-up visits in Specialty Units: patients and their families should be informed of the need to review medication regularly, as the patient may benefit from discontinuance, and put special emphasis on the idea that this medication is not necessarily lifelong.

- Another crucial moment of the information process is at discharge from specialized to primary care. The neurologist/geriatrist should inform the family and specify on the discharge report that dementia medication must be reviewed regularly in patients with GDS ≥6.

Considering the aforementioned, a decision-making algorithm is proposed to provide guidance for deprescribing AChEIs or memantine (Algorithm 1).

Algorithm 1. Deprescribing anti-dementia drugs (adapted from 19).



(*) Off label use except for rivastigmine capsules and solution. (**) Off label use.

Table 1. Summary of adverse reactions associated with anti-dementia drugs.[3,5]

Donepezil, galantamine, rivastigmine	Memantine
Cardiovascular Bradycardia, syncope, heart block, bradyarrhythmias, hypertension.	**Cardiovasculares** Hipertensión, trombosis.
Gastrointestinal Nausea *, diarrhea *, vomiting *, dyspepsia	**Gastrointestinales** Estreñimiento, vómitos, pancreatitis.
Psychiatric Nightmares, insomnia (donepezil> rivastigmine), hallucinations, agitation (initially).	**Hepatobiliares** Elevación de pruebas de función hepática, hepatitis.
Other Headache *, anorexia *, dizziness *, weight loss, muscle cramps, fatigue, urinary incontinence, falls, bronchospasm, urinary tract infections (rivastigmine), cold.	**Neurológicas** Vértigo, alteraciones del equilibrio o la marcha, convulsiones.
Dermatological (transdermal administration) Itching, dermatitis, edema.	**Otros** Disnea, cefalea, fatiga, somnolencia, insomnio, alucinaciones.

(*) Very common adverse reactions: >10% according to drug label. For more detailed information, see package leaflet.

Table 2. Summary of potential interactions associated with anti-dementia drugs.[3,5]

Drug	Potential interactions	Result of interaction
Donepezil Rivastigmine Galantamine	Drugs that may cause bradycardia. *E.g. beta blockers, antiarrhythmics, calcium channel blockers, ivabradine*	Additive risk for bradycardia
	Anticholinergics *E.g. tricyclic antidepressants, antihistamines, urinary antispasmodics (except for mirabegron)*	Opposite mechanism of action; may reduce the efficacy of the two medications
	Metoclopramide, antipsychotics (with rivastigmine)	Additive risk for extrapyramidal effects
	Drugs that may prolong the QT interval. *E.g. antiarrhythmic, calcium antagonists, escitalopram, citalopram, antipsychotics or antihistamines*	Additive risk for QT interval prolongation and torsade de pointes.
	Drugs with cholinergic effects. *E.g. succinylcholine*	Prolongation of the cholinergic effect: *E.g. Prolonged muscle relaxation after anesthesia*

Table 3. Precautions in subgroups of patients.[3,5]

Drug	Conditions where it must be used with caution
Donepezil Rivastigmine Galantamine	Cardiac conduction alterations Peptic ulcer COPD/asthma Convulsions Urinary tract obstruction Liver insufficiency with Child-Pugh >9 (galantamine is contraindicated; absence of data) Renal insufficiency with creatinine clearance < 9 mL/min (galantamine is contraindicated)
Memantine	Cardiovascular disease Liver insufficiency Renal insufficiency Convulsions Ocular pathology (corneal)

How to deprescribe?

Deprescribing should be undertaken in accordance with the following principles:[8]

- Deprescribing should be considered after an individualized evaluation of the patient and their environment (expectations of the patient and their family, frailty, life expectancy, among others).[7]
- The decision to deprescribe should be shared with the patient/family.[7]
- Before a decision is made, the patient or their family or caregiver, where appropriate, should be appropriately informed of the reasons why deprescribing is being considered, the withdrawal plan, and the actions to be taken in case adverse effects or withdrawal symptoms arise.[7]
- In patients with LBD, AChEIs may contribute to control hallucinations; therefore, before deprescribing is considered in this population, the clinician must ensure that the patient has not had disruptive hallucinations requiring medication at present or in the past.[20]
- The dose must be tapered and patient response monitored:[7]
  - » If the patient is receiving double-therapy, withdraw AChEIs first, as it is not indicated for advanced dementia, then discontinue memantine.[5,21]
  - » Reduce the dose progressively every four weeks, taking into account the time to reappearance of dementia symptoms and clearance time[22] (Table 4).

In case of clinical deterioration after dose tapering has been initiated, the actions needed will depend on the time elapsed since the start of dose tapering or since withdrawal. Table 5 provides guidance on the actions to be taken according to the situation detected.

The decision to prescribe/deprescribe medication should be shared with the patient/caregiver

What are the potential benefits of deprescribing?

Deprescribing AChEIs or memantine can exert the following beneficial effects:[22]

- Minimization of medication burden, which reduces the risk for adverse effects, drug-to-drug interactions, and medication errors.
- Improvement of treatment adherence.
- Treatment simplifications may contribute to reduce the burden of care, as these patients generally are high-need patients. In some cases, these patients have difficulty in taking their medication resulting in lack of adherence.
- Reduction in the cost of care for the patient and the community.

Table 4. Recommendations for dose tapering of AChEIs and memantine.[22]

Medicine	Presentations available	Dose tapering strategy	Time on each tapering phase
Donepezil tablets	5 mg (28 tablets) 10 mg (28 tablets)	10 mg/24h > 5 mg/24h > stop	4 weeks
Galantamine extended-release capsules*	8 mg (28 caps.) 16 mg (28 caps) 24 mg (28 caps)	24 mg/24h > 16 mg/24h > 8 mg/24h > stop	4 weeks
Rivastigmine capsules**	1.5 mg (28, 56 or 112 caps) 3 mg (56 or 112 caps) 4.5 mg (56 or 112 caps) 6 mg (56 or 112 caps)	6 mg/12h > 4.5 mg/12h > 3 mg/12h > 1.5 mg/12h > stop	4 weeks
Rivastigmine patches**	4.6 mg/24h (30 or 60 patches) 9.5 mg/24h (60 patches) 13.3 mg/24h (60 patches)	13.3 mg/24h > 9.5 mg/24h > 4.6 mg/24h > stop	4 weeks
Memantine***	10 mg (112 caps) 20 mg (56 caps)	20 mg/24h or 10 mg/12h > 10 mg/24h > stop	4 weeks

(*) Galantamine 4 mg/mL, oral solution 100 mL also available.
(**) Rivastigmine 2 mg/mL, oral solution 120 mL also available.
(***) Memantine 5 mg/puff, oral suspension 100 mL also available.

Table 5. Patient management in the presence of changes associated with dose tapering or withdrawal of AChEIs and memantine.[22]

Time from initiation of dose tapering to complete withdrawal	Type of symptoms	Action to be taken by the caregiver	Possible cause (after other organic or drug-induced causes have been excluded)
Less than one week	Severe symptoms: · Agitation · Aggressiveness · Hallucinations · Reduction of the level of consciousness	Restart previous dose and contact your healthcare provided immediately	Withdrawal syndrome
2-6 weeks	Worsening of symptoms of behavioural, cognitive or psychological function	Contact with the treating health-care professional and consider restoring the previous dose and/or make and appointment with the healthcare professional	Reappearance of symptoms for which the drug was intended
6 weeks – 3 months	Worsening of symptoms of behavioural, cognitive or psychological function	Make an appointment with your healthcare professional	Probable progression or reappearance of symptoms for which the drug was intended
More than 3 month	Any	Usual care	Disease progression

What are the limitations to deprescribing?

Deprescribing is often a complex process hindered by the presence of barriers to the patient, family, and healthcare professionals treating them.

To overcome family-associated barriers, when a medication is first prescribed, the family should be informed of the goals of the therapy, the need to review medication regularly, and the actions to be taken in case the therapy did not exert any benefit.[7] The negative connotations that medication withdrawal may have for the patient or their family should be minimized to facilitate deprescribing in the future, when needed.

The lack of scientific evidence on deprescribing is one of the main obstacles found by physicians when trying to optimize the treatment of dementia in older patients.[7] The purpose of this Bulletin is to provide guidance to clinicians in relation to the review of medication and consideration of deprescribing anti-dementia drugs.

Conclusions

The benefit-risk balance of approved drugs for dementia is unclear.

Deprescribing of AChEIs and memantine should be considered in patients with advanced dementia (GDS ≥6), patients who have experienced adverse events or interactions, and patients who no longer benefit from the therapy.

In view of the lack of consensus as to when and how to deprescribe anti-dementia drugs, our working group developed a set of guidelines for deprescribing anti-dementia drugs to help clinicians in their decision-making process.

The aspects to be taken into account whenever prescription/deprescribing is considered are not only technical, but also ethical, and a shared decision-making approach should be adopted where the patient or caregiver is informed and involved.

References

1. Gracia D. Procedimientos de Decisión en Ética Clínica. Madrid, Ed. Eudema S.A., 1991: 124-34

2. PHN Tasmania. A guide to deprescribing: general information. Mayo 2019.

3. Fernández M, Gardeazabal MJ, Gerediaga E, et al. Seguimiento y retirada de fármacos antidemencia. Vitoria: Departamento de Salud; 2016.

4. Know Alzheimer. [Internet] 2019. ¿Cuáles son las etapas de la enfermedad de Alzheimer? [Consultado el 27 de diciembre de 2019].

5. Agencia Española de Medicamentos y Productos Sanitarios.

6. PHN Tasmania. A guide to deprescribing cholinesterase inhibitors. Mayo 2019.

7. Reeve E, Farrell B, Thompson W, et al. Deprescribing cholinesterase inhibitors and memantine in dementia: guideline summary. Med J Aust. 2019 Mar;210(4):174-179. doi: 10.5694/mja2.50015. Epub 2019 Feb 16.

8. Servicio Navarro de Salud – Osasunbidea. Deprescripción en pacientes con demencia avanzada. 2019.

9. Lexicomp Online, Rivastigmine drug information, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; fecha de acceso 20 de noviembre de 2019.

10. Ministerio de Sanidad y Política Social. Guía de buena práctica clínica en Alzheimer y otras demencias.

11. McShane R, Westby MJ, Roberts E, et al. Memantine for dementia. Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD003154. DOI: 10.1002/14651858.CD003154.pub6.

12. UpToDate.[Internet] 2019. Treatment of dementia. [Consultado el 20 de noviembre de 2019].

13. Knight R, Khondoker M, Magill N, et al. A systematic review and meta-analysus of the effectiveness of acetylcholinesterase inhibitors and memantine in treating the cognitive symptoms of dementia. Dement Geriatr Cogn Disord 2018;45:131-151.

14. Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD009132. DOI: 10.1002/14651858.CD009132.pub2.

15. Médicaments de la maladie d'Alzheimer: enfin non remboursables en France! Rev Prescrire 2018 ; 38 (416).

16. Haute Autorité de Santé. Synthese d´avis de la commission de la transparence. Neurologie Mise au point Octobre 2016.

17. Dynamed. [Internet] 2019. Alzheimer-dementia. [Consultado el 18 de noviembre de 2019].

18. UpToDate.[Internet] 2019. Cholinesterase inhibitors in the treatment of Alzheimer disease. [Consultado el 16 de octubre de 2019].

19. Reeve E, Farrell B, Thompson W, et al. Cholinesterase inhibitor (ChEI) and memantine deprescribing algorithm. Sydney: The University of Sydney; 2018. [Consultado el 24 de abril de 2019].

20. UpToDate.[Internet] 2019. Prognosis and treatment of dementia with Lewy bodies. [Consultado el 2 de diciembre de 2019].

21. Rodríguez-Pérez A, Alfaro-Lara E, Albiñana-Perez S, et al. Novel tool for deprescribing in chronic patients with multimorbidity: List of Evidence-Based Deprescribing for Chronic Patiens criteria. Geriatr Gerontol Int 2017;17:2200-2207.

22. Reeve E, Farrell B, Thompson W, et al. Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine: Recommendations. Sydney: The University of Sydney; 2018.

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INFORMATION AND SUSCRIPTION
Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T 848429047
F 848429010

E-mail
farmacia.atprimaria@cfnavarra.es

Web site
www.dtb.navarra.es