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Strategies for discontinuing benzodiazepines

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abstract

Objectives: To establish recommendations for safe use of benzodiazepines, including protocols for withdrawal, strategies for detoxification, and alternatives for the management of insomnia. **Methods:** We searched PubMed, Cochrane library, TripDatabase and UpToDate in March 2014. Data on consumption of benzodiazepines in Navarre, Spain, were obtained from the Drug Prescribing Service of the Navarre Health Services. **Results:** Various areas for improvement with regard to the prescription of benzodiazepines have been described: number of patients treated, use of more than one active substance and treatment duration. Different strategies have been evaluated and employed to deprescribe benzodiazepines. A simple approach, with no follow-up visits and written instructions for patients on withdrawal, led to 45% of patients effectively discontinuing treatment after 12 months versus 15% in the control group. **Conclusions:** A simple approach to deprescription of benzodiazepines is effective and long lasting. This approach involves adequately informing the patient on the need to reduce consumption, giving written detailed instructions on withdrawal, pointing out the possible withdrawal effects and solutions for them.

Introduction

Benzodiazepines are amongst the most frequently prescribed drugs in developed nations. In Navarre, consumption has been stable in recent years (Figure 1). In 2013, 840,327 packages were sold, representing 8% of all prescription drugs. The most frequently prescribed active substances were lormetazepam (25%), lorazepam (24%) and alprazolam (19%). Up to 15% of the population uses benzodiazepines, of which two thirds are female. During 2013, nearly 2000 people received 25 or more prescriptions, and 604 were prescribed 4 or more different benzodiazepines.

At least half of people over 85 years and 2% of adolescents, ages 15-19, received at least one benzodiazepine (Figure 2). A total of 48% received benzodiazepines for longer than 4 months. Between October and December 2013, 86% took one active substance, while 13% were treated with at least two different benzodiazepines.

Although benzodiazepine prescription has been constant in Navarre over the last 6 years, prescribing could be improved with regard to the prolonged duration of treatment, prescriptions for more than one active substance, and the number of patients treated. Benzodiazepines cause adverse effects such as tolerance, dependence, addiction or cognitive deterioration, falls, motor vehicle crashes, etc. Furthermore, a recent observational study related their use to an increase in mortality.[1]

Is their popularity justified or do we underestimate their adverse effects and overrate their benefits?

General characteristics of benzodiazepines

Benzodiazepines act by potentiating the inhibitory effect of GABA. They are mainly used to manage insomnia and anxiety. They are sometimes used as anticonvulsants, muscle relaxants or in alcohol detoxification. In the short term, benzodiazepines act rapidly and are effective, and relatively safe. However, during prolonged treatment, dependence, abuse, abstinence syndrome and tolerance-related problems can appear even after a few weeks of therapy.

They are addictive drugs. According to some authors, the habituating potential of benzodiazepines is underappreciated.[2] Discontinuation should be carried out gradually, after establishing a patient-specific withdrawal protocol and considering alternative treatments (psychological and/or pharmacological).

Why are so many patients on long term treatment? A fundamental issue is patient resistance to stopping benzodiazepines. Other factors include limited physician time and the difficulties of managing withdrawal.

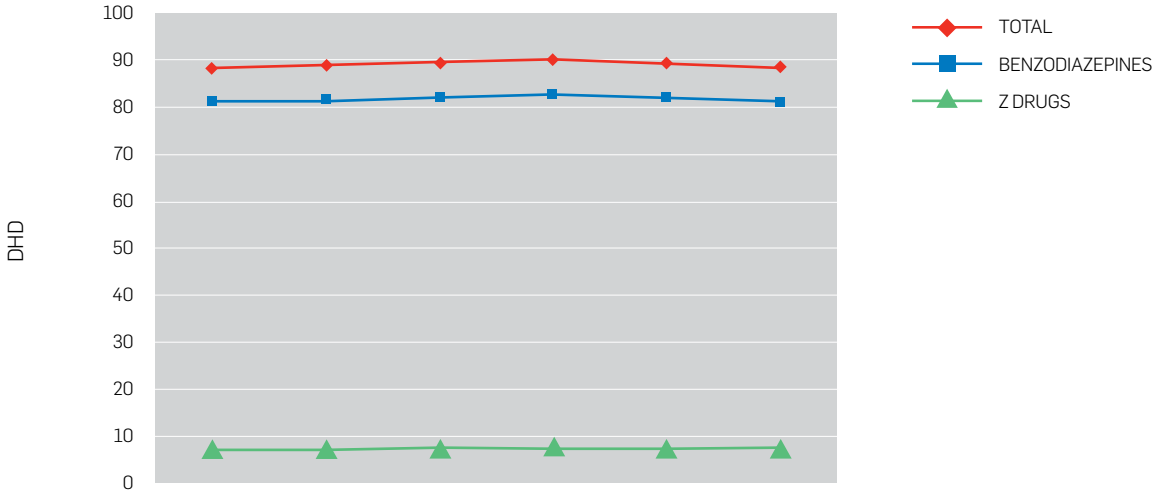
Officially recommended duration of treatment

Benzodiazepines should be employed at the minimum effective dose, in monotherapy and only for acute disorders for short treatment duration. The Spanish drug information leaflet recommends 2 to 4 weeks in the case of insomnia and 8 to 12 weeks in cases of anxiety. For both, withdrawal should be gradual. If the duration of treatment exceeds the recommended interval, the patient should be closely monitored for adverse drug reactions.

The *Committee on Safety of Medicines*[3] of the British Medicines and Health Products Agency is more conservative. It recommends that for insomnia or anxiety benzodiazepines should be employed only as symptomatic relief for a maximum of 2-4 weeks (including withdrawal period) and only when insomnia or anxiety are considered severe, disabling or subjecting the patient to extreme distress. In mild and transitory anxiety, benzodiazepine use is discouraged. For combined anxiety and depression, benzodiazepine use should not exceed two weeks.

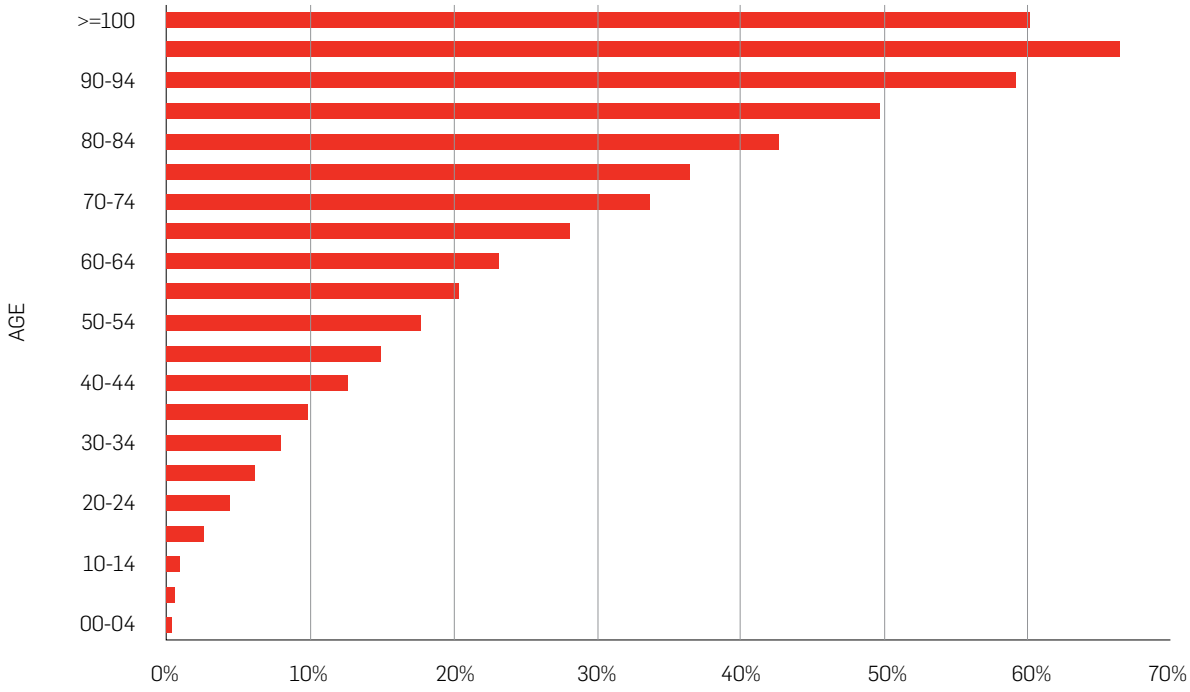
An observational study of 43,915 American veterans showed that after benzodiazepines were prescribed for combination treatment of depression, 14.1% continued after one year, and 0.7% were subsequently diagnosed with either anxiolytic dependence or abuse.[4]

Figure 1. Consumption of benzodiazepines/Z drugs in Navarre in DHD (DDD/1000 inhabitants/day).



	2008	2009	2010	2011	2012	2013
Total	88.30	88.78	89.52	90.05	89.56	88.72
Benzodiazepines	81.19	81.56	82.11	82.50	81.95	81.21
Z Drugs	7.11	7.22	7.41	7.55	7.61	7.51

Figure 2. Navarre: % of people treated with benzodiazepines by age.



Effects of benzodiazepines on the brain and behaviour

In both short and long term, benzodiazepines cause sedation, psychomotor deterioration, accidents and falls, deterioration of complex skills such as driving, and paradoxical behaviour.[2] Benzodiazepine-induced severe cognitive deterioration in elderly patients can be mistaken for the onset of dementia. For this reason benzodiazepines should be avoided in the elderly, but other sedating drugs can also cause the same problems.[2]

Adverse effects occur more frequently when long half-life drugs (over 24 h) are used, when the dose is higher than the recommended, when treatment duration is prolonged and when they are combined with other psychoactive substances such as alcohol (Tables 1 and 2).

Table 1. Hypnotics: equivalent doses to 5 mg Diazepam.

Active substance	Brand name (in Spain)	Elimination half-life (h)	Approximate dose (mg)
Short half-life (< 8 h)			
Brotizolam	Sintonal®	3 - 8	0.25
Midazolam	Dormicum®	1 - 5	7.5
Triazolam	Halcion®	3 - 5	0.125 - 0.25
Zolpidem	Dalparan®, Stilnox®	1.5 – 2. 4	10
Zopiclone	Datolan®, Limovan®, Siaten®, Zopiclona®	5	7.5
Intermediate half-life (8 – 24 h)			
Flunitrazepam	Rohipnol®	15 – 30	0.5 – 1
Loprazolam	Somnovit®	4 – 15	0.5 – 1
Lormetazepam	Noctamid®, Loramet®	11 – 30	0.5 - 1
Long half-life (> 24 h)			
Flurazepam	Dormodor®	24 – 100	15
Quazepam	Quiedorm®	40 – 55	10

Table 2. Anxiolytics: equivalent doses to 5 mg Diazepam.

Active substance	Brand name (in Spain)	Elimination half-life (h)	Approximate dose (mg)
Short half-life (< 8 h)			
Bentazepam	Tiadipona®	2 - 5	25
Clotiazepam	Distensan®	5.8 - 6.3	5
Intermediate half-life (8 – 24 h)			
Alprazolam	Trankimazin®	12-15	0.25 - 0.5
Bromazepam	Lexatin®	10 - 20	3 - 6
Clobazam	Noiafren®	18	10
Ketazolam	Sedotime®	6 – 25	7.5
Lorazepam	Orfidal®, Idalprem®	11 – 30	0.5 - 1
Long half-life (> 24 h)			
Chlorazepate	Tranxilim®	30 - 48	7,5
Chlordiazepoxide	Huberplex®	1.5 - 4	15
Diazepam	**Valium®, Diazepam®**	**20 – 100**	**5**
Halazepam	Alapryl®	30 – 100	10
Clonazepam	Rivotril®	20 – 80	0.5

Special precaution in elderly patients

Risk of dementia

Elderly patients are more susceptible to the adverse effects of benzodiazepines. The American Society of Geriatrics recommends against the use of benzodiazepines as a first choice for the management of insomnia, agitation or delirium as one of 5 key things to avoid in elderly patients.[5] When a benzodiazepine is prescribed to an elderly patient, health care providers should be alert for new cognitive problems. The relationship between benzodiazepines and acute cognitive deterioration seems clear. A French population-based study found that the risk of dementia increased by approximately 60% after starting treatment with benzodiazepines HR = 1.60 (CI95% 1.08-2.38).[6] This study followed 1,603 participants for 15 years (average age, 78.2 years, initially without dementia). Subjects started taking benzodiazepines at least three years after the study´s commencement. As this was an ecological study, a cause-effect relationship was not established.

Risk of falls and hip fracture

Benzodiazepines also increase the risk of falls in elderly patients treated with benzodiazepines. A meta-analysis found a 41% increase in risk in patients over 60 years, OR = 1.41 (95%CI 1.20-1.71).[7]

The impact of benzodiazepines on hip fractures was evaluated in five European countries (France, Germany, Italy, Spain and United Kingdom). The highest use of benzodiazepines was found in Spain (22.3% of the population were treated with benzodiazepines in one year) and the lowest rate in Germany (4.7%). The risk of hip fracture associated with benzodiazepines varied between 1.8% in Germany and 8.2% in Spain. The increase in risk of falls was 40%, RR = 1.40 (95%CI 1.24-1.58).[8]

Shorter elimination half-life benzodiazepines are not associated with lower risk of falls than longer half-life drugs, hence neither can be recommended for elderly patients.[9]

Increase in mortality

One retrospective cohort study using prescription data from people over 16 years over a mean of 7.6 years (range: 0.1-13.4 years) identified an increase in mortality during the first year after use of hypnotics and anxiolytics; HR = 3.32 (95%CI, 3.19-3.45) after adjusting for age and other confounding factors.[1]

Are the Z drugs better than benzodiazepines?

The Z drugs, zolpidem, zopiclone, zaleplon and eszopiclone (the last two not available in Spain) are promoted as hypnotics with better pharmacokinetic profile than benzodiazepines. Their ostensible advantages were rapid action, a short half life, reduced sleep latency without changes in sleep structure, and a reduction of residual effects during the day. However, their benefit-harm relationship is similar to that of benzodiazepines, especially for elderly people, and they require the same precautions.[10] The UK NICE guidelines classify Z drugs as having "no advantages compared to benzodiazepines".[11]

Zopiclone and its single enantiomer eszopiclone have a longer elimination half-life (about 5 h) than zolpidem (2 h) or zaleplon (1 h). These drugs can be useful for initial insomnia but their effects wear off rapidly during the night. Currently Z drugs are being promoted for shift workers, pilots or military personnel.[10]

In January 2013, the FDA recommended an initial dose of 5 mg zolpidem for women and 5-10 mg for men. If the 5 mg dose is not effective then 10 mg can be used. It also warns that use of the higher dose could increase the risk of daytime sleepiness the following day, which should be taken into account if driving is considered and/or any activity requiring focussed attention is planned.[12]

Benzodiazepines should be prescribed for insomnia only when hygiene related measures have failed.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) agreed that to mitigate the risk of next-morning impaired driving ability and somnambulism, there should be a rest period of at least 8 hours after zolpidem administration before performing activities that require mental alertness such as driving. The PRAC considered that the recommended daily dose should remain at 10 mg of zolpidem, and that this dose should not be exceeded. Zolpidem should be taken as a single dose immediately before bedtime without being re-administered during the same night. The PRAC agreed that the available efficacy data did not provide robust evidence that a lower dose was effective for most people. However, it also considered that for some individual patients a lower dose could be effective; therefore as for any other drug used to control symptoms, individual patients should take the lowest effective dose. In elderly patients and in patients with reduced liver function, the recommended dose of zolpidem remains 5 mg per day.[13]

Recommendations for stopping benzodiazepines

Discontinuation of benzodiazepines can be expected to improve a typical patient's health. In one group of 192 people over age 65, 60% had taken benzodiazepines for at least 10 years (27% for more than 20 years). Gradual dehabituation improved cognitive and psychomotor measures, with little discomfort due to withdrawal symptoms. Due to tolerance, a lack of efficacy was also observed for benzodiazepines used as hypnotics. 80% of the patients completely withdrew treatment after 6 months.[14]

A common regimen for withdrawal involves an initial reduction of the total daily dose by 10-25%, depending on the degree of dependence. The reduced dose is maintained for 2-3 weeks, before considering further dose reductions. Dose reduction can be accomplished with the original benzodiazepine, or after switching to an equivalent dose of diazepam, to take advantage of its long elimination half-life (1-3 days) and the even longer t½ elimination of its active metabolite nordiazepam

(t½ elimination = 2-7 days). Diazepam is available in multiple formulations, which permits flexibility in dose adjustments. Changing temporarily to another benzodiazepine can also be helpful in patients with a strong psychological dependence on a "sleeping pill." While long-acting benzodiazepines should typically be avoided, the aim of this substitution is eventual drug withdrawal rather than mere substitution.[15] It is helpful to specify the tapering schedule in writing, and stick to it.

Should withdrawal symptoms develop, the reduced dose can be maintained for a few more weeks, or until the symptoms disappear, before reducing it further. This is preferable to resuming the original dose, which undoes any benefit already achieved. Very slow tapering may be easier to accomplish than rapid withdrawal, potentially requiring from 4-6 weeks up to one year or more.

If withdrawal fails, then intermittent use of benzodiazepines is recommended. Different studies have shown the benefits of intermittent therapy, both as fixed regimens or "on demand".[15]

A prediction test for hypnotics dependence can help establish the degree of dependence (Table 3).

Withdrawal strategies

A non-systematic review published in 2010 documents interventions for benzodiazepine withdrawal.[16] The most frequently used were: a letter to the patient, an interview or structured talk with health care professionals and interview-talk with the support of psychotherapy or drugs.

Treatment duration should be limited.

'Minimal' intervention. Letter to the patient

In this approach the patient is in charge of a gradual withdrawal without specific support or contact with health care professionals. The strategy consists of identifying susceptible patients for discontinuation and sending them a letter informing them of the need to reduce benzodiazepine dose, the undesirable effects of long-term consumption and offering them a tapering schedule.[17-18] A published sample letter is available[19] and Appendix 1 is a letter used by the French Ministry of Health in a campaign on sleep-related problems in elderly patients.[20] This campaign includes posters, patient videos on YouTube, and supporting material which can be found in the Ministry's website.

This "minimal strategy" has led to a withdrawal rate, measured as no consumption after 12 months, between 18% and 22%.[15]

Table 3. Predicting dependence on hypnotic drugs*.

	Score
Benzodiazepine	3
High mean dose	2
Duration > 3 months	2
Dependent personality (or previous dependence on drugs or alcohol)	2
Short elimination half-life (< 8 h)	2
Evidence of tolerance or escalation of dose	2

Results

1 - 4 =	Some risk of dependence Gradual withdrawal over 2 weeks
5 - 8 =	Strong risk of dependence Gradual withdrawal over 4 -12 weeks
8 - 13 =	Dependence almost certainly present, gradual reduction associated with formal withdrawal programme

*Tyrer P. ABC of sleep disorders: Withdrawal from hypnotic drugs. BMJ 1993;(306):706-8.

'Structured intervention': interview with a physician or health care professional

An interview should remind the patient of the temporary benefits of short-term treatment, discuss dependence and tolerance, abstinence syndrome, consequences of chronic consumption (reduction of reflexes, falls, fractures, memory alterations, the need for tapering off the drug, potential symptoms during dose reduction, the convenience of follow-up visits and provision of support throughout the whole process. Withdrawal rates accomplished after 12 months vary between 24% and 62%.[15]

Follow-up visits are not always necessary, simplifying the intervention. In Finland a randomized controlled trial was carried out including 591 people over age 65 who received one discussion session, with no further follow-up visits. After 12 months, the use of benzodiazepines decreased by 35% in the intervention group, compared with 4% in the control group.[21]

'Forced' intervention: structured interview, psychological support and/or drugs

Psycotherapy

This consists of supporting a withdrawal strategy through cognitive behavioural therapy. It requires identification and correction of behaviour problems and learning sleep hygiene habits (Appendix 2), control of stimuli or relaxation techniques.[22] Various studies support the efficacy of cognitive behavioural therapy in addition to a benzodiazepine tapering schedule. In two studies,[23-24] this intervention proved adequate for elderly patients with chronic insomnia, although benefits may be obtained some months after initiating withdrawal.

Drugs

Few studies support the effectiveness of pharmacological management to facilitate benzodiazepine dehabituation programs. The most frequently studied drugs are melatonin and the antihistamine hydroxizine.

Melatonin. Two randomized clinical trials carried out in a primary care setting evaluated whether melatonin was useful in the context of a benzodiazepine withdrawal programme for patients with insomnia.[25-26] These trials involved low potency benzodiazepines at low doses, and the sample sizes were small, and no conclusions can be drawn.

Hydroxizine. One study on benzodiazepine withdrawal included 154 outpatients with general anxiety who had been taking lorazepam 2 mg for at least 3 months. Hydroxizine 25-50 mg during the dehabituation period did not significantly improve symptoms of anxiety nor abstinence from lorazepam.[27]

The use of benzodiazepines in elderly patients increase the risk of cognitive deterioration, falls and fractures.

Effectiveness of withdrawal interventions

Various meta-analyses have compared the effectiveness of different benzodiazepine withdrawal strategies.[28-29] Any intervention, even the simplest (letter, talk or interview) improves the results. In general, the best results are obtained when the intervention is accompanied by psychotherapy OR = 5.06 (95%CI, 2.68–9.57). Minimal interventions are also effective OR = 1.43 (95%CI, 1.02-2.02), while addition of drugs did not improve routine interventions, OR = 1.31 (95%CI, 0.68-2.53).[30]

In a study carried out in The Netherlands, ten years after benzodiazepine discontinuation achieved through simple interventions (letters), 59% of former users did not resume benzodiazepine use; 14% took minimum doses, consistent with intermittent but not chronic use.[31]

Some experiences of deprescription in Spain

In 2012, a benzodiazepine withdrawal programme was conducted by nurses in two primary care centres in Barcelona.[33] Standard interviews with patients recorded patient beliefs about their sleep and about benzodiazepines. Patients were informed about harms and benefits of long-term consumption, and the possibility of developing dependence.

During the interview a date was fixed to decide about treatment withdrawal; follow-up visits were scheduled every 4 weeks during the first 3 months. Patients could continue with the same benzodiazepine or switch it to an equivalent dose of diazepam. Every 2-4 weeks, the dose was gradually reduced by 25%. When necessary, hydroxizine or valerian root (*Valeriana officinalis*) was offered. The primary endpoint was absence of benzodiazepine consumption after 6 and after 12 months.

After one year, 64.7% maintained abstinence. This result was similar to that obtained when the interview was carried out by either physicians or psychologists. Participants completed n a validated questionnaire (SF-12) at the beginning and after 24 weeks of the intervention.

Improvement in mental faculties but not in physical factors was observed in the group that achieved dehabituation. A statistically significant reduction of anxiety and depression was reported by the patients evaluated through the Goldberg scale (GADS).[32]

Another recent randomized controlled trial compared two interventions carried out in primary care.[33] A total of 532 patients who had received benzodiazepines for at least 6 months were randomly allocated to one of 3 groups:

- structured interviews and follow-up visits
- structured interview and written instructions, but no follow-up visits
- regular management (control group).

The primary endpoint was rate of abstinence after 12 months. Efficacy in both intervention groups was similar; 45% discontinued benzodiazepine treatment versus 15% in the control group. The most frequent adverse effects during withdrawal were insomnia, anxiety and irritability. The authors concluded that a simple intervention including written information on gradual withdrawal obtained the same results as a more time-consuming intervention.

Drugs for the management of insomnia

Melatonin

This is indicated in patients over 55 years with primary insomnia, characterised by poor quality sleep, and during a maximum period of 13 weeks.[34]

Symptoms of jet lag may improve, but melatonin is not effective either in shift workers or for secondary insomnia. For children, two guidelines mention possible beneficial effects in sleep disorders,[35-36] especially in children with certain associated pathologies such as autism, epilepsy, ADHD, or neurological disorders. Nevertheless a joint report of the Spanish Society of Paediatrics[37] along with other scientific societies does not advise general use of melatonin in children, and suggests using the minimum effective dose.

Melatonin use in insomnia remains controversial. It can modify sleep latency in the short term, total sleep duration and the quality of rest, but improvement is not clinically relevant.[38] Nevertheless its use can be considered when all other therapeutic alternatives have failed and always under medical supervision.

Antidepressants

Antidepressants are used frequently off-label for insomnia. Doses lower than those traditionally recommended for depression are often employed to take advantage of their antihistaminic properties. However, "low" doses of many antidepressants might also exert profound anticholinergic and alpha-blocking effects. The most frequently used antidepressants include doxepin, mirtazapine, amytriptilline, trimipamine, and trazodone. However evidence of their efficacy in primary insomnia or long-term use is very limited.

Whenever treatment exceeds a 3-month period, deprescription should be considered.

Histamine-1 receptor antagonists

Older antihistamines produce somnolence as a side effect. This has led to their use in the management of insomnia, and some of them are marketed for this indication. The most frequent agents used include diphenhydramine, clorpheniramine, promethazine, hydroxizine and doxilamine.[39] An abrupt withdrawal of the drug can cause rebound insomnia.[40]

Definitively their numerous anticholinergic side effects, the possibility of cognitive alterations, daytime somnolence, accumulation of those with long elimination half-lives, and uncertainty about optimal dosing for insomnia, makes their harm-benefit relationship unfavourable, especially in the elderly.[41-42]

Clomethiazole

This is indicated in some countries as an alternative to benzodiazepines in elderly patients who suffer from confusional states and sleep disorders related to old age. Some studies carried out in the elderly have compared it to benzodiazepines, showing no significant differences in terms of efficacy or adverse effects.[43-44] Tolerance and physical and mental dependence can occur when treatment lasts beyond 7-10 days, thus limiting its use to minimum doses and brief periods.[45]

Valerian root

This is the most studied natural product given its hypnotic effects. Currently available evidence from controlled trials does not justify its use for insomnia. A meta-analysis[46] that evaluated the efficacy of valerian root compared with placebo, showed an insignificant increase in sleep latency in favour of valerian root (0.7 minutes) and an improvement in the subjective quality of sleep.

Despite its modest efficacy, the existing evidence is insufficient to recommend its use in insomnia, as in the case of other sedative herbs. Perhaps, consumption at night time before going to bed could offer some tranquility and help the transition to sleeping.[47] Pharmacologically inactive therapies may be useful for their placebo effects, while avoiding the adverse effects associated with prescription drugs.

Final reflections

Discontinuation of treatments when patients do no longer need them is part of good medical practice. There are many studies focusing on treatment initiation, but comparatively little evidence on the best approach to discontinuing treatment. The inertia of prescription explains why some prescriptions become chronic, despite being recommended only for short periods. Examples include not only prescription of benzodiazepines, but NSAIDs (including COX-2 inhibitors), proton pump inhibitors, and analgesics.[48]

For benzodiazepine deprescription, a simple intervention can be effective and long lasting. This starts with making patients aware of the need to reduce consumption, providing instructions for withdrawal, and informing patients about the possible adverse effects of dose reduction and withdrawal and how to address them. The 'minimum strategy' successfully used to taper and discontinue other drugs such as oral corticosteroids is a useful precedent: motivated patients leave the consultancy with precise information on the recommended tapering schedule and themselves finish the task.

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A minimum intervention, with no follow-up visits has proven effective in the deprescription of benzodiazepines.

Conclusions

The prescription of a benzodiazepine or its continuation should never be routine.

Use of two benzodiazepines is not recommended.

Benzodiazepines should be prescribed for a maximum of 2-4 weeks for insomnia and 8-12 weeks in case for anxiety. For both indications, after prolonged use, dose tapering should be gradual, progressive and never abrupt.

Prolonged use of benzodiazepines can provoke tolerance and dependence, abstinence syndrome, abuse and paradoxical behaviour.

Benzodiazepines should be avoided in elderly patients whenever possible, given their greater sensitivity to adverse effects. When benzodiazepines are prescribed, health care professionals should watch for cognitive impairment, motor impairment, or falls and fractures.

A 'minimum strategy' which includes informing the patient about problems related to long-term consumption and providing a dose tapering schedule is useful in the deprescription of benzodiazepines.

Appendix 1. Letter to patients in the French Health Ministry's campaign.

Dear Sir/Madam,

One of the drugs you are currently taking is (commercial name of the benzodiazepine) at this dose (tablets per day). This drug belongs to a class known as benzodiazepines and related drugs. A close study of your medical records shows that you can stop taking this drug without affecting your health or wellbeing. In fact today it is known that benzodiazepines' efficacy decreases the longer they are used, as in your case. Moreover, these drugs can have undesirable effects, especially in elderly patients: they can cause falls, memory-related problems and increase their risk of accidents in drivers who take them.

I would like to propose that we gradually reduce its consumption with the aim of stopping it completely, should all go well in a few weeks. To avoid problems it is very important that this withdrawal be done progressively under medical supervision.

In case it helps you, I have sent you a calendar to mark the withdrawal schedule that we can fill in together in my consultancy. If it is convenient for you we can schedule an appointment sometime soon.

Should you have any query please let me know.

Yours sincerely,

Appendix 2. Sleep hygiene.

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