Factsheet deprescribing Antiepileptic Drugs

This factsheet can be used when considering continuation or discontinuation of antiepileptic drugs in patients aged 70 years and older. All recommendations are based on chronic use of antiepileptic drugs (≥ 1 month) in the context of neuropathic pain, epilepsy, and migraine. The decision to continue or discontinue medication depends on the medical history, the effects of antiepileptic drugs, and the (current) side effects. All pros and cons should always be carefully weighed in consultation with the patient or their (informal) caregiver and any other involved prescriber to reach a well-informed decision. Switching antiepileptic drugs and application for psychiatric conditions are beyond the scope of this factsheet. **Note**: If the antiepileptic drugs were originally prescribed by a neurologist, it is strongly advised always to consult a neurologist (preferably the prescriber).

Recommendations for reducing and stopping medication

Limited estimated remaining life expectancy: No considerations for reducing or stopping.

Frail older adults

Neuropathic pain: consider dose reduction or stopping antiepileptic drugs in cases of:

- Cognitive decline
- Side effects
- Combination of multiple drugs
- Insufficient effectiveness

See further under "Older adults"

Older adults

Migraine (neurologist): consider dose reduction or stopping antiepileptic drugs in cases of:

- Reduction in migraine attacks

Epilepsy (neurologist): consider dose reduction or stopping antiepileptic drugs in cases of:

- Acute symptomatic epileptic seizures after a stroke: consider tapering off after 6-12 weeks
- Long-standing epilepsy: consider tapering off after a long seizure-free period (> 2 years)

Method of tapering off

- For neuropathic pain and migraine, taper off gradually over 2 to 8 weeks, monitoring for recurring symptoms and withdrawal symptoms.
- For epilepsy, taper off gradually under the monitoring of epilepsy symptoms and withdrawal symptoms, in consultation with or under the supervision of a neurologist. Preferably, maintain a tapering-off period of at least 2-3 months, and for phenobarbital, at least 6 months.

Be cautious with reducing and stopping antiepileptic drugs in:

- Epilepsy that started at an older age (except for acute symptomatic epilepsy after a stroke).
- Presence of predictive factors for recurrence of seizures in epilepsy, such as a higher total number of seizures before remission, developmental delay, or a shorter seizure-free period.
- Other indications than epilepsy, migraine, and neuropathic pain, such as psychiatric disorders. In that case, involve the prescriber.

Explanation of recommendations for reducing and stopping medication

Limited estimated remaining life expectancy:
No considerations for reducing or stopping in this phase. The focus is on comfort care, where pain and epileptic seizures should be prevented. Only in the very last phase tapering off and stopping could be considered if side effects become predominant or swallowing is no longer possible.

Frail older adults:

Neuropathic pain: consider dose reduction or stopping of an antiepileptic drug in cases of:

- **Cognitive decline** [note 6,9]
  If antiepileptic drugs are used for neuropathic pain, it is difficult to determine how effective they (still) are. The expected effect on neuropathic pain is often moderate. Older adults with dementia or reduced cognition may find it harder to indicate the degree of pain perception. At the same time, the use of antiepileptic drugs can further impair cognition.
  - Try to estimate the patient's pain perception. Use an observational pain scale (PAINAD, REPOS, or PACSLC-D) for patients with cognitive impairments who cannot indicate their pain with a VAS or NRS.
  - If possible, gradually taper off according to the 'Step-by-Step Plan for Tapering Off Antiepileptic Drugs' to a lower dose or, if possible, to cessation.
  - Evaluate after each dose reduction to ensure no withdrawal symptoms or worsening of pain occurs. Adjust the dosage as needed.
  - Involve informal caregivers wherever possible. In addition to pain, evaluating withdrawal symptoms can also be challenging in this population.
- **Side effects** [note 6]
  Older adults are more sensitive to side effects of antiepileptic drugs, e.g. drowsiness (increasing fall risk), osteoporosis, hyponatremia, and tremor. The side effects may vary depending on the antiepileptic drug used.
  - Check if the patient is experiencing side effects associated with antiepileptic drug use.
  - Check if there is any co-medication that may also cause these side effects.
  - Weigh the side effects against the benefits of the antiepileptic drug on neuropathic pain.
  - If possible, gradually taper off the antiepileptic drug according to the 'Step-by-Step Plan for Tapering Off Antiepileptic Drugs' to a lower dose or, if possible, to cessation.
- **Combination of multiple drugs** [note 7]
  The combination of multiple drugs with different mechanisms of action for neuropathic pain may be indicated and initiated in secondary care. Among antiepileptic drugs, gabapentin and pregabalin are mainly used for neuropathic pain. The effect of medication on neuropathic pain is limited, and a recent meta-analysis indicates no convincing evidence of superiority of combination therapy over monotherapy. If an antidepressant (TCA, such as amitriptyline, nortriptyline, or SNRI, such as duloxetine, venlafaxine) or an opioid is used alongside an antiepileptic drug, consider reducing or stopping one of the two drugs.
  - Check if the patient is using multiple drugs for neuropathic pain.
  - Check if the drugs are effective and if the pain is sufficiently under control. Measure pain score with NRS if needed.
  - Choose, based on side effects, ease of use, and patient preference, whether to taper off the antidepressant, opioid, or antiepileptic drug. See also Factsheets on Antidepressants and Opioids.
  - If possible, gradually taper off the antiepileptic drug according to the 'Step-by-Step Plan for Tapering Off Antiepileptic Drugs' to a lower dose or, if possible, to cessation. Preferably consult the prescriber who started the combination therapy.

- **Insufficient effectiveness** [note 7]
  The response to medication treatment for neuropathic pain is often moderate, making regular evaluation important.
  - Check if the patient notices any effect of the antiepileptic drug for neuropathic pain. Measure pain score with NRS if needed.
  - If insufficient effect, gradually taper off the antiepileptic drug according to the 'Step-by-Step Plan for Tapering Off Antiepileptic Drugs'.

Older adults

Migraine *(neurologist).* Consider dose reduction or cessation of antiepileptic drugs in cases of:

- **Reduction in migraine attacks** [note 5]
  Antiepileptic drugs can be used as migraine prophylaxis on a neurologist's prescription. Preferably, after 6 months, it is evaluated whether the prophylaxis is effective, after which it is decided whether the patient continues use or not. If migraine attacks have reduced over time, consider reducing or stopping the antiepileptic drug. Tapering off should be done by or in consultation with a neurologist.
  - Check if migraine attacks have decreased.
  - If desired by the patient, gradually taper off the antiepileptic drug according to the 'Step-by-Step Plan for Tapering Off Antiepileptic Drugs' to a lower dose or, if possible, to cessation.
  - Evaluate after each dose reduction to ensure no withdrawal symptoms or extra migraine attacks occur. Adjust the dosage as needed.

Epilepsy *(neurologist).* Consider dose reduction or stopping antiepileptic drugs in cases of:

- **Acute symptomatic epileptic seizures (after a stroke)** [note 4]
  If antiepileptic drugs were started after an acute symptomatic epileptic seizure following a stroke, consider tapering off and stopping these 6-12 weeks after starting the antiepileptic drugs. Tapering off should be done by or in consultation with a neurologist.
  - Check if the patient is seizure-free.
  - Check if the patient has been using the antiepileptic drug for longer than 6-12 weeks.
  - If possible, gradually taper off the antiepileptic drug according to the 'Step-by-Step Plan for Tapering Off Antiepileptic Drugs' to a lower dose or, if possible, to cessation.
- **Long-standing epilepsy** [note 1]
  In long-standing epilepsy, there is no evidence for an optimal treatment duration. Based on expert opinion, a minimum treatment duration of 2 years after the last seizure is considered. This, however, should be determined on an individual patient basis. A longer treatment duration is often maintained. The longer the patient is seizure-free, the greater the chance of successfully tapering off. Check how long the patient has been seizure-free.
  Tapering off should be done by or in consultation with a neurologist.
  - If possible, gradually taper off the antiepileptic drug according to the 'Step-by-Step Plan for Tapering Off Antiepileptic Drugs' to a lower dose or, if possible, completely.
  - Evaluate after each dose reduction to ensure no withdrawal symptoms occur. Adjust the dosage as needed.
  - Instruct the patient (and/or their (informal) caregiver) to always report a new epileptic seizure to the neurologist after tapering off and to discuss possible follow-up steps.

Be cautious with reducing and stopping antiepileptic drugs in case of:

- **Epilepsy that started at an older age** (except for acute symptomatic epileptic seizures after a stroke). [note 3, 4]
  Epilepsy that started at an older age usually concerns symptomatic epilepsy caused by brain damage and often has a focal component. Causes can include a stroke, brain hemorrhage, traumatic brain injury, brain tumor, or neurodegenerative brain disease. There is a higher

chance of seizure recurrence when stopping an antiepileptic drug. Often, lifelong treatment with antiepileptic drugs is required.

- **Presence of predictive factors for recurrence in epilepsy** [note 2]
  Certain factors increase the risk of a seizure recurrence when stopping an antiepileptic drug, such as a longer duration of active epilepsy, a shorter seizure-free interval before tapering, a higher total number of seizures before remission, a developmental delay, or epileptiform abnormalities on the EEG before medication tapering.
- **Other indications than epilepsy, migraine, and neuropathic pain** [note 8]
  Antiepileptic drugs are used for various indications. Besides the discussed epilepsy, migraine, and neuropathic pain, they are also used for psychiatric disorders such as bipolar disorder and mania. In this case, involve a psychiatrist when discussing potential tapering. Additionally, there are many other indications where an antiepileptic drug (off-label) may be used. Always involve the prescriber. Tapering also occurs gradually with the evaluation of withdrawal symptoms and any (recurring) symptoms.

Step-by-Step Plan for tapering off antiepileptic drugs

Informing and finding agreements with the patient

- Find out what the patient's motivation is for tapering off the antiepileptic drug.
- Provide information to the patient, their family, and/or (informal) caregivers, and make clear agreements with the patient about the pros and cons of tapering off the medication.
- Together with the patient and/or (informal) caregivers, make agreements and a plan about the speed of going through the steps when tapering off antiepileptic drugs, based on shared decision-making and guidance. Also, discuss what to do if complaints (withdrawal symptoms or recurrence of pain or seizures) arise.

Neuropathic pain

- Discuss with the patient that it is important to monitor the pain and explain that the pain may temporarily worsen at the beginning of tapering off.
- Pay attention to other ways of coping with pain.
- Involve a pain specialist if necessary.

Migraine

- Always taper off by or in consultation with a neurologist.
- Agree with the patient to keep track of migraine attacks in a headache diary.
- Discuss the use of any attack medication.

Epilepsy

- Always taper off by or in consultation with a neurologist.
- Discuss with the patient what to do if a seizure recurrence occurs and the chances that it will not happen.
- Temporarily resume any precautionary measures.
- Consider prescribing escape medication to interrupt a possible epileptic seizure.
- Agree on a relapse plan with the patient, their family, or (informal) caregivers, and the treating neurologist or physician in case of a recurrence.

Gradually taper off to the lowest possible dose or stop and monitor

Neuropathic Pain

- An antiepileptic drug must be gradually tapered off to the lowest dose, after which it can be stopped. This can occur for neuropathic pain over 2 to 8 weeks.
- Monitor the patient during tapering off for recurring pain and withdrawal symptoms.
- If there is an increase in pain perception or the onset of withdrawal symptoms, one step back can be taken in the tapering schedule. Then, consult with the caregiver whether tapering can proceed further.

For Migraine (by or in consultation with neurologist)

- An antiepileptic drug should be gradually tapered off to the lowest dose, after which it can be stopped. This can occur for migraine over 2 to 8 weeks.
- Monitor the patient regularly during and after tapering off for the frequency of migraine attacks and withdrawal symptoms.
- If the frequency of migraine attacks increases after tapering off, restarting by slowly increasing the dosage may be considered.

For Epilepsy (by or in consultation with neurologist)

- An antiepileptic drug should be slowly and gradually tapered off to the lowest dose, after which it can be stopped. Preferably maintain a tapering-off period of at least 2-3 months and for phenobarbital at least 6 months to prevent withdrawal symptoms. The pace of tapering off may vary per patient.

- In combination therapy, taper off the different antiepileptic drugs consecutively. Keep in mind the influence of antiepileptic drugs on each other due to enzyme induction, which may sometimes require adjustment of the dosage of the other antiepileptic drug.
- Monitor the patient during and after tapering off for withdrawal symptoms or recurrence of seizures.
- Instruct the patient and family or (informal) caregivers to always contact the neurologist in case of a new epileptic seizure during or after the tapering off of the antiepileptic drugs.
- Stop tapering immediately if a patient experiences an epileptic seizure. Usually, it will be decided to revert to the previous effective dose of the antiepileptic drug.

If tapering off has not been (fully) successful

- For some patients, complete cessation may not be possible, but tapering off to a lower dose can help reduce experienced side effects. This should always be discussed with the patient.

Withdrawal symptoms

Withdrawal symptoms that may occur include insomnia, headache, nausea, diarrhea, flu-like symptoms, nervousness, depression, pain, sweating, and dizziness. These symptoms often occur shortly (within 48 hours) after reducing or stopping the medication.

Neuropathic pain

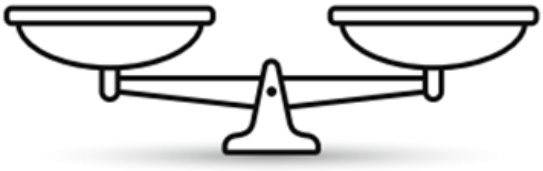
Temporary increase in pain symptoms: if tapering off too quickly with neuropathic pain, the suppression of the irritated nerve falls away, causing temporarily increased pain perception.

Migraine

Recurrence of attacks: Migraine attacks may return after tapering off the antiepileptic drug. It is important to keep track of the frequency to determine if restarting is necessary.

Epilepsy

Withdrawal seizure in epilepsy: if the medication is tapered off too quickly or stopped suddenly, there is a chance that stopping suddenly will trigger epileptic seizures.
A recurrent seizure often occurs some time after tapering off. Therefore, it may be useful to have seizure medication available to the patient when tapering off antiepileptic drugs for epilepsy, especially if the patient frequently needed escape medication for seizures in the past. Most recurrences occur in the first year after reducing or stopping. The consequences of a recurrent seizure differs per individual.



Considerations in favor of reducing and stopping

Long seizure-free period
The longer the seizure-free period, the greater the chance of successfully tapering off an antiepileptic drug. The seizure-free period for epilepsy must be at least 2 years. Also, a long seizure-free period is a reason to taper off in cases of migraine. [note 1]

Acute symptomatic seizure after stroke
If only acute symptomatic epileptic seizures have occurred after a stroke, consider tapering off the antiepileptic drug after 6-12 weeks. [note 4]

Limited effectiveness in neuropathic pain
The response to medication treatment for neuropathic pain is often moderate. Evaluation of the effect should be done regularly. [note 7]

Side effects
In the presence of side effects such as drowsiness, reduced cognition, fall risk, or osteoporosis, consider reducing or stopping antiepileptic drugs. [note 6]

The patient's desire to stop
The desire to use less medication or to reduce or stop antiepileptic drugs.

Considerations against reducing and stopping

Presence of risk factors for the likelihood of recurrence of epilepsy
If there are risk factors for the recurrence of epilepsy, be cautious with tapering off antiepileptic drugs. [note 2]

Epilepsy that developed at an older age
This variant often involves a focal component caused by brain damage. The risk of recurrence is higher, meaning that medication usually needs to be continued. [note 3]

Indications other than epilepsy, migraine, and neuropathic pain
Antiepileptic drugs are also used in psychiatric disorders such as bipolar disorder. Always consult the prescriber in these cases. [note 8]

The patient's desire to continue
If the patient does not experience problems, fears recurring pain or seizures, or wishes to avoid changes in medication use, weigh the pros and cons carefully.

What is known about reducing and stopping antiepileptic drugs in the older adults?

Research in older adults

There is little known about tapering off antiepileptic drugs specifically in older adults.

Gradual tapering off [note 10]

Antiepileptic drugs should always be gradually tapered off to prevent withdrawal symptoms and withdrawal seizures or recurrence of pain.

Epilepsy at an older age [note 3]

In epilepsy that developed at an older age, it is challenging to taper off medication because it often involves symptomatic focal epilepsy caused by brain damage.

Notes

Note [1]: Effect and treatment duration in epilepsy

There is little known about the effectiveness of antiepileptic drugs in older patients. [MDR Epilepsy 2023]. The available literature is of low to moderate quality, and definitive statements about the choice of antiepileptic drugs in older adults with epilepsy cannot be made. Research indicates that levetiracetam, compared to carbamazepine with delayed release, may lead to a greater reduction in seizures and fewer side effects in older adults with epilepsy. [Werhahn 2015, MDR Epilepsy 2023] Additionally, lamotrigine also shows a slightly higher reduction in seizures than carbamazepine but slightly lower than levetiracetam. However, these differences were not significant. [Werhahn 2015, MDR Epilepsy 2023] The Dutch MDR Epilepsy suggests a preference for the use of lamotrigine and levetiracetam as first-choice drugs for the treatment of epilepsy in older adults based on the mentioned literature.

There is no clear evidence that antiepileptic drugs behave differently in older patients. However, it should be acknowledged that older adults often have comorbidities and therefore often use various medications. Older adults are often cognitively vulnerable. Additionally, older adults frequently have reduced kidney or liver function, which means a dosage reduction may be required. For these reasons, it is important to conduct regular follow-up with a neurologist.

Regarding the optimal timing to reduce or stop antiepileptic drugs, there is also little scientific evidence. It remains unclear what the best moment is to begin tapering off medication in seizure-free adults. [Schachter 2018] A Cochrane review examined the ideal timing to discontinue treatment. It found evidence suggesting tapering off after at least two years of seizure-free status in children. There is no further research available that supports the best timing to cease antiepileptic drugs in adults. [Strozzi 2015] The current standard is to wait at least two years after the last seizure. Furthermore, Lamberink et al. indicate that this should be considered more as a continuous scale, where each seizure-free year reduces the risk of a recurrent seizure. [Lamberink 2017] The tapering-off document for antiepileptic drugs from Australia states that it may be desirable for adults to be seizure-free for at least 3-4 years before considering tapering off. [Peterson 2020]

Note [2]: Risk factors for recurrence of epileptic seizures

Several risk factors have been identified to determine the likelihood of a recurrent epileptic seizure when stopping antiepileptic drugs. [Lamberink 2017] These factors include:

- A longer duration of active epilepsy.
- A shorter seizure-free interval before tapering.
- Epilepsy that first developed at an older age.
- A history of febrile seizures.
- A higher total number of seizures before remission.
- The absence of certain favorable epilepsy syndromes (Panayiotopoulos syndrome, Rolandic epilepsy, absence epilepsy).
- A developmental delay.
- Epileptiform abnormalities on the EEG before tapering off medication.

These factors have been compiled into a calculation tool that is available.

Note [3]: Epilepsy at an older age

Epilepsy that developed at an older age can have various causes. Sometimes the cause is unclear, but it often involves a stroke (see note 4). Epilepsy is also seen in other brain disorders such as dementia, brain inflammation due to an infection, brain injury due to an accident or oxygen deprivation, or a

brain tumor. [Epilepsy NL 2023]
Epilepsy that occurs at an older age is almost always a focal form of epilepsy. This implies a relatively high chance of a recurrence after a first seizure and a lower chance of successfully stopping medication. [MDR Epilepsy 2023]

Note [4]: Antiepileptic drugs after a stroke: differentiation between acute and late symptomatic seizures
After a stroke—either a cerebral infarction or a brain hemorrhage—epileptic seizures can occur. When these occur within a week after the stroke, the seizures are classified as 'acute symptomatic.' The guideline indicates that treatment with antiepileptic drugs after an acute symptomatic seizure following a stroke should be reconsidered to stop. Arbitrarily, this guideline chooses a period of six weeks to three months after the stroke. [MDR Epilepsy 2023]
When the first epileptic seizure occurs more than a week after the stroke, it is classified as 'late symptomatic.' In daily practice, it is common to start treatment with antiepileptic drugs after a late symptomatic seizure. This choice is mainly based on the high risk of recurrence (47-93%) [Hesdorffer 2009]. Given the high likelihood of a recurrence, a single late symptomatic seizure may already be considered epilepsy, and antiepileptic drugs are often continued long-term. [MDR Epilepsy 2023] In rare cases, after long-term use (>2 years), tapering off may be considered for this indication.
If no epileptic seizures occur after a stroke, there is no indication for prophylactic treatment with antiepileptic drugs according to the guideline. [MDR Epilepsy 2023]

Note [5]: Effect and treatment duration in migraine
The use of antiepileptic drugs, such as topiramate and valproate, has been proven effective as a prophylactic treatment for migraine in adults. [MDR Medicamenteuze behandeling migraine en MOH 2017 NHG Hoofdpijn 2021] In older adults, the severity and/or frequency of migraines often decreases but not always. [van Oosterhout 2015] Specific guidelines for treating migraine in older patients do not exist. Treatment choices should therefore be made pragmatically and individually based on effectiveness, side effects, and comorbidities. It is possible that older adults still use antiepileptic drugs as a prophylactic treatment for migraine. There is little data available to help to determine the optimal time to stop effective prophylactic treatment. Generally, the effect is assessed after three months, and it is recommended to continue effective treatment for at least 3-6 months before considering dose reduction or complete tapering off. Reducing or stopping treatment should be considered on a case-by-case basis, depending on the duration, type, and severity of the migraine and the patient's preferences. [van Hanewinckel 2021]

Note [6]: Side Effects
The use of antiepileptic drugs is often associated with relatively many side effects, which are often dose-dependent. Almost all antiepileptic drugs have a general inhibitory effect on the central nervous system. Central side effects (such as sedation, lethargy, ataxia) and gastrointestinal complaints mainly occur at the start of treatment and are more common with the simultaneous use of multiple antiepileptic drugs. Common side effects that can occur with the use of antiepileptic drugs include: [FK 2023, KNMP Kennisbank 2023]

- Relatively common: fatigue, sedation, lethargy, ataxia, gastrointestinal complaints such as nausea and vomiting, nystagmus, and mild hypersensitivity reactions (rash, urticaria).
- Less common: severe hypersensitivity reactions such as Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN); behavioral changes; disorders in bone metabolism leading to osteopenia, osteoporosis, or fractures.

Behavioral changes (e.g., increased irritability, aggression, dyskinesia) are regularly seen in patients with pre-existing behavioral problems.

With prolonged use, particularly of the enzyme-inducing antiepileptic drugs, there is an increased risk of reduced bone mineral density leading to osteoporosis, osteopenia, and fractures. The cause of this cannot be explained by a single mechanism. The enzyme-inducing antiepileptic drugs could cause accelerated breakdown of vitamin D in the liver through induction of the CYP-450 enzyme system. Valproic acid may have a direct negative effect on osteoblasts. Other mechanisms are likely to play a role as well. [FK 2023]

Pack et al. investigated the possible increased risk of osteoporosis with the use of antiepileptic drugs. [Pack 2005] This study showed an increased risk of osteoporosis with the use of carbamazepine, phenytoin, and valproate due to causing calcium deficiency. There is currently no evidence whether this is the case with other antiepileptic drugs, so this cannot be ruled out. However, this side effect can have a significant impact on the older population, and this should be taken into account. Schousboe et al. also showed that the use of enzyme-inducing antiepileptic drugs for more than two years is associated with an increased prevalence of vertebral fractures. [Schousboe 2023]

A study investigating medication groups that increase the risk of falls in older people found a strongly increased risk of falls with antiepileptic drugs. [STOPPFALL 2021] This position comes from an expert group indicating that particularly the first-generation antiepileptic drugs (such as phenobarbital, phenytoin, and primidone) increase the risk of falls. Another study concluded that there is a higher risk of recurrent falls (OR 3.15 and OR 4.7 in two studies) compared to not falling or falling once with the use of antiepileptic drugs. [Ming 2018]

Additionally, in older people, reduced kidney and liver function should be considered. Many antiepileptic drugs are cleared renally or hepatically, which means that with a decrease in these functions, higher blood levels and side effects of the used antiepileptic drugs may occur. A dose reduction should then be considered.

Also, in older people with reduced cognition, the central side effects of antiepileptic drugs may further deteriorate cognition. This is an additional reason to reconsider the use of the antiepileptic drug.

Note [7]: Antiepileptic drugs for neuropathic pain
Estimates for the prevalence of neuropathic pain vary between 2-8% of the population. [NHG Pain 2023] According to figures from Nivel, the prevalence of neuropathy increases with age, reaching 18% among those aged over 65 and almost 34% among those aged over 80. [Nivel 2022] If antidepressants (TCAs) are not effective, a gabapentinoid such as gabapentin or pregabalin is recommended as a second choice. For the indication of trigeminal neuralgia, carbamazepine is recommended as the first choice. Antiepileptic drugs can be effective for neuropathic pain, but the response is often moderate, and there are significant differences between individuals. [NHG Pain 2023, MDR Polyneuropathy 2019] Medicines used for the treatment of neuropathic pain often do not demonstrate sufficient efficacy when administered as monotherapy and also often have side effects that limit dose escalation. There are studies showing that combinations of, for example, TCAs with gabapentin for the treatment of neuropathic pain are more effective than monotherapy with either drug. However, more side effects occur with combination therapy. [Gilron 2009, Chaparro 2012]

The MDR Polyneuropathy indicates that the effect of pharmacological treatment is limited, with less than 50% of patients achieving a maximum of 50% pain reduction. The effect of most drugs can only be adequately assessed after several weeks. The treatment can only be considered ineffective if the drug has been increased multiple times and tried for a sufficient duration at an adequate dose (minimum of 3 weeks). [MDR Polyneuropathy 2019]

A recent meta-analysis compared combination therapy with monotherapy. For combinations of opioids-antidepressants, opioids-gabapentinoids, and gabapentinoids-antidepressants, meta-analyses could not demonstrate superiority over either monotherapy. Overall, the side effect profiles were not substantially different for combination therapy compared to monotherapy. Despite widespread use and a growing number of studies, no convincing evidence has yet emerged suggesting the superiority of any combination over the respective monotherapies. Therefore, when implementing combination therapy as a second- or third-line treatment in situations where monotherapy is inadequate, adequate monitoring should take place in terms of safety and effectiveness. [Balaneser 2023]

Since antiepileptic drugs can also cause many side effects in older people, it is advisable to consider whether the antiepileptic drug can be discontinued in combination therapy or in the case of insufficient efficacy in neuropathic pain. If tapering off is initiated, it is important to thoroughly evaluate pain during the tapering process and also to pay attention to broader pain management approaches, such as exploring other ways to cope with pain.

Note [8]: Other indications besides epilepsy
Antiepileptic drugs are primarily prescribed for all forms of epilepsy and additionally for neuropathic pain, migraine, and psychiatric disorders such as bipolar disorder, mania, and post-traumatic stress disorder. There are also many other (off-label) indications for antiepileptic drugs. This varies by antiepileptic drug. These indications can include: hot flushes after breast cancer treatment, complex regional pain syndrome type 1 (CRPS-1 or post-traumatic dystrophy), hiccups, possibly in combination with baclofen, myoclonus caused by opioids, moderate to severe symptoms of restless legs syndrome, palliative relief of itching in end-stage chronic kidney disease, palliative treatment of dry cough in advanced COPD when strong opioids are insufficient, glossopharyngeal neuralgia, alcohol withdrawal syndrome, central diabetes insipidus, and polydipsia and polyuria of neurohormonal origin; insomnia; hereditary 'stiff person' syndrome (hyperreflexia), panic disorder, generalised social anxiety disorder, cardiac arrhythmias, particularly if caused by a digoxin overdose, 'short-lasting unilateral neuralgiform headache with conjunctival injection and tearing' (SUNCT), essential tremor as an alternative to propranolol, ataxia, and myokymia. [KNMP Knowledge Bank]
Additionally, antiepileptic drugs are sometimes prescribed for sexually disinhibited behaviour in older people with dementia. [Dijkema 2015]
For the tapering off of antiepileptic drugs, the same principle applies as for the other indications: taper off slowly and stepwise while monitoring for recurrent symptoms and withdrawal symptoms. For these indications, there should always be a consultation with the prescriber first.

Note [9]: Epilepsy in older people with dementia in a care institution
In older people in a care institution, it is difficult to diagnose epilepsy and also to evaluate whether people are seizure-free. The history can be complicated by aphasic disorders/cognitive disorders of the patient. There may be nocturnal seizures. Complex partial seizures are difficult to distinguish due to aphasic/cognitive disorders, and the seizures are often more subtle. Post-ictal confusion can be

interpreted as part of existing cognitive disorders or delirium. It is important to differentiate between an epileptic seizure manifesting as confusion or behaviour and a delirium.
The guideline indicates that, in this setting, antiepileptic drugs should be considered for tapering if there are long seizure-free periods, interactions with (new) medications, or side effects. They advise considering tapering, stopping, or switching in these cases in consultation with a neurologist. The tapering advice is the same as previously mentioned: taper over a minimum of 2-3 months and for phenobarbital over at least 6 months. [van Gelder 2017]

Note [10]: Method of tapering off
There is little scientific evidence on the best way to taper off antiepileptic drugs. A Cochrane review among epilepsy patients concluded that there is no evidence regarding the best rate at which medication can be tapered off, as only two studies with children were available. The studies compared a tapering period of 1 month with 6 months, and 6 weeks with 9 months, without significant differences. [Ayuga 2020] The MDR Epilepsy of the Dutch Society for Neurology (NVN) mentions the NICE Guidelines (2012), which recommend slow tapering, usually over at least 2-3 months. This is primarily based on expert opinion. [MDR Epilepsy 2023] Furthermore, it states: immediately stop the drug in case of a severe idiosyncratic reaction. In such a case, consider temporarily prescribing clobazam for bridging. In combination therapy, stop the different antiepileptic drugs consecutively. For barbiturates, a tapering period of at least 6 months should be maintained to prevent withdrawal symptoms or seizures. [MDR Epilepsy 2023]
In this factsheet, the minimum tapering duration from the MDR Epilepsy has been maintained for epilepsy. A longer tapering duration can also be considered. Regarding neuropathic pain, it depends on the dosage. Advice given ranges from 2-8 weeks. Several example schedules are available, as mentioned earlier in this document from various pain centres. It is important to taper off with small steps per week.
Finally, in the tapering protocols from Australia for antiepileptic drugs for epilepsy and gabapentinoids (pregabalin and gabapentin) for neuropathic pain, the following tapering advice is given: at least 3-6 months for antiepileptic drugs for epilepsy and at least 4-8 weeks for gabapentinoids for neuropathic pain. [Peterson 2022, Peterson 2022a]

Note [11]: Effects of stopping
In a document with practical considerations by Lamberink et al. on epilepsy, it is described that stopping antiepileptic drugs improves self-esteem and quality of life. There is evidence that even without medication, 30-50% of people with epilepsy become seizure-free again. In many people, lifelong therapy with antiepileptic drugs is not indicated. [Lamberink 2020]
The article by Lamberink also describes risks of seizure recurrences in epilepsy. According to a meta-analysis of the literature, the average risk of a seizure recurrence 1 year after starting tapering is 22%, and after 3-4 years, this risk is 34%. However, the found risks strongly depend on the studied population and range from 12-66%. Additionally, if a seizure recurrence occurs and the medication is restarted, a patient is not immediately seizure-free and under control. Four out of five people with a seizure recurrence will become seizure-free again with medication, but in half of them, this takes longer than 6 months. [Lamberink 2020] Finally, continuing the medication also carries a risk of new seizures. This must be considered in weighing the pros and cons of reducing or stopping the antiepileptic drug. Two studies compared tapering off medication with continuing medication. It turned out that the risk of a seizure after 1-2 years is about twice as high for people who stop medication versus those who continue. However, the differences in both studies were not significant. The difference in recurrence risk between the groups decreased over time. [Lamberink 2020]

There is little known about the effects of stopping antiepileptic drugs for other indications. A review has been published on strategies for tapering off or stopping gabapentinoids, but it also shows that there is still too little known about this. [Anderson 2023]

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