WeMeReC
Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Bulletin

"Independent prescribing information for NHS Wales"

June 2015

Sedative medicines in older people

A demographic shift in the UK is leading to a greater proportion of older people in the population. Older patients have a higher likelihood of co-morbidity and are more likely than their younger counterparts to receive multiple medications. Polypharmacy may complicate the prescribing of sedative medicines and increases the chances of deleterious interactions and adverse drug reactions (ADRs). The additional 'pill burden' also increases the risk that medicines are not taken as prescribed.[1]

In addition to polypharmacy, changing pharmacodynamic and pharmacokinetic characteristics, caused by disease or the ageing process, contribute to an increasing risk of ADRs; see Table 1. Some ADRs result in inappropriate sedation and effects on cognition; a cause of morbidity such as falls, fractures, and decreased quality of life. In addition, some medicines are prescribed, not always appropriately, for their direct sedative properties.

Table 1. Drug-handling in older people.

Pharmacokinetic changes
Absorption Extent not significantly altered – some changes in rate.
Distribution May change due to reductions in lean body mass, total body water, and plasma albumin concentration.
Metabolism Slow decline in some pathways of hepatic metabolism. Biological age, i.e. frailty, may provide a better guide to metabolic capacity than chronological age.
Excretion Glomerular filtration rate (GFR) tends to decline with age even in the absence of overt renal disease. GFR declines by 30% on average between ages 30-80.

Older, frailer patients or those with multimorbidity are rarely enrolled onto clinical trials. Therefore, it is often difficult to determine whether a medicine will have the full desired effect and to what extent ADRs might affect this highly susceptible population. This bulletin will discuss some of the strategies to reduce ADRs – especially those related to sedation with the use of benzodiazepines, anticholinergics, and antipsychotics – and to increase appropriate prescribing of these medicines, guided by principles of Prudent Healthcare.

Summary

- The ageing process and concomitant disease can alter drug-handling in older people.
- It may be difficult to determine to what extent a medicine will have its desired effect or produce adverse drug reactions in older people as this group is often excluded from clinical trials.
- Use of benzodiazepines and z-drugs is rarely appropriate, especially in the long-term – the aim should be to stop therapy with patient agreement.
- Older people have more to gain from cessation and can withdraw such medication just as successfully as younger patients, provided guidance on withdrawal rate is followed.
- Medicines with anticholinergic properties are particularly troublesome in older people and should be prescribed with caution and due regard to total anticholinergic load.
- Pharmacotherapy should not be first-line for the majority of people with behavioural and psychological symptoms of dementia.
- Regular medication review has an important role to play in prudent prescribing and can support the reduction of medication load.

Benzodiazepines and 'z-drugs'

Although the exact mechanisms are unclear, advancing age is associated with an increased sensitivity of the central nervous system to benzodiazepines and z-drugs, e.g. sedation is induced at lower doses and adverse effects such as postural sway are increased.[2] Additionally, decreased metabolism and clearance can lead to drug accumulation.[2,3] The increased risk of ataxia, cognitive effects, falls, and injury associated with the use of these agents, especially in older patients, has been recognised for some time and, in association with the marginal benefits, is one of the reasons to consider whether their use is appropriate in this population.[4] There is evidence to link benzodiazepines with Alzheimer's disease and also a suggestion that this risk increases with the longer-acting agents, the cumulative dose, and longer treatment duration.[5,6]

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Anxiolytics and hypnotics should be avoided where possible in older patients. Non-drug approaches, such as increased social support, relaxation exercises, and sleep hygiene measures should be used. The British National Formulary (BNF) warns that prescribing is not desirable, should not be indiscriminate, and should be stopped as soon as feasible. It also notes that benzodiazepines and z-drugs should be avoided in the elderly.[7] Where they are prescribed, benzodiazepines are only indicated for the short-term (2-4 weeks) relief of anxiety or insomnia, which is severe, disabling, or causing the patient extreme distress. Z-drugs are indicated for short-term management of severe insomnia that interferes with daily life and should not be used for longer than two (zaleplon) or four (zolpidem and zopiclone) weeks.[7]

It can be seen therefore, that in most cases, if a person has been taking one of these agents in the longer term, if they are older, or particularly if both, then prescribing is probably inappropriate. However, studies indicate a benzodiazepine prescribing rate of 12-32% in older people, rising to 57-59% in those with psychiatric disorders.[3] It is postulated that prescribing rates may remain so high due to:

- lack of knowledge about the harms of prescribing these agents in older people
- difficulties in translating prescribing guidelines into practice
- a lack of evidence-based alternatives
- an unwillingness of older people to discontinue treatment
- lack of priority for physicians due to the greater health needs of this population
- physiological and psychological dependency.[3]

Although direct evidence in older people is somewhat limited, a meta-analysis reviewing interventions for reducing benzodiazepine use in this population found that a simple stepped-care approach, using advisory letters, consultations with healthcare professionals, and medication review coupled with education and a defined withdrawal schedule, resulted in significantly higher odds of cessation in the short term.[3]

Any reduction of dose or withdrawal should be gradual and carried out at a rate tolerable for the patient. Sudden withdrawal may lead to confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens, which may develop any time up to three weeks post-cessation.[7] The schedule should be dependent on the initial dose and duration of use, coupled with the patient's clinical response. Use for 2-4 weeks can be tapered and stopped in a similar period of time, but stopping longer-term use may take considerably longer; perhaps months or more than a year.[7] In older patients there may be a case for a slower reduction, although it is useful to stay focussed on the potential benefits of cessation.

Many cessation schedules advise a conversion to diazepam – as this agent has a longer half-life and can be more readily slowly titrated due to the wider range of strengths and formulations available – followed by gradual withdrawal. It is recommended that patients are transferred one dose at a time over the period of about 7-14 days.[7-9] Dose equivalences with diazepam are approximate and vary somewhat, but those recommended by the BNF and Clinical Knowledge Summaries (CKS) are provided in Table 2.

Table 2. Approximate equivalent doses.

Diazepam 5mg	BNF[7]	CKS[8]
alprazolam	250 micrograms	
chlordiazepoxide	12.5mg	15mg
clobazam	10mg	
clonazepam	250 micrograms	
flurazepam	7.5 - 15mg	-
loprazolam	0.5 - 1mg	
lormetazepam	0.5 - 1mg	
nitrazepam	5mg	
oxazepam	10mg	15mg
temazepam	10mg	
zaleplon	-	10mg
zopiclone	-	7.5mg
zolpidem	-	10mg

Examples of cessation schedules can be found at: http://cks.nice.org.uk/benzodiazepine-and-z-drug-withdrawal and in the 'Ashton Manual' at: www.benzo.org.uk. It is recommended that schedules allow flexibility, but patients should be dissuaded from prolonging the withdrawal to a very slow rate, especially towards the end.[9] Adjunct therapy should not be routinely prescribed, especially antipsychotics which may worsen withdrawal symptoms and have their own inherent risk of harm (see Pages 3 and 4).[8]

It should be noted that older people can withdraw from benzodiazepines and z-drugs just as successfully as younger people and that they have more to gain from cessation.[9] In addition to the reduction of adverse effects already mentioned, cessation in older people has been shown to improve working memory and reaction times, increase levels of alertness, and improve concentration.[10] In difficult cases, although the preferred goal is to withdraw therapy completely, this may not be achievable. However, there is still benefit to be gained from a reduction in dose and/or the avoidance of long-acting agents such as nitrazepam.

Drugs and driving

It is the duty of prescribers to advise a patient if a medicine, such as a sedative, is likely to impair their ability to perform skilled tasks, e.g. driving. In March 2015, a new offence of driving, attempting to drive, or being in charge of a vehicle, with certain controlled drugs in excess of specified limits came into force. In addition to some illegal drugs of abuse, this also covers benzodiazepines such as diazepam, temazepam, clonazepam, flunitrazepam, oxazepam, and lorazepam, and opioids including morphine and methadone.[7,11] A person found driving with these drugs (and certain others related or metabolised to them) above specified limits in their blood will have committed an offence, whether or not their driving was impaired. Limits are generally in excess of the 'normal' therapeutic range.

Where driving is **not** impaired, a patient will be entitled to raise a statutory 'medical defence' if the medicine was lawfully prescribed or purchased and was used according to the instructions supplied. Patients should be advised to carry 'suitable evidence' with them that this is the case. However, it remains the patient's responsibility to consider whether their driving could be affected, e.g. if they feel drowsy, as the offence of driving while impaired has no such medical defence.[7,11] Prescriber information, patient information leaflets, and promotional materials are available at: www.gov.uk/government/collections/drug-driving.

Anticholinergic medicines

Medicines with anticholinergic (antimuscarinic) adverse effects should be prescribed with caution to older patients. Adverse effects including sedation, impaired cognition and confusion – which may lead to an incorrect diagnosis of dementia – and falls are more common in this population, as are other anticholinergic effects such as constipation, urinary retention, dry mouth and eyes, and photophobia. There is evidence to suggest a link of increased mortality to the number and potency of anticholinergics prescribed and also an increased risk of dementia with higher cumulative anticholinergic use.[12,13]

It is useful to remember that many medicines have anticholinergic effects, not just those used therapeutically for these properties. Table 3 compares the relative anticholinergic effects of some medicines, but many more also have these effects. The table is based on several studies of the agents listed; the higher the number of points, the greater the anticholinergic effect.[14] Several of these medicines are available without prescription and careful questioning and a full medication history is therefore advised to ensure that the true anticholinergic load is established.

Table 3. The *Anticholinergic Risk Scale*.[14]

1 point	2 points	3 points
haloperidol	baclofen	amitriptyline
mirtazapine	cetirizine	chlorphenamine
paroxetine	cimetidine	chlorpromazine
quetiapine	clozapine	hydroxyzine
ranitidine	loperamide	imipramine
trazodone	loratadine	oxybutynin
	nortriptyline	
	prochlorperazine	

When considering prescribing a medicine with anticholinergic properties, it is useful to adhere to the following principles:

- minimise or avoid use where possible
- consider total burden when a patient is using more than one medicine with anticholinergic effects
- the effect of acetylcholinesterase inhibitors, e.g. donepezil and rivastigmine, may be antagonised by medicines with anticholinergic effects – the combination should be avoided where possible as this can worsen cognitive impairment
- proactively monitor patient for both efficacy and tolerance at regular intervals, e.g. annually (or 6-monthly for over-75s)
- use mini mental state examination or equivalent if anticholinergic-induced impaired cognition is suspected – consider switching or stopping if confirmed
- consider referral to an appropriate specialist if there are significant anticholinergic adverse effects from psychotropic medication.[14]

Second-generation antipsychotic medicines

The development of behavioural and psychological symptoms is a core part of dementia.[15] Patients with dementia may develop non-cognitive symptoms such as hallucinations, anxiety, agitation, and aggression. Additionally 'behaviour that challenges' has been defined as a specific set of symptoms including aggression, agitation, wandering, hoarding, sexual disinhibition, apathy, and disruptive vocal behaviour such as shouting. Behavioural and psychological symptoms of dementia are very common, with estimates of a point prevalence of 60-80% and a cumulative risk of up to 90%.[15]

It is recognised that the assessment and management of these behaviours is complicated; but an early, comprehensive assessment should be undertaken to establish any factors that may generate, worsen, or improve non-cognitive symptoms or behaviour that challenges. Many factors are significant, although they

are not always recognised as such; assessment should include the following:[15,16]

- physical health
- depression
- pain or discomfort
- adverse effects of medicines
- 'biography' including beliefs
- psychosocial factors
- physical environment
- behavioural and functional analysis.

Investigation of existing medication use is important and any issues should be addressed, e.g. benzodiazepine use may result in paradoxical adverse effects, ranging from talkativeness and excitedness to hostility, aggression, and antisocial acts.[7]

In most cases, first-line treatment should be non-pharmacological. A quiet and relaxing environment may have a beneficial effect and, depending on local availability, aromatherapy, multisensory stimulation, therapeutic singing and dancing, animal-assisted therapy, and massage are all indicated prior to medication. If a person fails to respond to one such therapy, the National Institute for Health and Care Excellence (NICE) suggests that another should be tried as people may respond to a therapy even if another has failed.[16]

Although the data are derived from a predictive model and should be interpreted with some care, it is estimated that at least 50% of people with dementia are prescribed an antipsychotic in any given year.[15]

> "Although they (antipsychotics) are important for a minority of people with dementia, disturbingly they are still often prescribed inappropriately or unnecessarily."[17]

Where medication is required, risperidone is licensed for the short-term management of persistent aggression in patients with moderate to severe Alzheimer's dementia when there is a risk of harm to the person or to others. It should not be used for more than six weeks, in mild Alzheimer's or, in most cases, before non-pharmacological assessment and treatment.[7,16] It is the only agent licensed for this indication in the UK, but olanzapine, quetiapine, and aripiprazole are also used off-label.[15] Any use of antipsychotics should include a full discussion with the person and carers about the possible benefits and risks of treatment.[16]

All antipsychotics, including second-generation or 'atypical' agents, have been linked with increased morbidity and mortality in dementia patients. There is evidence to associate use with a higher risk of mortality when compared to non-use, which may be further increased at higher compared to lower doses;[18] the rate of stroke and transient ischaemic attack is thought to be increased, especially in older patients;[7] and there may be a greater risk of falls and fractures, possibly due to sedation, gait changes, and hypotension.[19] An online *Antipsychotics learning module* is available at: www.mhra.gov.uk/antipsychotics-learning-module/con155606.

Medication review

Although polypharmacy is not an issue that exclusively affects older people, it is particularly important that medication reviews are undertaken regularly for this age group to support scaling back – or even sometimes increasing – treatment where appropriate.[1] Any risks from a treatment should always be considered alongside its potential benefits and it is a good rule of thumb to regard any new medication as a trial, with a view towards withdrawal if it is ineffective or produces intolerable adverse effects.

A comprehensive document on *Polypharmacy: Guidance for prescribing in frail adults* has been produced by the All Wales Medicines Strategy Group and is available from: www.awmsg.org/medman_library.html. Previous WeMeReC bulletins have also covered the topics of medication in older people, medicines review, and stopping medicines and can be found at: www.wemerec.org.

Conclusion

Many commonly prescribed medicines with sedative properties have the potential to cause serious adverse effects in older patients. Such patients are particularly susceptible to these effects due to changes in drug handling, sensitivity to drug effects, and co-morbidities resulting in a decreased physiological reserve, together with a greater likelihood of polypharmacy.

Careful consideration of risks and benefits when prescribing and regular review with a view to stopping unnecessary medicines and switching those likely to cause harm is desirable within the context of Prudent Healthcare. Although not always easy, there are numerous tools available to aid prescribers – many of which are discussed in this bulletin. Even a seemingly small reduction in a patient's medication load can result in a large difference to their quality of life.

References available at www.wemerec.org

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